DOCTOR OF PHILOSOPHY

Fine chemicals from cashew nut shell liquid

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FINE CHEMICALS FROM CASHEW NUT SHELL LIQUID

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BY

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2003

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ABSTRACT

Cashew nut shell liquid, a potentially important commercial source of biological active natural phenols, is a mixture of alkenyl salicylic acid, and alkenylresorcinols. This mixture undergoes thermal degradation in the industrial cashew kernel shelling process to give a mixture of alkenylphenols (cardanols) and alkenylresorcinols.

Using the Kamlet-Taft classification of solvents as an heuristic guide, a solvent system allowing selective extraction of alkenyl salicylic acid, alkenylphenols and alkenylresorcinols has been found, allowing a cheap, large scale separation of cashew nut shell liquid constituents. Others approaches tested (complexes with divalent metals, alkaline extraction, or chromatographic techniques) were not so successful.

Vacuum pyrolysis of cardanols on copper has been found to be a useful technique to synthesize 3-vinylphenol, a synthon for the production of a variety of pharmaceutical drugs. In comparison with others materials, copper inhibited coke deposition, increasing yields so that the commercial value of the reaction products is higher than that of the starting material. Pyrolysis of cardanols follows the same characteristic pattern as the pyrolysis of alkylaromatics, i.e. giving as the main products vinylphenol and ethylphenol in place of styrene/toluene. Yields of minor compounds are a function of operational conditions. Pyrolysis of cardanol (15:0) in the same apparatus and conditions to the ones used for mixed cardanols, gave a smaller conversion. This is consistent with the possibility that the reaction is initiated by homolytic scission of a carbon-carbon bond which is simultaneously α to a double bond and β to another one in the alkyl chain.

3-Pentadecylsalicylic acid provided in 3 steps 8-pentadecyl-1-oxa-spiro-[5,7]-dien-4-one, which undergoes a rearrangement to 4-pentadecyl-benzo[1,3]dioxole, under a variety of conditions. The oxaspirodienone was unreactive in a range of Diels Alder reactions.

Synthons for the synthesis of diaromatic compounds with HIV integrase inhibition properties were provided by a selective cleavage of double bonds in the carbon chain of CNSL constituents.

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REACTION SCHEME

ABBREVIATIONS AND NOMENCLATURE

CNSL- Technical cashew nut shell liquid

N-CNSL-Natural cashew nut shell liquid

BSL-Bilhawan shell liquid, also called Semecarpus shell oil

RMR-Relative molar response factor

IPA, DEA, and TEA

K-T-Kamlet Taft

MC-*meta* cresol

EP-*meta* ethylphenol

MVP- *meta* vinylphenol

PP-*meta* propylphenol

TFE—trifluoroethanol

ACN- acetonitrile

NM-nitromethane

THF-tetrahydrofuran

DMF-dimethylformamide

BDXO-benzodioxole

DA- Diels Alder

g-gram

h-hour

min-minute

ODS- Octadecyl silane

LC- Liquid Chromatography

Cardanol, cardol, methylcardol, and **anacardic acid**, are the common name of the saturated and side chain unsaturated analogues of 3-alkylphenol, 5- alkylresorcinol , 6-methyl-5-alkylresorcinol, and 2-hydroxyalkyllbenzoic acid. While there is no accepted nomenclature for the individual analogues, **15:0, 15:1, 15:2, 15:3** are suffixed in brackets following the name of the parent compounds for the saturated, mono-, di-, and trienes by analogy to the fatty acid nomenclature.

Bilobol is another trivial name of cardol (15:1).

Hydrobilobol and Adipostatin-A are other trivial names of cardol (15:0).

Ardisinol II is the trivial name of Z- 5 – 8'-tridecenyl resorcinol.

Cardol, in the chapter 2 of this work, is used as a generic name for both cardol (15:0), cardol (15:1), cardol (15:2), cardol (15:3), methylcardol (15:0), methylcardol (15:1), methylcardol (15:2), and methylcardol (15:3).

CHAPTER 1- CNSL; SOURCES, USES, AREAS OF RESEARCH AND AIMS OF THIS PROJECT

1.1. Sources of Cashew Nut Shell Liquid

1.1.1.The cashew tree

The cashew *(Anacardium occidentale Linn)* is a tree originally from the Amazon.[1] In 1578, it was commonly cultivated by the Indians from the rain forest; the Portuguese took the tree to India, Eastern Africa, and others countries. Its name derives from Acaju, the name given by the Tupi Indians from Brazil,[2,6] thence 'caju' by the Portuguese. It grows on the drier sandy soils from these tropical countries, frequently reaches up to 15 metres in height, and has a thick and tortuous trunk and branches so winding that they usually reach the ground. The cashew tree produces very peculiar apples (a swollen peduncle that gives a sweet flavourful juice). At the end of this peduncle, the cashew nut grows externally in its own grey coloured kidney shaped hard shell, which is 2.5 - 4 cm long. This shell (about 0.3 cm thick) has a soft leathery outer skin and a thin hard inner skin.

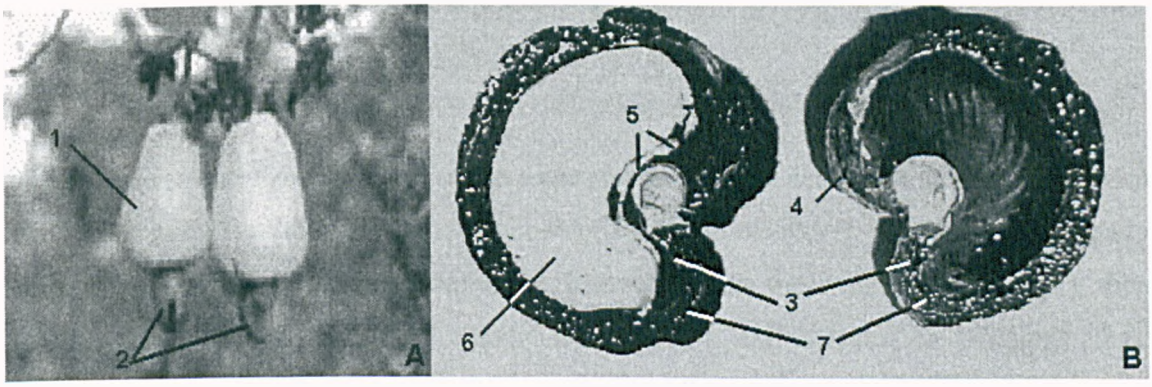


FIGURE 1 - 1: CASHEW APPLE AND KERNELS

A-Cashew apple and nut/ B-Split cashew nut/
1-cashew apple, 2-cashew nut hanging at the base of cashew apple, 3- thin hard inner shell skin, 4-soft leathery shell skin, 5-cashew testa, 6-cashew kernel, 7-honeycomb structure containing the cashew nut shell liquid, CNSL.

Between these skins is a honeycomb structure containing a liquid called the cashew nut shell liquid or, more commonly, CNSL. The nuts consist of the kernel (20 - 25 % by mass), the shell liquid (20 - 25 %), and the testa (2 %), the rest being the shell.[3]

The kernel is the more valuable product from the cashew factories: the cashew nut shell liquid is a by-product looked on mainly as a waste.

1.1.2 Extraction of the CNSL

It is not possible to use straightforward nut-cracking techniques to recover the kernel and extract the shell liquid and more specialised processes have been introduced:

(i) The Hot-bath method

This is the most popular technique. The principle is to soften the outer shell, by immersion in water at 22 - 25 °C, treatment with steam to open the pores, followed by heating in a bath of hot (180 °C) CNSL-itself for 1.5 - 4 min.[4] (See Figure 1-2).

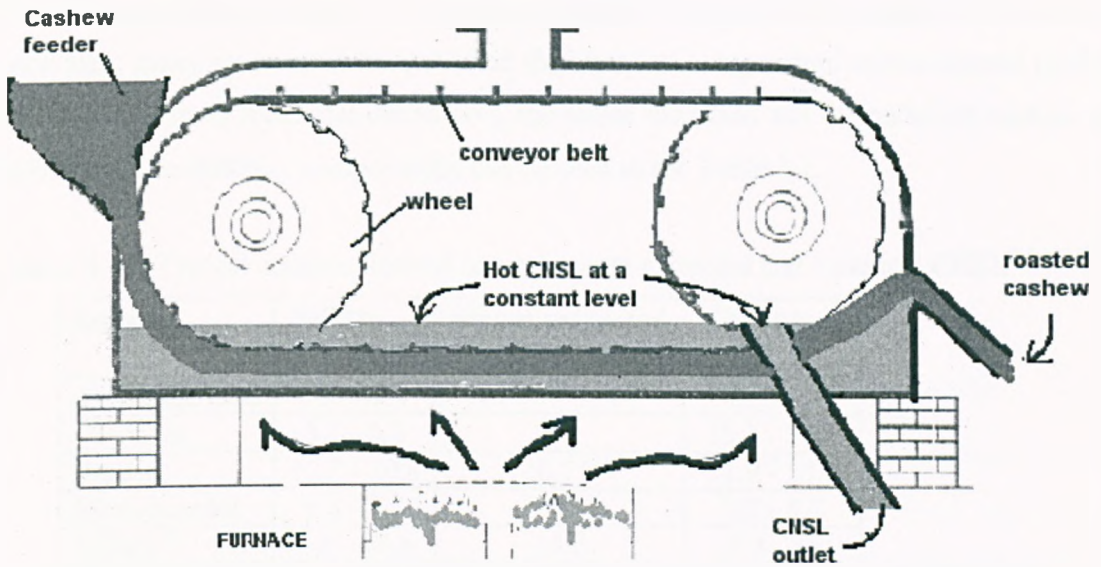


FIGURE 1 - 2: DIAGRAM OF HOT OIL CASHEW PROCESSING EQUIPMENT [5,6]

The excess moisture (around 8 %) of the outer part of the shell causes the cells to burst, with the result that most of the CNSL oozes into the bath (50 % recovery). The shell is then easily broken, allowing the roasted kernel to be recovered with the inner peel. They are then centrifuged or rolled in sawdust to remove residual CNSL, and then shelled, mechanically or manually. The shell with residual CNSL is sold as a solid combustible.

(ii) Sun dry/steam/expeller method

Another less used technique involves sun drying, softening of the whole nuts (by high pressure steam, 2 - 3 bar) and hammering/cutting the shell with a manual guillotine. The oil is then obtained with an expeller. As will be seen later, these two different methods lead to oils with somewhat different chemical compositions.[7]

1.2. Chemical characterization of CNSL

A lot of confusion existed between the chemistry of Natural (solvent extracted) and Technical (hot extracted) CNSL. The first oil exists in the plant, and the second one, obtained in factories that use the hot-bath oil process, is thought to have a composition modified during the extraction process.

1.2.1 Natural and Technical CNSL

Staedeler[8] (1847) was the first to report that natural cashew nut shell liquid contained about 90 % of anacardic acid and 10 % cardol, although he incorrectly assigned the structures. Since then, many researchers have studied the chemical composition of this natural product and of its two main industrial derivatives, the steam extracted and the technical cashew nut shell liquid.The different compositions can be seen in the Table 1-1.

TABLE 1 - 1: Typical compositions of natural, steam extracted and technical CNSL[7, 9,10, 11,12]

Source	Natural CNSL (%)	Steam extracted CNSL (%)	Technical CNSL (%)
Anacardic acid	61 - 72.9	57.4	0.0 - 1.8
Cardanol	3.1 - 6.2	6.7	55.3 - 78.1
Cardol	17.2 - 20.8	20.7 [a)]	11.9 - 18.3
Methylcardol	3.8 - 7.2	-----	2.2 - 5.2
Others [b)]	8.8 - 18.8	15.2	9.9 - 25

a) refers to methylcardol and cardol, b) Most of these compounds are reported to be non-volatile, and are assumed to be polymeric. (%) refers to mass.

This difference was shown by Wasserman to be due to the decarboxylation of the anacardic acid during the heat treatment in the process for obtaining the cashew nuts.[20]

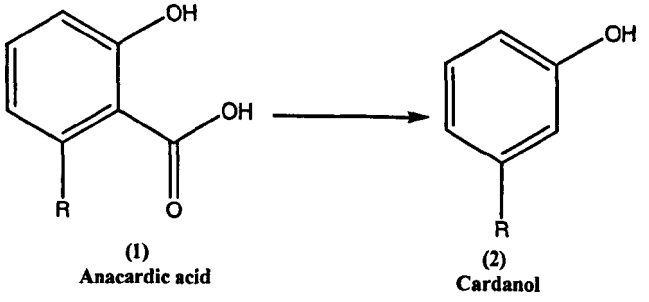


FIGURE 1 - 3: Decarboxylation of the anacardic acid

In the case of the steam extracted CNSL, analysis of the solvent extracted shell before and after the industrial process indicated that only 20 % of the original anacardic acid is decarboxylated. The compositions of Natural and Technical CNSL have been reported to vary with time and with the country of origin of the plant. [10, 11]

1.2.2 Anacardic acids, cardanols, cardols, and methylcardols

(i) Anacardic acid

Forty years after Staedeler, Ruheman and Shinner were able to determine the molecular formula of anacardic acid as being $C_{22}H_{32}O_3$. [13] Smit [14] recognized that it contains a salicylic acid system substituted with a carbon chain, and Pillay[38] suggested the presence of two double bonds in the alkyl side chain on the basis of bromination and catalytic hydrogenation techniques, and proposed structure (3) for the acid.

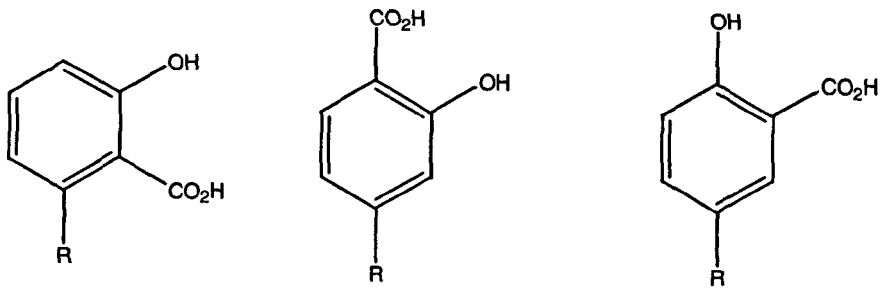


FIGURE 1 - 4: Structures for anacardic acid suggested by Pillay and Gokale

By synthesizing saturated analogs of (3) and (4), Gokale [15] was able to work out that the structure was (1), which was confirmed by Baker and Haack using quantitative hydrogenation and oxidative degradation.[43] Izzo and Dawson (1950) showed that what had been believed to be one compound was in fact a mixture of components having various degree of unsaturation in the alkyl side chain.[16]

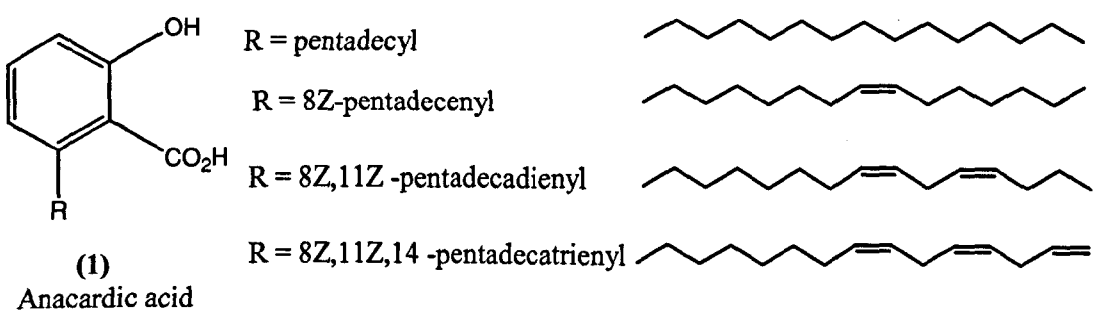


FIGURE 1 - 5: Main constituents of anacardic acid

Paul separated four different components of anacardic acid by fractional crystallization, and identified them via permanganate oxidation as : a) 1-hydroxy-2-carboxy-3-pentadecylbenzene, b) 1-hydroxy-2-carboxy-3-(8'-pentadecenyl)benzene, c) 1-hydroxy-2-carboxy-3-(8'-11'pentadecadienyl)benzene, d) 1-hydroxy-2-carboxy-3-(8' -11'-14'-pentadecatrienyl)benzene. [17,18]

(ii) Cardanols

As stated above, the cardanols, (see Table 1-1) although present only in small amounts in natural CNSL, are the major component of technical CNSL. Harvey[19] (1940) stated that the side chain of cardanols, obtained by "in vacuo" distillation of CNSL, contained 14 atoms of carbon, and only one double bond, but Wasserman (1945) showed that this was an experimental error, and that the chain in fact contains 15 carbons.[20,42]

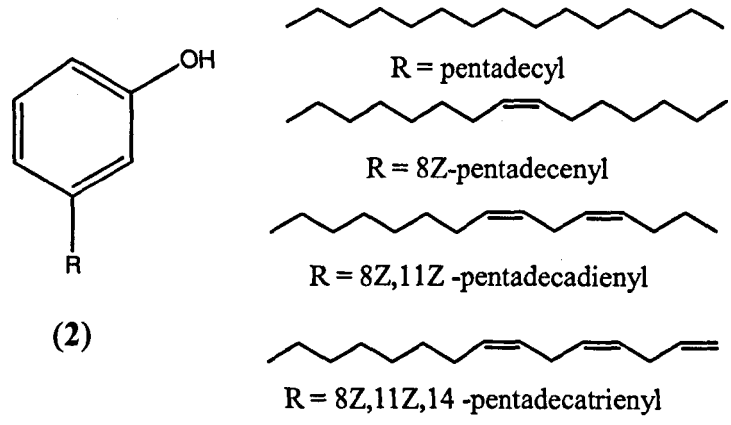


FIGURE 1 - 6: Cardanols main constituents

By oxidation of the alkene bonds of the methoxy derivatives of cardanols and isolation of the resulting glycols, Sleztzinger demonstrated that what was thought to be one compound, was a mixture of olefinic congeners, but stated that the double bond were *trans*.[21,22,23] Later Loev (1958) found the IR spectrum of the cardanols, to have a band characteristic of a *cis*-olefin, and no band for *trans*-alkene, and assigned a *cis* configuration (see Figure 1-7).[24]

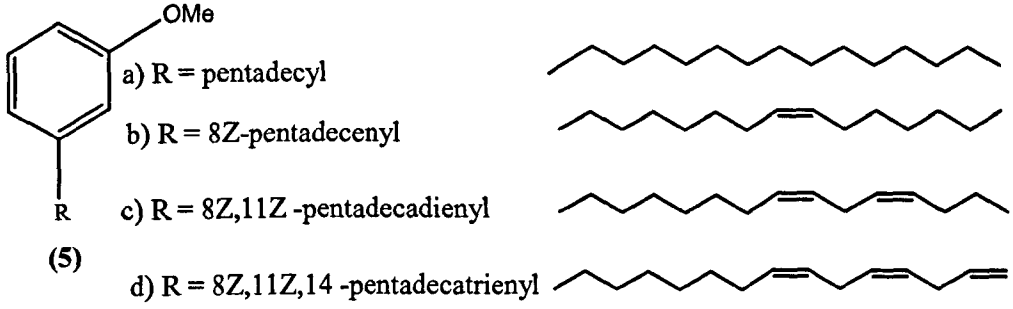


FIGURE 1 - 7: Methoxy cardanols

Symes and Dawson (1953) separated the four olefinic congeners of the methoxycardanols by column chromatography, and found via ozonolysis that these were (5a), (5b), (5c), (5d).[25,26,27] The positions of the double bonds in the chain were confirmed by Strocchi[28] (1975) who oxidized cardanol and used spectrometric methods to locate the OH groups of the resulting alcohols. By analyzing HPLC chromatograms Tyman, Tychopoulos, and Colenutt[35] stated that cardanols present in CNSL contain other minor constituents, with 13 and 17 atoms of carbon in the chain, but were not able to deduce the correct structures. After hydrogenation of the sample most of the small peaks disappeared, and were replaced by peaks with the

same retention time as cardanol (C15:0), cardanol (C17:0) and one estimated to be for cardanol (C13:0).

(iii) Cardols

Backer and Haack (1941) showed by oxidative degradation that cardols are resorcinol substituted at C_5 with a pentadecane chain. [43] It was believed at that time that the chain was a pentadecadiene, but later, Paul (1956) by fractional crystallization and oxidative degradation, showed that cardols were a mixture (see Figure 1-8) with the double bonds situated at carbons eight, eleven and fourteen. [18]

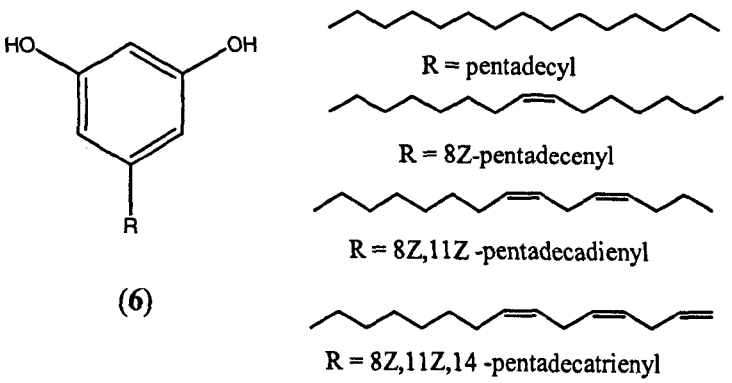


FIGURE 1 - 8: Cardols main constituents

(iv) Methylcardol

Murthy[29] (1973), Tyman and Morris[30] (1973) were the first to notice the existence of a tiny amount of methylcardols in technical CNSL. 2-Methylcardol is a mixture of four components differing in their side chain unsaturation, and, using NMR, Tyman established the structures shown in Figure 1-9.[30]

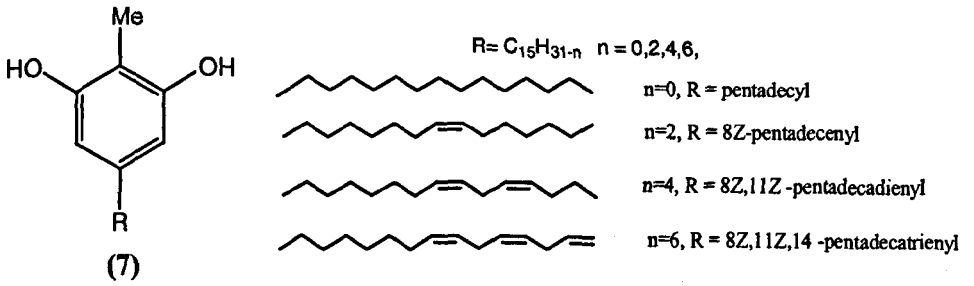


FIGURE 1 - 9: Methylcardols main constituents

(v) Distribution of the constituents of the CNSL

The composition of the alkyl chain in Technical CNSL is given in Table 1-2.

TABLE 1 - 2: Constituent's distribution as a function of chain unsaturation[31,35,10,11]

Distribution of the unsaturation	Cardanols (%)	Cardols (%)	Methylcardols (%)
Saturated	1.42-3.98	0.09-0.07	0.01-0.00
Monoene	16.69-31.83	1.00-1.06	0.01-0.00
Diene	11.85-17.15	5.44-2.57	0.41-0.20
Triene	28.45-45.50	17.73-6.59	1.2-0.6

1.2.3 Unknown compounds and unsolved problems

(i)Non- phenolic fractions

Harvey and Caplan [19] (1940) reported a nitrogenous fraction that accounted for 5 % of technical CNSL, with nicotine like odour, and Gellerman[32] (1968) found linear fatty acids in a ratio 1:4 to anacardic acids in natural CNSL. Both finding were not confirmed in later studies, and the experimental procedures are difficult to understand.

(ii)The non-volatile fraction

Using a GC technique and internal standards, Tyman and co-workers,[33] found a non-volatile fraction, not only in hydrogenated and methylated Technical CNSL, but also in the natural material. They assumed that this corresponded to a polymer. They also determined the GLC-MS of the trimethylsilyl derivatives of the fractions obtained by molecular distillation of the oil, and found peaks attributable to dimeric and trimeric substances. [34] TLC analysis of the distilled oil, the hydrogenated and the methylated derivatives showed spots with small Rf values that could be related with dimers and trimers of the main constituents. Some years later using HPLC, a fraction was obtained from CNSL, that was assumed to correspond to the polymer, despite the fact that when characterized by TLC, the material gave spots with the same retention times as those for cardanols, cardols and methylcardols. [35] Subsequently the same research group studying samples of cardanols and cardols obtained by column chromatography, found, using a preparative HPLC technique, not only the four constituents of each phenol previously cited, but also a polymeric fraction.[36] Although dimeric and polymeric material may be expected in technical CNSL, because of the relatively high temperature of the oil bath process, Tyman explained the non-volatile fraction (which exists also in its natural precursor), by a photochemical or biogenetic route. He believed that these kinds of reaction are most likely to occur with *trans* compounds so he suggested that the trienoid constituents undergo isomerisation to the *trans* isomers.

Measuring the relative concentration of the constituents from an Indian CNSL before and after processing, Shobba and co-workers reported that the relative proportion of the diene/triene is almost constant (which may suggest that polymerisation is not an important

process). Furthermore, they found an increase in the cardol concentration, suggesting the presence of a thermolabile compound (they proposed 4-hydroxyanacardic acid), which could yield cardols during the industrial processing of the nut. They reported 10 % of unidentified material. [11]

(iii) The challenge for improving the knowledge about CNSL

It has never been fully explained whether the non-volatile material is a polymer or not and if it is in some way related with hypothetical nitrogenous components, fatty acids, or 4-hydroxyanacardic acid constituents. Clearly, as it represents an important fraction of the oil (in some cases 20 %), its proper isolation and chemical characterisation could present an important step to an improved knowledge about the oil.

1.3. Chemical reactions investigated

Chemical reactions, involving either cardanol or cardol, and anacardic acids reported in the technical literature are indicated in the Table 1-3. As can be seen, quite a few reactions have been reported with components from CNSL, mainly with pentadecylphenol (hydrogenated cardanol). At present, no reactions have been reported in the Beilstein CrossFire database using, for example the different components of cardol.[i] Many others reactions have however been done, mainly to obtain monomers for different kind of resins (see 1-4-2 for details) with mixes of components often leading to unspecified products.

[i] However cleavage of cardol by ozonolysis of the double bond from the carbon chain have been reported, more details in the Chapter 4.

TABLE 1 - 3: Chemical reactions involving CNSL constituents. **SOURCES: BEILSTEIN, CHEMICAL ABSTRACTS**

CNSL constituent	Kind of reaction	Main products	Sources
Cardanol	Hydrogenation	1) Pentadecyl-cyclohexanol 2) Pentadecylphenol	Sethi, 1964 [37]
Cardanol	Oxidation	Oxalic and palmitic acid	Pillay, 1935 [38]
Pentadecylphenol	Chlorination	trichloropentadecylphenol	Ramalingam, 1987 [39]
Cardanol	Epoxidation	Epoxycardanol	Swalkwyk, 1976 [40]
Cardanol	Ozonolysis	8-(3,5-Dihydroxy-phenyl)-octanal	Swalkwyk, 1976 [40]
Cardanol	Protection/ by esterification	3-pentadecyl-phenylester acetic acid	Pillay, 1935 38
Cardanol	Protection/by etherification	Benzyl-3-pentadecyl-phenyl ether	Loev, 1958
Cardanol	Protection/by etherification	Benzoic acid ester	Pillay, 1935 [41]
Cardanol	Protection/ with methoxy	Pentadecylanisole	Wasserman, 1945 [42] Backer, 1941[43]
Pentadecylphenol	Nitration	4-Nitro-5-pentadecylphenol, 2-Nitro- 5 pentadecylphenol 2,4- Dinitrophenol	Latham, 1951[44]; Wasserman, 1950 [45]
Cardanol	Coupling with butoxycarbonyl-oxazolidine-carbalhdehyde	$C_{32}H_{55}NO_5$	Ramalingam, 1987 [39]
Pentadecylphenol	Coupling with formaldehyde /dimethylamine	$C_{21}H_{43}NO$, $C_{27}H_{50}NO$	Tychopoulos, 1986 [46]
Pentadecylphenol	Coupling with propan-2-one	3-pentadecylphenoxy-isobutyric acid	Ramalingam, 1989 [47]
Pentadecylphenol	Coupling with thiophospho ester	$C_{25}H_{45}O_3PS$	Atanasi, 1988 [48]
Pentadecylphenol	Bromination	$C_{25}H_{45}OBr$	Atanasi, 1995[49]
Pentadecylphenol	Alkylation	2 Tertbutyl 5pentadecylphenol	Atanasi, 1991[50]
Pentadecylphenol	Coupling	Pentadecylbenzofuran	Barker,1989 [51]
Cardanol	Nitration followed by coupling with glucose	Nitro-pentadecyl-phenyl-tetra-O-acetyl-b-D-glucopyranoside	Latham, 1951[44]
Cardanol	Amination (?)	Sulfobenzenediazonium	Su, 1999 [52]
Cardanol	Protection-oxidation-halogenation/nitration	Methoxy-aryloctanoicacids (a)Bromo, b) Chloro, c)Nitro)	Bolton, 1994 [53]
Cardanol	Oxidation	5-Pentadecyl quinone	Saladino, 2000 [54]
Anacardic acids, mixture	Hydrogenation	Anacardic acid (15,0)# 2-Hydroxy-6-penntadecyl-benzoic acid	Sethi [37]
Anacardic acids, mixture	Esterification	2-Hydroxy-6-penntadecyl-benzoic acid methyl ester	Pillay[38]
Anacardic acids, mixture	Acetylation	2-Acetoxy-6-penntadecyl-benzoic acid	Ramalingam[39]
Anacardic acid (15:0)	Decarboxylation	3-Pentadecylphenol	Neuse[40]
Anacardic acid (15:0)	bromination	a)---3-Bromo-2-hydroxy-6-pentadecyl-benzoic acid b)---3,5-Bromo-2-hydroxy-6-pentadecyl-benzoic acid	Pillay[38]
Anacardic acid (15:1)	hydroxylation	2-Methoxy-2-(threo-8,9-dihydroxy-pentadecyl)-benzoic acid methyl ester	Loev[24]
Anacardic acid (15:0)	Reduction	2-Hydroxymethyl-pentadecylphenol	Pillay [38]

1.4.Commercial uses of CNSL

1.4.1.Technical specifications

Cashew nut shell liquid is currently traded using the Indian Standard specifications reported in Table 1-4.[55]

TABLE 1 - 4: CNSL technical specifications (Indian Standard 840-1986).

Characteristic	Requirement
Specific gravity, 30 C	0.950- 0.970
Viscosity, (Cp, *max*)	550
Moisture (% weight, *max*)	1.0
Matter insoluble in toluene	1.0
Loss on heating (% weight, *max*)	2.0
Ash (% weight, *max*)	2.0
Iodine value (Wij's method, *min*)	250
Polymerisation (time in minutes, *max*)	4

These specifications were developed to trade CNSL as a raw material for resin manufacture and obviously were not useful to characterise it for organic synthesis.

1.4.2.Main uses of Technical CNSL

Raw-material for polymer manufacture

As Technical CNSL is a mixture of natural phenols, one of the 'natural' industrial applications is in the field of phenolic or modified phenolic resins.[56]

(i) Brake liner component

This is the one of the main applications of the oil. Brake liners made with polymers from raw cashew nut shell liquid wear less quickly than ones made from other chemicals. It was shown in 1975, [57] that the consumption of CNSL in developed countries is proportional to the number of brake systems manufactured.

(ii) Coating resins/ varnishes

A number of coating resins have been obtained from modified cardanol, mainly alkyd, epoxy, polyurethane, and polyalkylamino resins.[56] They are characterized not only by good adhesion to metal, but also by the substantial increase in life of the substrate. An advantage of the epoxy resins is that they are solvent soluble and do not need any expensive hardener

as do the conventional ones. Polyaminophenol resins have been found to have good curing characteristics.

(iii) Adhesive/Sealant

CNSL-formaldehyde polymers have been also used to manufacture a variety of materials such as slate composites,[58] resins to seal porous brickwork, steel and carbon blocks,[59] and particleboard resins.[60, 61] Ozonolysis of CNSL and of cardanol have provided free formaldehyde wood resins.[62]

Raw-material for industrial chemicals

(i) Rubber additives

Phenolic sulphides derived from hydrogenated cardanol are used as antioxidants for natural rubber and channel black compounds.[63] Sulphur, epoxy and phosphorated derivatives of cardanol have been used as accelerators,[64] or plasticisers [65,66] in the rubber industry.

(ii) Azo-dyes

Azo dyestuffs were prepared by coupling a hydrogenated cardanol with an aromatic diazonium salt in the presence of an alcoholic solvent. [67]

(iii) Surfactants

Anionic surfactants from hydrogenated cardanol are used as levelling and dye dispersing agents.[69] They are suitable for high temperature processes.

(iv) Multipurpose lubricant additives

Base treated and phosphorated compounds are currently used as multipurpose additives in the manufacture of motor oils. [68]

(v) Pentadecylphenol[i]

Pentadecylphenol (cardanol (15:0)) obtained by hydrogenation of cardanols is used as carrier[69] for active ingredients in paste formulations (pesticides, cosmetics and drugs). Triethanolamine pentadecylphenol sulfonate surfactants are reported to give better consistency and give better drug release than sodium lauryl sulfate.[70]

[i] 3-n-Pentadecyl Phenol, Cardolite® NC-510, has proven performance in the photographic industry when used in, e.g. resins, coupling agents, silver diffusion elements, thermo-sensitive materials, dyes, and antistatic agents. NC-510 also provides special properties when used in pharmaceutical, agricultural/insecticide, surfactant, lubricant, pigment/dye, thermoset/thermoplastic resin modifier, fuel additive, and coupling agent product.

1.4.3 Main uses of Natural CNSL & constituents

(i) General

High purity grades of cardols and anacardic acids, are not available in the market, as no commercial application has been found for these products. However both these families of compounds present distinctive biological activities (both mediate DNA scission,[71,72,73] and a range of enzyme activities), and recently a number of end use patents have been filed. It is interesting to note that both anacardic acids and cardols interfere with the same type of enzymes; however in certain cases it has been established that the mechanism is different. They both inhibit prostaglandin synthase,[74] glycerol-3-phosphate dehydrogenase,[i,75] glucosidase and invertase,[ii,76] tyrosinase,[77] hyaluronidase, and interfere with lipoxygenase oxidation,[78] have bactericide and fungicide activity. Anacardic acids have shown bactericide activity against *Bacillus subtilis, Escheria coli, Streptococcus mutans* (bacteria responsible for tooth decay), *Propionibacterium acnes* (bacteria responsible for the acnes),[79] *Helicobacter pilori*,[80] *Mycobacterium smegmatitis*,[81] molluscicide, [10, 82] antiaflatoxigenic[83] and fungicide activity against *Colletotrichum capsici* [84], and spooricide activity against *Alternaria, Phytophtora*,[85iii] *and Aphanomyces cochlioides*. Against the latter, anacardic acid (15:2) shown an activity similar to fluazinam, a commercial fungicide.[86]Anacardic acids have been considered as the main cause of the resistance to aphids, spiders and small pest of pest resistant geraniums.[87]

Anacardic acids also exhibits an uncoupling effect on oxidative phosphorylation of rat liver mitocondria[iv,88,89] inhibit β-lactamase,[90] and the tissue factor (TF)[v] VIIa complex,[91] and mediate anxiolytic activity.[92]

Cardols, have been detected recently in plants as active ingredients with cytotoxic, [93,94,95] anti-tuberculosis [96] and cardiological[97] related properties. An important property of cardol is their ability to form liposomes,[vi] vesicular structures that show high capacity of solute entrapment and slow release. [98]

---

[i] The inhibition of this enzyme is related with prevention of the triglyceride accumulation in cells.

[ii] Both glucosidase and invertase are known to degrade dietary carbohydrate to monosaccharides which can be absorbed through the gastrointestinal tract. Inhibition of these enzymes should decrease or slow the absorbtion of starch or sucrose and so decrease the energy intake of the cell.

[iii] Some of these experiments were done at Bangor. In these experiments anacardic acids showed capacity to inhibit mycelial growth of *Alternaria*, *Phytophtora*, and *Rizoctonia* at a concentration of 100µl/ml. (Earnshaw, D. M., unpublished results, UWB, 2001).

[iv] The inhibition of mitochondrial electron transport has been reported as a key characteristic of a new class of fungicides. (87)

[v] TF is a membrane bound glycoprotein, which leads to the generation of thrombin and fibrin clots. Inhibition allows treatment of certain thrombotic and cardiovascular diseases. This report has been published by a Monsanto researcher (Richard.c.durley@montsanto.com) who concludes: *"it may be possible to design more effective inhibitors based on anacardic acids ."*

[vi] This property is used to improve drugs transport and delivery.

Due to the interest to its biological activities, and because the accessibility of cardols is poor, several synthesis of cardols and analogues have been published in the recent years.[99,100,101,102, 73] Unfortunatly high yields imply costly starting materials and catalysts (a Grignard coupling on dimethoxybenzaldehyde gave cardol with a reported yield of 20 %, while the use of dimethoxyphenol with triflic anhydride and borane catalysts gave a yield of 90 %).

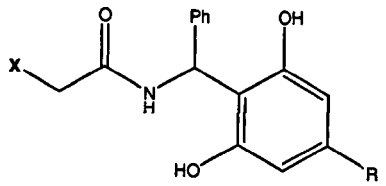
The biological properties described here are directly related with potential commercial applications described in the literature:

(ii)Anacardic acid

- as a potentiator of penicillin, [103]
- in the prevention or treatment of coccidiosis,[104]
- as an anti-obesity and fat reducing agent. [105]

(iii) Cardols

-intra-occular pressure lowering agents (patented by Abbott, see (8)),[106]



(8)

2-(amidobenzyl) 5-alkylresorcinols

(patented by Abbott Lab ltd)

FIGURE 1 - 10: INTRA-OCCULAR PRESSURE LOWERING AGENT

-as an anti-obesity and fat reducing agent,[107]

-cardol (15:0) is 100 times more active than diethylcarbamazine, a drug commonly used against worms.[108]

-cardols (with a 13 carbon chain), have been isolated as the active ingredient in a medicinal Chinese plant which demonstrated 80 % efficiency in tuberculosis treatment. The syrup of this plant is commercial in the USA.[109, 110]

1.5.Other non-isoprenoid phenols

The non-isoprenoid phenols are long chain phenols having an unbranched chain. In nature, three of such phenolic moieties are found: the alkenylphenols, the 5-alkenylresorcinols, and the alkenylcatechols (3-and 4-alkenylcatechol).

Cashew nut shell liquid is the most important source of non-isoprenoid phenols, due to the extensive cultivation.[1] To analyse whether the chemistry developed in this work could cover all non-isoprenoid phenols, the phenolic oil of the pericarp of *Semecarpus Anacardium* was chosen as an additional source, as it is reported to contain mainly long chain catechols.

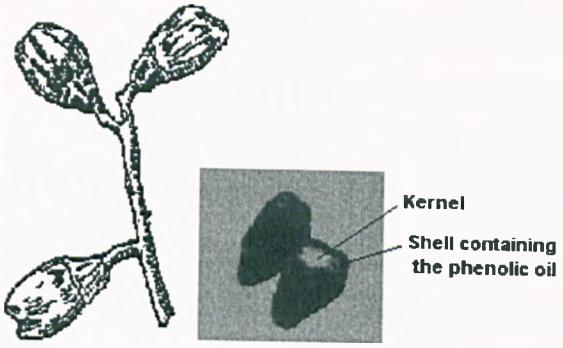


FIGURE 1 - 11: *SEMECARPUS ANACARDIUM* –FRUITY BRANCH, NUT, AND HALF NUT.

Like the cashew, the *Semecarpus Anacardium* kernel is enveloped in a shell containing a phenolic oil (28 – 36 % of the nut), known in India as Bhilawan Shell Liquid (BSL).

1.5.1.Bilhawanol

Reports on the composition of the oil seem to agree that it contains alkenylcatechols, but some of the finer details are contradictory. Pillay was the first to report that the main constituent was a catechol with a doubly unsaturated C_{15} chain. Mason[111] found the oil to be a mixture and that its major compound was 8-pentadecenyl-3-catechol, while Loev[112] on basis of hydroxylation studies, claimed that it contains a mixture of *cis* and *trans* 8-pentadecenyl-3-catechol.

Further investigation by Rao using GC-MS and NMR suggested that the oil contains at least 7 compounds, and that five are 3-substituted catechols with double bonds at carbon 6, 7, and 8, and 9 of the chain.[113] The molecular weights of the methylated compounds vary between 168 and 358. Two major compounds (ratio 60 : 30) were then identified as (**9**) (named Bhilawanol-A) and (**10**) (named Bhilawanol-B).

[1] This class of phenols exist not only in plants, (in the *Anacardiaceae*, the *Rhus* genus, and to a limited extend the *Proteacae*, the *Compositae*, the *Gymnospermae*, and the *Triticum*), but also in the animal kingdom (in the marine sponge *Haliclona*, and in strains of the *Azobacter* and *Pseudomonas*).

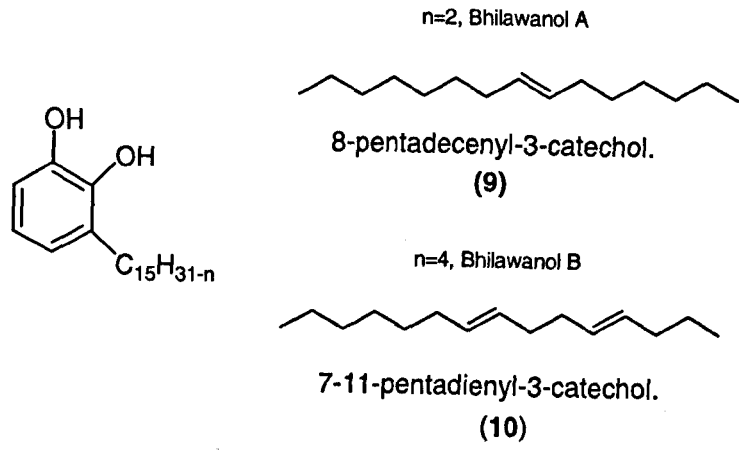


FIGURE 1 - 12: MAIN CONSTITUENTS OF BILAWANOL SHELL LIQUID

Later NMR analysis of the crude oil Gedam (1974) showed that it contains mainly the above compounds in a ratio of 1:3.[114]More recently Shin (1999) identified (9) and (10) by HPLC-electrospray/ MS-NMR.[115]

1.5.2. Minor compounds

Two incompletely identified phenols are claimed to exist as minor compounds in Semecarpus oil, dodecenyl and undecenyl phenol (semicarpol, around 0.1 %).[116,117] Chattopadhyaya & Khare[118] (1969) claimed that semecarpus oil contained anacardic acids that could be precursors of the previously indicated phenols.

1.5.3.Uses of the Bilhawan Shell Liquid

Bhilawan Shell Liquid was used, for centuries, to produce wood artistic coating. The kernels have an almond-like taste and are used in the formulation of Indian herbal medicine. They have been reported to have anticancer, anti-inflammatory, and anti-arthritic properties. An Indian company, Apurva Organics Ltd., claimed to be able to collect thousands of tons of the oil if a suitable market existed.[119]

1.6.Chemical research

1.6.1 Current research trends

Most research concerning technical CNSL is carried out in two of the major producing countries, India and Brazil and, in the USA, Europe and Japan. Information about commercial research released in the last nine years from US patent abstracts (from the US

Patent office web site), shows clearly that the main focus is in the field of brake liners, paint and rubbers additives.

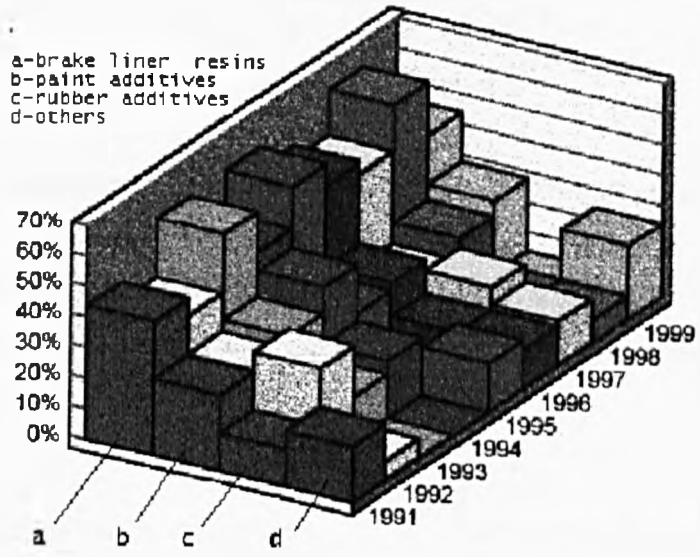


FIGURE 1 - 13: US PATENTS ABOUT CNSL END-USES

No recent research has been published on BSL.

1.7.Purpose of this research work

As demonstrated, the possibilities for research on the uses of this natural product are very broad. To demonstrate potential applications providing high value compounds, the purpose of this thesis is focussed in obtaining synthons for further organic synthesis.

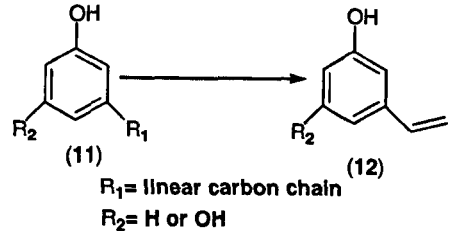
1.7.1 Novel methods to separate CNSL into its constituents

The lack of commercial availability of individual components of CNSL or even of cardanols, anacardic acids or cardols/methylcardols as families of congeners, led to, as a prime objective of this work, the development of separation methods that could hopefully be easily scaled-up to industrial quantities.

1.7.2. Short chain phenols from natural, commercially available non-isoprenoid phenols

Meta-substituted phenols are costly to obtain through synthesis, because alkylation in the meta- position of a phenol is not favoured; a cheap way to reduce the chain length of CNSL would be an interesting route to short chain meta-substituted phenols from a renewable source. The basic idea of the research was to investigate a method that cleaves the chain of

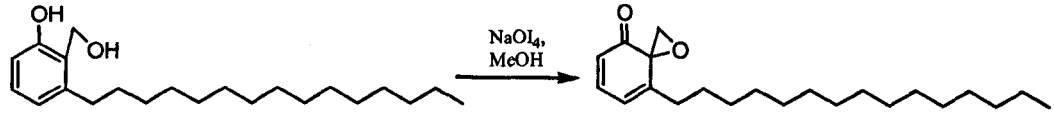
the non-isoprenoid phenols in order to obtain in high yield a short chain meta-substituted phenol that could be used in further synthesis, e.g.:



SCHEME 1 - 1: REDUCTION OF LATERAL CHAIN OF CARDANOL

1.7.3. Spirodienone reactions

Tyman,[120] reported that the salicylic alcohol (**13**), obtained by the reduction of anacardic acid (15:0) afforded the oxaspirodienone (**14**).



(**13**)
2-Hydroxymethyl-3-pentadecyl-phenol

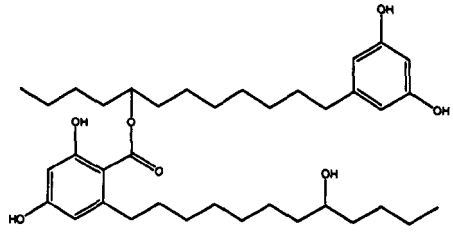
(**14**)
8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

SCHEME 1 - 2: OXIDATION OF SALICYLIC ALCOHOL

Because of the three functional groups in (**14**) , the latter could be involved in an array of potentially useful reactions. The exploration of unknown spirodienone chemistry, was defined as a purpose of this research.

1.7.4. HIV-integrase inhibitors

The recent discovery[121] of efficient integrase inhibitors (targets of novel anti-HIV therapies) having a substructure related to cardols (Figure 1-14) and the knowledge that pharmacophores associated with the inhibition of integrase activity are connected with depsides and depsidones,[122] led us to analyse routes to obtain this kind of compound from CNSL.



(**15**)

FIGURE 1 - 14: ANTI-INTEGRASE NATURAL DIHYDROXYRESORCINOL

CHAPTER 2- CNSL & BSL-SEPARATION TECHNIQUES

1. INTRODUCTION

In the current project, the purpose in studying the composition and methods of separations of the cashew nut shell liquid or bilhawan shell liquid was two-fold:

- to obtain the major constituents as a single family of components, and
- to obtain a quick and accurate method to assess quantitatively the content of the oils, clarifying some questions connected with the identity of the constituents.

Useful hints, in a search for new (or improving existing) procedures could be obtained from an analysis of previously used techniques.

1.1.Separation techniques on an analytical scale

Many separation and elucidation techniques (see **Table 2 -1**) have been employed to extract pure compounds from CNSL.

TABLE 2 - 1: Techniques to separate / analyse CNSL and constituents

Year	Constituent	Method	Authors
1946	Anacardic acid	Crystallization	Paul [17]
1953	Cardanols	TLC-Silver nitrate chromatography	Symes [27]
1956	Cardol	Crystallization/ oxidation	Paul [18]
1972	Cardanol/cardol	NMR	Gedam [123]
1973	2-Methylcardol	NMR, MS, IR, Argentation TLC, Synthesis	Tyman [30]
1978	Non-volatile	GC-MS, Distillation, derivatization, MS	Tyman [33]
1981	All	HPLC	Tyman [35]
1986	Cardanols	Silver nitrate column	Sood [124]
1986	Natural CNSL	Silica gel and ODS column	Kubbo [10]
1987	Cardanol,	Silver nitrate TLC, IR, MS, NMR	Strocchi [28]
1991	Natural CNSL	CO_2 extraction	Shobha [11]
1998	Technical CNSL	Silica gel and silver nitrate silica gel column	Roth [125]

Most of the recent analytical and laboratory scale work is based on column chromatography, using gradient elution, separating congeners with different chain saturation by argentation chromatography, or on octadecylsilane columns. The recoveries of pure compounds reported are moderate (around 70 %) because these methods cannot provide enough resolution, or need a high ratio of adsorbent to compound. [10,124]

Chromatography is also used on a large scale (hundreds of tons/year) to separate

terpenoids, steroids, alkaloids, metal chelates and close boiling isomers, but as it is an expensive technique, only separations that provide high value products, and are difficult to achieve by others means, are economical by chromatography.[126]

1.2.Separation techniques on a preparative scale

1.2.1 Technical CNSL

For many years, the main use for technical CNSL was as a commercial source of friction dusts for brake-clutch linings. Since all the phenolic components contribute to the final product, no emphasis was placed on separating it into its main components. The main purification was a chemical treatment to remove part of the polymeric and other materials (mainly coloured) present in the oil. Different applications (paints, resins and others) were developed for the main component of the oil, cardanol (with some cardol). This led to the development of distillation techniques to separate CNSL into its main components. In commerce the distilled fraction is called "cardanol" (confusingly as it contains both cardanols and cardols). Trade specifications for different grades of "cardanol" are provided in the Table 2-2.

TABLE 2 - 2: TRADE SPECIFICATIONS OF CARDANOLS

"Cardanols"	**"Distilled"**	**"Double distilled"**
Specific gravity	0.94 - 0.96	0.92 - 0.93
Viscosity (cp)	50.0 - 75.0	42 - 52
Iodine number	220 min	220 max
Ash (%)	Negligible	Negligible
Volatile loss	1 % max	1 % max
Colour	Brown reddish	Yellow straw

Source: Cardolite Corp., Primatherm

However, these cardanols are not good enough to be considered pure compounds for organic synthesis, therefore others methods must be developed.

i). Acid-treatment method

A partial removal of the polymeric and nitrogenous material from technical CNSL was achieved by flocculation with dilute sulphuric acid followed by centrifugation to separate the precipitate.[127]

ii). Distillation

As the above technique was not good enough for specific applications (specialized resins, dyes etc...), the distillation technique was introduced. Because of their high boiling points and their tendency to co-distil, high temperatures and a high reflux ratio are needed to separate of cardanol and cardol. This led to significant polymerisation and consequently to a low yield as shown in Table 2-3.

TABLE 2 - 3: Typical yields in a cardanol distillation pilot plant [128]

Distillation Vacuum pressure 3 - 34 min, 260 - 310 °C	**Cardanol recovery (%)**
8 mm Hg	45 - 68
3 mm Hg	66 - 71

It must be added that the distillate did not correspond to spectroscopically defined cardanols, but to a mixture that distils between 225 and 275 °C at 10 - 15 mm Hg. Different approaches have been attempted to improve the yield of the distillation (e.g the use of steam distillation, inert gas with agitation, or an antioxidant[129] and the use of specialized equipment (a 10 stage rotary still) separated cardanols (99 % purity) in 58 % yield.[130] One of the approaches was to change the properties during the distillation step by modifying the CNSL by treatment with an amine,[131] and the resultant amine with formaldehyde in methanol.[132] In this case, the cardol forms a Mannich salt that can be separated from cardanol prior to the distillation. However, none of these methods led to a significant improvement in the yield and/or the possibility of obtaining pure compounds. Part of the cardol remains with the polymeric fraction of the oil as a residue with little commercial value. While the distillate contains both cardanols and cardols, the non-volatile fraction (so-called polymer) of the oil is removed by this process, so it is possible to argue that the main purpose of this distillation is to get rid of it.

iii). Liquid-Liquid extraction with immiscible non-aqueous solvents

Liquid-liquid extractions of phenols from industrial effluents are currently performed on a large scale. In the case of CNSL,[133] this technique uses the selective partitioning of the main constituents of technical and/or natural CNSL between a non-aqueous, non-polar solvent like petrol and an insoluble non-aqueous polar solvent (like ethylene glycol, propanediol, etc.). A fraction of the cardanols remains in the non-polar solvent while the remainder, with all the cardols, migrates to the polar solvent. In the case of natural CNSL,[134,135] anacardic acid remains in the non-polar layer and cardol migrates to the polar one. One disadvantage of this method is that it does not allow the separation of the polymeric fraction from

cardanols. It is known that these two constituents (polymer and cardanols) have different properties in various applications.[136]

iv) Supercritical extraction with carbon dioxide and propanol

Cardanols and cardols have been extracted from CNSL by supercritical extraction with carbon dioxide using propanol as co-solvent, cardanol being concentrated in the critical phase, and cardol in the residue. Due to the high pressure involved this process is not cheap, and could just be justified on the grounds of the high potential value of cardols.[137]

v) Fractional crystallization

Separation of sun dry/steam extracted cashew nut shell liquid (see page 3) was reported to be done by fractional crystallization in pentane. The crystals collected at –65 °C gave anacardic acids (purity 99.7 %), while the fraction that crystallized at –180 ° C gave cardols (purity 90.5 %). Data on recovery were unclear.[138,139]

1.2.2.Natural CNSL

i) Isolation of cardols from natural CNSL by acid base treatment and crystallization

The separation of cardols from natural CNSL has been achieved by removal of the anacardic acid with a methanolic solution of lead hydroxide,[43] of calcium hydroxide,[140] and recently using resins followed by fractional crystallisation. In the latter case, after removing the anacardic acid with a resin, cardols were re-crystallised by cooling to a temperature between – 25 °C and – 195 °C. [141] An unverified report also indicates that cardols could be removed from natural CNSL by simply leaching the oil with a solution of sodium hydroxide.[142]

ii) Anacardic acids by Petrol-Diol solvent partition

Japanese Patent 8217720[143] uses liquid-liquid extraction with a petrol-diol solvent system to separate anacardic acid from natural CNSL. Reported anacardic acid recovery varies between 8 - 14 %.

1.3.Hints for screening new procedures

1.3.1.Technical CNSL

With the exception of chromatography (which is expensive) none of the methods reported afford CNSL constituents in high yields. There are, however, a number of observations that could lead to the design of new methodologies.

i) Acid-base extraction

Tychopoulos[132] reports that when technical CNSL was mixed with a base (an amine or an hydroxide of a Group IA or IIA metal) in a 1:1 molar ratio, over 24 h, and then distilled, most of the cardols could be removed. Residues of these distillations contain cardanols and cardols, typically a mass ratio of 55 : 45 when the bases are amines and 71 : 29 when the base is sodium hydroxide. This suggests the possibility of a selective reaction between the base and cardols, and that a selection of an appropriate solvent could eventually increase the selectivity of the process.

ii) Complexes with solids

An important solid system to separate mixtures of alcohols is the Sharpless method, using preferential complexation of a metal dihalide with one of the alcohol groups of the mixture.[144] Isolation of the complex formed and regeneration of the alcohol has been used to separate geraniol-citronellol, and mixtures of p-cresol and o-cresol. Urea complexes have been used to separate m-cresol from others cresols. [145]

iii) Liquid-liquid extraction

Bruce reported,[133] that when technical CNSL was distributed between two non-miscible solvents, petroleum and a diol, some cardanol migrated to the non-polar layer, while the remainder and all cardol remained in the polar phase. A possible explanation is that the two OH groups of the diols, interact preferentially (by hydrogen bonding and dipole interactions) with the two OH groups of cardols.

Because only a small amount of cardanols was recovered in this process, Bruce didn't use his own technique in his subsequent work to separate cardanols from CNSL. A search for solvents with better selectivity is necessary. Solvents which could provide possible bi-centred interactions with cardols, with at least two polar groups that could provide similar interaction to, but could have better selectivity than, glycols, can hopefully be found.

Solvent-solute interactions are correlated with a number of chemical and physical parameters of solvents, so relationships between physical characteristics and selectivity may hopefully be obtained, and additional selective solvents found. One of the most popular relationships to describe solvent behaviour is the Kamlet-Taft relationship:

Property = function (Hildebrand parameter, dipolarity/polarizability (Π) , hydrogen bonding acidity (α), hydrogen bonding basicity (β)).[146147]

Property is reported to be either the distribution of the solute between solvent phases, or the free Gibbs energy, retention index in a chromatographic separation, or even biological functions.

The Hildebrand parameter is the cohesive energy density, a term which depends on the forces holding the solvent together, and defined as the enthalpy of vaporisation of the solvent per unit volume. The dipolarity/polarizability (Π) parameter measures the ability of the solvent to stabilize a charge or a dipole, and is related with dielectric constant and the refractive index. Hydrogen bond acidity (α) describes the ability of the solvent to donate a proton to solute. Hydrogen bonding basicity (β) provides a measure of the solvent's ability to accept a proton. These last two terms were historically derived from spectral shifts (for example basicity has been calculated with ^{19}F NMR shifts of 5-fluoroindole complexes with bases, or from the frequency of the electronic transition of dissolved 4-nitrophenol and 4-nitroanisole) but have been also derived by others methods; for example, the acidity of the solvent has been related with LUMO-HOMO energies, or with the electrostatic potential at the donor hydrogen nuclear position. [148,149,150]

Quantitative prediction, using Kamlet-Taft methodology, would involve deducing the mathematical relation (**1**) developed by Abraham and collaborators, between the properties of the solvents and the coefficient of distribution. This would imply measuring this coefficient with a statistically significant number of solvents, needed to perform a regression, in the form of :

$$\text{Log K} = a + b(\Pi + c\,\delta) + d\,\alpha + e\,\beta + f\,\delta_h + g\,\zeta \ldots\ldots \text{(Equation 1)}$$

Where: a) K represents the equilibrium constant,

b) δ is a "polarizability correction term" equal to 0.0 for unchlorinated aliphatic, 0.5 for polychlorinated aliphatic and 1 for aromatic solvents.

c) ζ is a coordinate covalency measure, -0.2 for P=O bases, 0.0 for C=O, S=O, N=O bases, 0.2 for single bonded bases, 0.6 for pyridine bases, and 1.00 for sp^3 –hybridized amine bases.

d) (Π) polarizability, (α) hydrogen bond acidity, and (β) hydrogen bonding basicity.

e) a , b, c, d, e, f, g, .. coefficients that are determined by regression against known log K values.

Solvent-water partition coefficients were successfully[i] modelled using Equation (**1**).[151, 152]

There are others possibilities for studying the solvent-solute relationship, notably quantum mechanics/statistical thermodynamics and Factor Analysis (FA). The use of the former has been fairly limited, mainly because, due to calculation time restrictions, the size of the molecules to be considered must be small. Both Chastrette and Svoboda independently applied FA to solvent properties and obtained four parameters to classify most of them.[153] Svoboda chose factors to which were associated physical significance: AP, electrophilic

[i] however a separate equation needed to be written for each solvent considered.

solvation, NP, nucleophilic solvation, EP, polar dispersion and PP, dispersion solvation. Use of these relationships is therefore somewhat equivalent to the use of the Taft-Kamlet relationship.

To solve problems of solvent choice in liquid extraction problems, Hampe suggested the use of the "Kortum und Buchholz-Meisenheimer classification", as miscibility gaps are likely to occur between certain classes. The classification is based in the entropy of vaporisation at the normal point and the existence of donor and acceptor sites.[154] This method suggests that systems equivalent to petrol-glycol would be petrol-any polyalcohol, petrol-diamines, petrol-polyphenols, petrol-amines, petrol-nitroalkanes and petrol-nitriles and the same pair of solvents using instead of petrol, paraffinic, naphthalenic and some aromatic hydrocarbons, carbon disulphide, or carbon tetrachloride.

Another popular technique for analysing liquid-extraction calculates the activity coefficient of the compounds to be separated in each phase. These are obtained on the basis of complex algebraic systems known as UNIFAC or NRTL[i].[155, 126, 156] This more complex approach is not used in this work for a number of reasons:

- The methods are an approximation, and do not take into account how and where the groups are joined to each other, so the results need to be cross-checked practically.
-There is a lack of parameters for groups that could be important in the present case (for example fluorinated groups).
- Because the purpose is to develop a method which could be used on an industrial scale, unusual solvents with configurations which could result from computerized molecular studies have no interest, as they would not be commercially available, of known toxicity, or cheap .

1.3.2.Natural CNSL

Because of the different functionalities, the separation of anacardic acid from cardols in natural CNSL is easier than the separation of cardanols from cardols.

i) Alkaline treatment

Despite the fact that the methods from the patent literature are quite clear, the fact that they don't claim to obtain pure cardols, and the lack of spectral information to characterize the products obtained, imply a need for this to be checked.[140]

ii) Liquid-Liquid Extraction

[i] based on a contribution group approach

The fact that in the reported petrol-diol partition of natural CNSL,[143] anacardic acid was recovered in the non-polar layer suggests a similar situation to that in the separation of cardanols-cardol, and therefore the same solvent system used in the liquid-liquid extraction of technical CNSL may be used in the separation of natural CNSL.

1.4.Conclusions

Methods for obtaining pure cardanols/cardols or anacardic acid/cardols are the first step to determine if CNSL could provide a source of important intermediates for applications in the fine chemicals industry. A number of indications have been provided for developing such methods based on past attempts to separate CNSL and from the general literature.

2. METHODOLOGY

The primary purpose of this part of the project was to determine whether CNSL could be separated.

1) Since as has been described above, both technical and natural CNSL contain a complex mixture of phenols with a variety of alkyl chain substituents, the prime target was to establish whether this mixture could be separated into individual components. Different approaches (alkaline extraction, solid complexes, adsorption, liquid-liquid extraction) were to be tested.

2) In order to determine whether each component had been separated, it was necessary to analyse the fractions by TLC, NMR, and HPLC.

3) An efficient method of separation would provide standards for quantitative determination of the composition of different samples of CNSL.

As a corollary it was hoped to:

a) Clarify the structure of the non-volatile fraction, possibly to allow the design of depolymerisation reactions and recovery of the corresponding phenols.

b) Check the claims of the presence of nitrogenous compounds, because many solid catalysts used in cracking reactions are poisoned by such compounds.

4) An additional purpose was to analyse whether the chemistry developed with CNSL could cover another non-isoprenoid phenolic oil, that of the pericarp of *Semecarpus Anacardium*.

3. RESULTS AND DISCUSSION

3.1.Origin and characterisation of the CNSL samples

3.1.1 Origin

This study used a number of different samples of CNSL.

(i) Technical CNSL

a) from Brazil, labelled as CNSL Bras (from BioComposites Centre, UWB),
b) from Mozambic, Machava Factory, labelled as CNSL Moz,
c) from India, Ajay Metachem (this sample has been refluxed with sulphuric acid/hydrochloric acid by the manufacturer),
d) from India, Villa Maya Scientific Research Foundation,
e) one sample, from unidentified origin, supplied by Cardolite.

Most of the work in this thesis was done using CNSL Bras.

(ii) Natural CNSL

Natural CNSL was obtained by solvent extraction from shells of Indian and Tanzanian cashew nuts (see later).

3.1.2.General characterization of Technical CNSL

(i) Standard characterization

The IS standard (see 1.2.2, Chapter 1), was inadequate for research in organic synthesis, and so was not used.

(ii) TLC

TLC of crude CNSL was performed using as a general guideline the solvent systems used by others to separate the component phenols in CNSL – mainly petroleum-ether, petroleum-ethyl acetate.[131] The plates were visualised using UV, vanillin-hydrochloric acid, potassium permanganate, and molybdeno-phosphoric acid. The latter was the one used in the study. Petrol-ethyl acetate (5 : 2 vol/vol) gave the best resolution. A characteristic CNSL TLC plate, with this system, showed a prominent spot in the middle, one on the base line, a medium one near the base line and two small ones in between the medium and the big one. The difference between the R_f values showed that it should be possible to separate the components by column chromatography.

(iii) By NMR

Proton NMR spectra of all Technical CNSL samples were essentially identical to the one shown in the Figure 2-1:

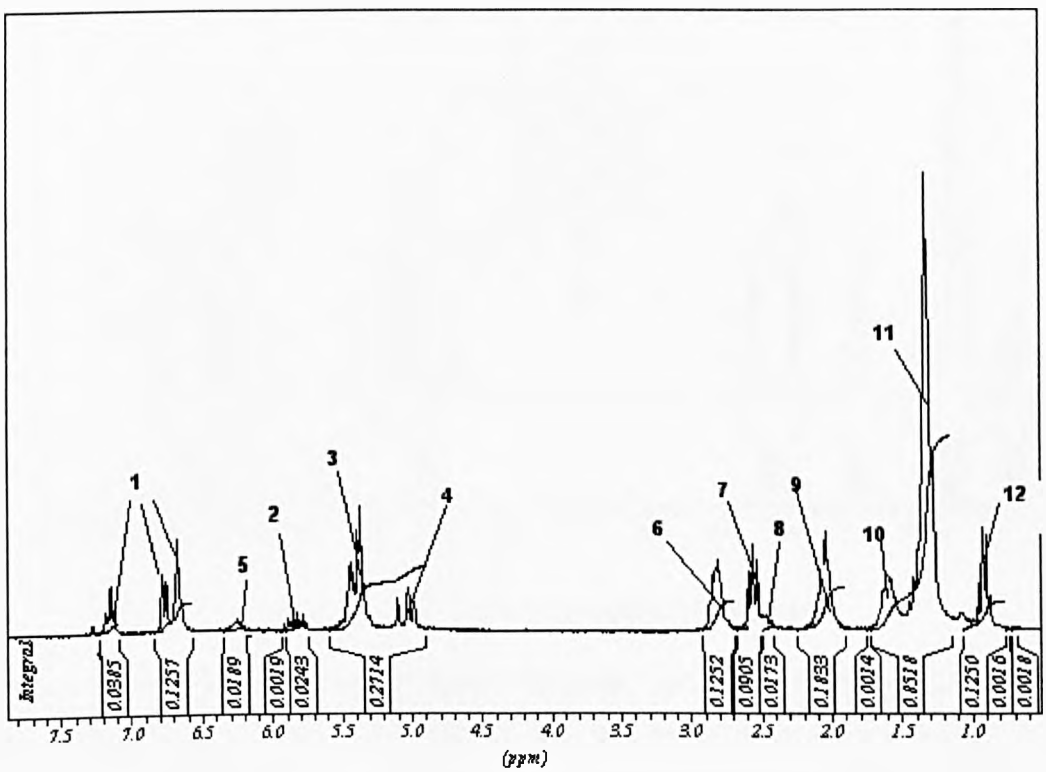


FIGURE 2 - 1: ^{1}H NMR spectrum of CNSL Braz

Signals labelled "1" correspond to the aromatic protons of cardanols, and the signal "5" to both cardols and methylcardols, which are minor compounds in the oil. The signals corresponding to the protons of the terminal vinyl groups are "2" and "4". Signal "3" represents the hydrogens of the internal alkenes. Signal "7" corresponds to the benzylic protons of cardanols, and the small shoulder labelled as "8" to the benzylic protons of cardols and methylcardols. The shifts corresponding to the saturated CH_2 groups of the chain for both families of alkenylphenols overlap; signal "6" corresponds to the protons α to two double bonds, "9" to those α to one double bond, "10" to those α to the benzylic protons, "11" to the remaining hydrogen in the carbon chain, and "12" to the terminal methyl groups. The integrals corresponding to the aromatics protons allowed a molar ratio between cardanols and cardols to be calculated. These assignments were supported by HNMR spectra of the separated compounds. As reported,[124] it was possible to separate the cardanols and cardols by chromatography on silicagel using petrol-ethyl acetate as eluting solvent. The NMR spectra of cardanol and cardol obtained by this method (see Figure 2-2 and 2-3) provide standards for the products obtained by various separation methods. The

main differences are in the aromatic region. Other characteristics of these two spectra have been discussed above.

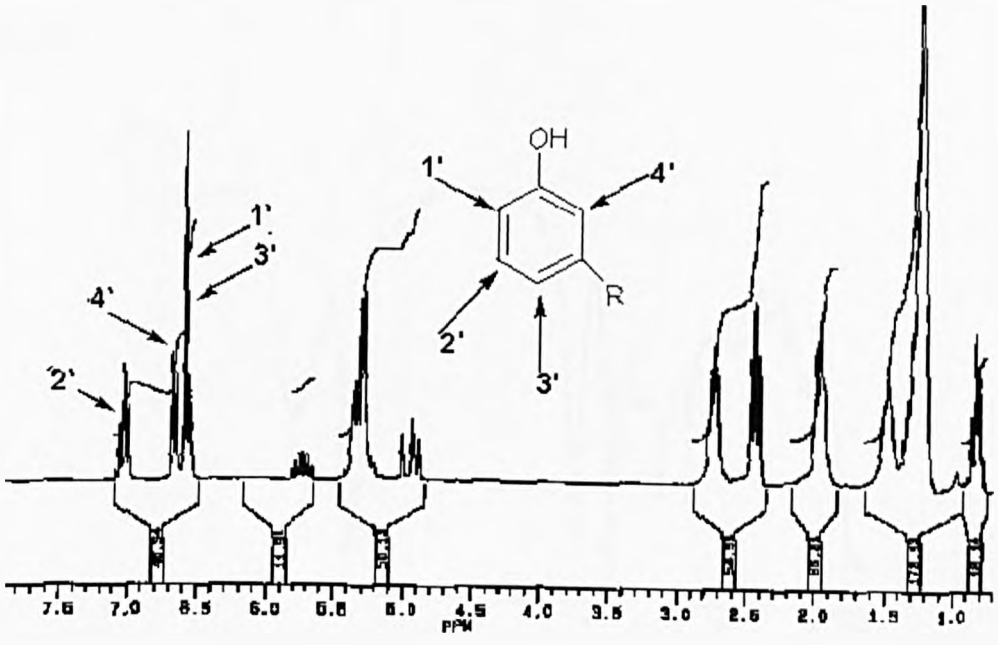


FIGURE 2 - 2: ^{1}H NMR spectrum of cardanols

The aromatic protons of the cardanol spectrum are labelled as 1', 2', 3'and 4', corresponding, as confirmed by the gNMR simulator, to the chemical shifts of 6.5, 7.1, 6.7 and 6.6 ppm respectively. Proton 2' appears as a triplet as it couples with the protons 3' and 1' with equal J values. Protons 1' and 3' correspond to two doublets, and proton 4' to a triplet due to the long range coupling with protons 1 and 3.

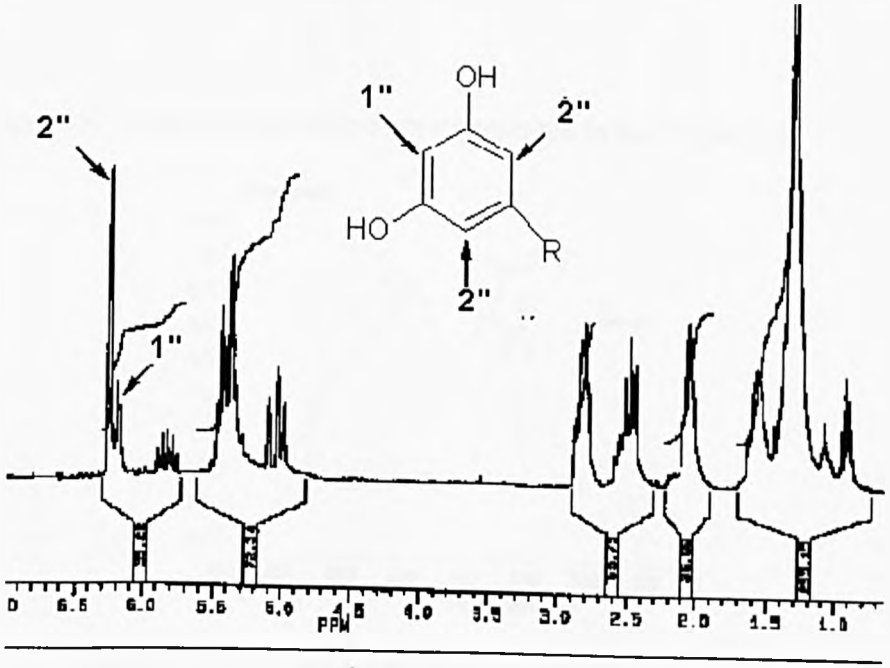


FIGURE 2 - 3: ^{1}H NMR spectrum of cardols

The signals of the aromatic protons of the cardols is shown in the Figure 2-3. The protons labelled as 1'' and 2'' correspond to the chemical shifts of 6.1 and 6.2 ppm respectively.

(iv) By IR

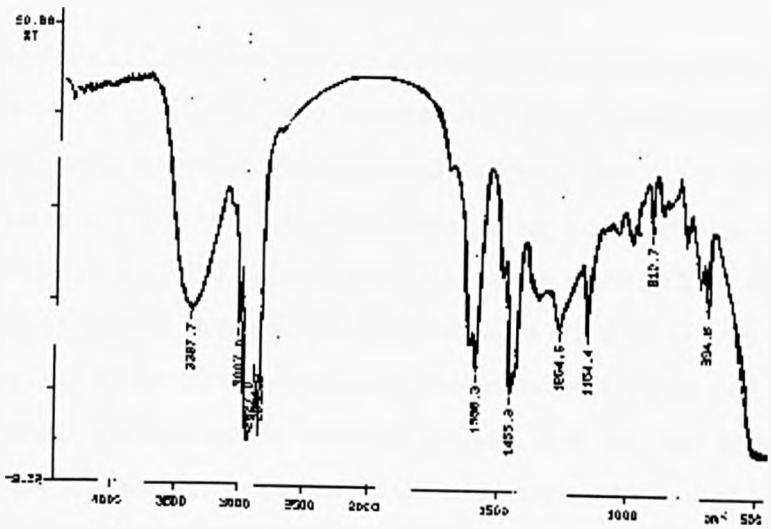


FIGURE 2 - 4: IR spectrum of CNSL BRAZ

The IR spectrum of CNSL from the Brazilian batch (see Figure 2-4) showed a large band in the O-H stretching region around 3400 cm^{-1}, and a peak at 3010 cm^{-1} for the olefinic or aromatic C-H stretch. The peaks at 2925 and 2856 cm^{-1} are the saturated C-H bonds stretches. The peak at 1600 cm^{-1} is the C=C of the aromatic ring. The stretch of the C-O bond was observed at 1262 cm^{-1}.

(v) By UV

The UV spectra of cardanols and cardols are represented in the Figure 2-5.

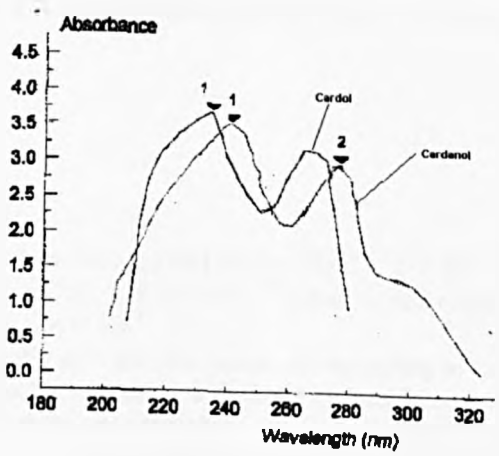


FIGURE 2 - 5: UV absorbtion of cardols and cardanols

For cardanols λ_{max} (MeOH) (ϵ) (nm) = 232 (ϵ=13450), 273 (ϵ=1120) for cardols λ_{max}(nm) (MeOH) (ϵ) 238 (ϵ= 12650), 273 (ϵ=223).[i] The flocculated solid gives one maximum absorbtion at 240 nm.

(vi) HPLC

Quantitative analysis of CNSL has been the subject of detailed investigation by Tyman et al. (1985) and Bruce et al. (1990), who describe high-performance liquid chromatography (HPLC) analysis using an octadecylsilyl-bonded stationary phase (5 μ of Magnusphere and Spherisorb packed in a 4.6mm x 250 mm column), using first a gradient acetonitrile-water-acetic acid (64:33:2) to (100:0:2), and then THF, as the mobile phase at 2.7 ml/min, and p-t-butylphenol as internal standard. The disadvantages are that: a) each analysis requires about one hour and b) the wide differences in the retention times as well as relative molar responses between the fast-eluting internal standard and the late eluting analytes are potential sources of error. In the present study two columns were used, a 4.6 x 250 mm, Waters Spherisorb, packed with 5 μ ODS2 and a 4.6 x 150 mm (Phenomenex Luna) column packed with 5 μ PhenylHexyl silica. The first column gave a marginally better resolution. Both were better than the ones used previously as resolution of the CNSL constituents could be obtained in less than 30 minutes. Samples were dissolved in THF and filtered through a nylon Aldrich cartridge. Different mobile phase were tested, using combinations of acetonitrile, THF, methanol, acetic acid and water. Reproducible good resolution was obtained with acetonitrile-water-acetic acid (78:20:2) gradient elution with THF. The relatively low polarity solvent system allowed a faster analysis (around 15 minutes), and the gradient elution of THF allowed the flocculated solid to be eluted, which appeared as a broad peak.[ii](A broad peak was suggested by Tyman[iii] to be a polymeric substance).[35] At 280 nm wavelength the relative molar response factor of cardanol (15:0) to cardol (15:0) was 1.09.[iv]

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[i] Literature values: For cardanols are: λ_{max}(nm) 201(ϵ=16582) , 273 (ϵ= 1356), and for cardols are λ_{max}(nm)207(ϵ=3306), 273 (ϵ= 209), 278 (ϵ= 169).[133] Relative molar response value, at 273 nm, for cardol (15:1) to cardanol (15:1) was 1.3.[8]

[ii] Injecting the flocculated solid gave the four peaks corresponding to each of the cardanols, and a broad peak. Removal of the cardanols by washing with dilute hydrochloric acid and re-flocculating the mixture in petrol-acetonitrile give another flocculate which gave only the broad peak

[iii] Tyman used chloroform as a solvent and found a broad peak suggested to be a polymeric substance (ref.9), Shobba using acetonitrile could not find this peak. (ref.7). In CNSL analysis (see later) a fraction insoluble in acetonitrile but soluble in both THF and chlorofom was found to give a broad peak., suggesting that the choice of the solvents could explain the different reported results.

[iv] The relative molar response factor (RMR) was calculated with the formula:
$(RMR)_A/(RMR)_B$ = (peak area in HPLC)$_A$/(mol)$_A$/(peak area in HPLC)$_B$/(mol)$_B$

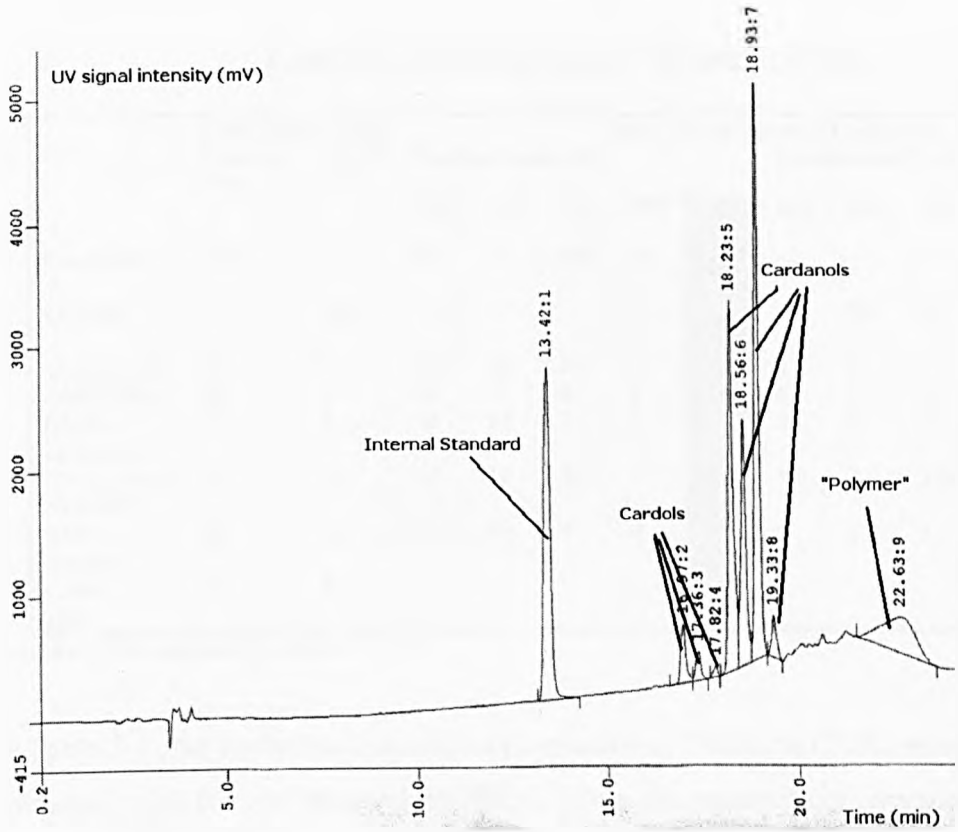


FIGURE 2 - 6: HPLC chromatogram of CNSL –BRAZ

4-Hexylresorcinol was preferred as the internal standard, for the following reasons: (a) Its retention time was in a similar range to the ones of the prominent peaks, (b) its detector response was expected to be comparable with that of the CNSL constituents because of a similar aromatic chromophore. 4-Nonylphenol was also tested as an internal standard, but was slightly overlapping with cardol diene and was therefore not used. This chromatogram was obtained with a Hexylphenyl Phenomenex 5μ column, with gradient elution with acetonitrile-water-acetic acid (60 - 40) to (100 - 0) and THF. The detector was set at 280 nm since the maximum absorption of CNSL was in the range 275 - 280 nm. Since each individual compound was not available for accurate determination of the response factors, the responses of the cardanol analogues were assumed to be equivalent to that of cardanol (15 : 0).This seems reasonable as they have the same aromatic chromophore and comparable molecular weights. The same procedure was applied for cardol analogues. This allowed the composition of the technical CNSL to be determined as % cardanols, % cardols, and others. (See Table 2-4 for details).

TABLE 2 - 4: COMPOSITION OF TECHNICAL CNSL

	NMR information		HPLC Preliminary information									
	Cardanols (%)	Cardols (%)	Cardanols area (%)					Cardols area (%) a)				Oth. (%)
			15:3	15:2	15:1	15:0	Tot.	15:3	15:2	15:1	tot	
Cardanols	**100**		**25.**	**21**	**49.**	**5.**						
Cardols		**100**						**63**	**25**	**11**		
Cnsl Brasil	**92**	**8**	26.	16.	33	4	79	4	2	1	7	14
CNSL Moz	**91**	**9**	25	11	40	2	78	4	3	.6	8	14
CNSL cardolite	**91**	**9**	36	14	21	3	83	5	2	.6	8	9
CNSL from VMSRF	**83**	**17**	38	16	28	3	85	12	2	1.0	15	0
CNSL Marlin	**86**	**14**	26	19	45	4	94	4	1	1	6	0
CNSL ajay-	**91**	**9**										

a) cardol (15:0) overlap with cardanols (15:2)

In Table 2-4 , the cardol/methylcardol concentration in Technical CNSL, obtained by NMR, correlates with the one obtained by HPLC, while the cardanol concentration obtained by NMR, is slightly higher. However the fact that concentration of cardanols + "others" obtained by HPLC correlates with that deduced by NMR suggests that "others" detected by HPLC have aromatic protons similar to those in cardanols. Samples without "others" (from AJAY, VMSRF) were significantly less viscous than the others (CNSL MOZ, and CNSL BRA and in a smaller measure CNSL Cardolite).

3.1.3.General characterization of Natural CNSL

(i) Oil extraction

Cashew nuts from India were extracted using three different techniques: .

a) Dichloromethane, ethyl acetate, and methanol were passed down a column filled with the powdered shells.
b) The shells were solvent extracted using a soxlhet apparatus for 3 h, using petrol, acetone and methanol in separate experiments.
c) The shells were extracted by churning during 3 days, using, in separate experiments, the three above indicated solvents.

The results are presented in Table 2-5.

TABLE 2 – 5: SOLVENT EXTRACTION OF NATURAL CNSL

Extraction method	Solvent	Yield (mass of oil/mass of shells)	cardols/anacardic acid (mol/mol) by NMR
Percolation	Dichloromethane, ethyl acetate and methanol	0.27	0.22
Soxlhet	Petrol	0.23	0.21
Soxlhet	Acetone	0.26	0.22
Soxlhet	Methanol a)	0.20 b)	0.11
		0.08 c)	0.28
Churning	Petrol	0.16	0.21
Churning	Acetone	0.20	0.21
Churning	IMS	0.21	0.20

a) Methanol provided two fractions: one soluble in petrol and the other one insoluble, b) liquid fraction soluble in petrol, c) fraction insoluble in petrol

Oil yields obtained by percolation and soxlhet were similar[i] but the yield from churning in solvent was much smaller. Extraction by percolation used a high ratio of solvent to oil recovered and was not repeated. Because one of the methods used to separate Natural CNSL into its constituents used acetone or methanol (see page 59 - 60), extraction was also performed (by soxlhet) using acetone and methanol as this would allow a separation without elimination of the extracting solvent. NMR analysis and physical properties (density and colour) of the methanol extract[ii] showed the existence of other compounds beside anacardic acids and cardols, and this solvent was not further investigated; IMS was used in the next method investigated - extraction by churning shells. The small additional yield obtained with IMS did not justify its use as the extraction solvent as it was more difficult to eliminate. The yield and nature of the cashew nut shell oil obtained with petrol and acetone were similar. On the basis of oil yield and time of extraction, method b) using petrol or acetone was performed in subsequent extractions.

(ii) Spectral and chromatographic information

(a) NMR

Figure 2-7 shows the HNMR of Indian cashew nuts obtained by Petrol soxlhet extraction. Signals labelled "1", "2" and "3" correspond to the aromatic protons of the anacardic acids,

[i] These are in the same range of values as reported in the literature,[6,10] except one which reported a 48 % yield. [148]

[ii] This extract was not investigated any further.

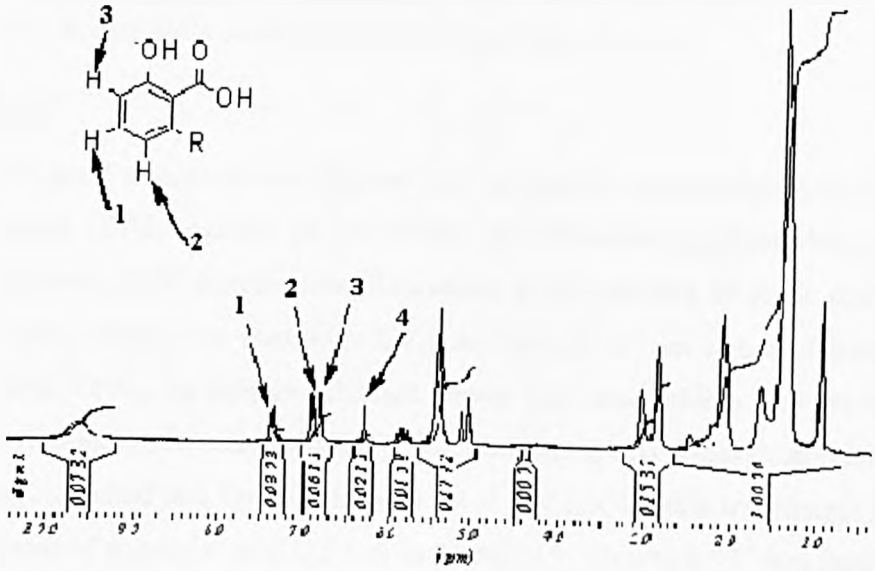


FIGURE 2 - 7: ^{1}H NMR crude Natural CNSL

(see HNMR of anacardic acid, in Figure 2-8) and "4" to both cardols and methylcardols. The remaining signals are also in the technical CNSL HNMR and correspond to the terminal vinyl groups, the internal alkenes, the benzylic protons, protons α to two double bonds, α to one double bond, α to the benzylic protons, to the remaining hydrogen in the carbon chain, and to the terminal methyl groups.

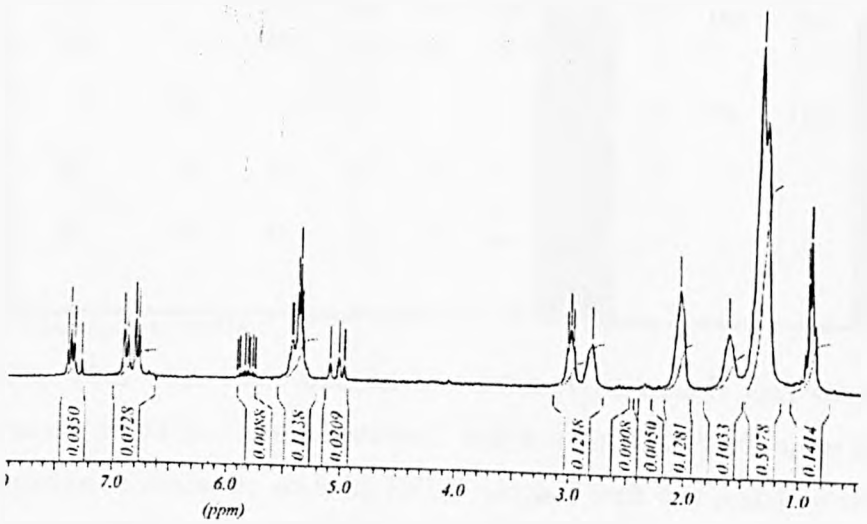


FIGURE 2 - 8 : ^{1}H NMR OF ANACARDIC ACID

The spectrum of pure anacardic acids (Figure 2-8) obtained later in this work, shows that the chemical shift corresponding to the aromatics protons is different from the ones of cardols

and cardanols. The corresponding integrals allowed the composition of CNSL to be calculated as a percentage of anacardic acids and cardols. No aromatic protons corresponding to cardanols could be observed in the natural CNSL.

(b) By HPLC

Reproducible good resolution was obtained with acetonitrile-water-acetic acid (78 : 20 : 2). Because natural CNSL samples do not contain any flocculate, gradient elution with THF was not necessary (THF dissolved the flocculate). In the absence of acetic acid, anacardic acids gave tailing peaks. The maximum UV absorbtion at 313 nm was not found suitable to analyse natural CNSL, as cardols exhibited almost zero absorbtion at this wavelength. To allow an easy comparison with technical CNSL chromatograms, 4-hexylresorcinol was used as an internal standard and the detector was set at 280 nm. At this wavelength the relative molar response of anacardic acid (15 : 0) to cardol (15 : 0) was 0.97.[1] Resolution between anacardic acids and cardanols was however poor, as in most previously published work, where the concentration of cardanols was calculated as a function of the area of the shoulders of anacardic acids peaks.[9,10] For natural CNSL samples analysed in this work, NMR spectra showed that there was no cardanol present and therefore no effort was made to improve the resolution. The composition of CNSLs is given in Table 2-4.

TABLE 2 - 4: COMPOSITION OF NATURAL CNSL

	NMR information		**HPLC Preliminary information**									
	Anacardic acids (%)	Cardols (%)	**Anacardic acids area (%)**					**Cardols area (%) a)**				**Others . (%)**
			15:3	15:2	15:1	15:0	Tot.	15:3	15:2	15:1	tot	
Anacardic Acid (a)	**100**		**25.**	**19**	**51**	**5.**						
Cardols		**100**						**63**	**25**	**11a)**		
Nat Indian CNSL	**81**	**19**	27	14	37	---	**77.4**	14	3	-	**17**	**6**
Nat Tanzanian CNSL	**85**	**15**	33	14	30	----	**77.1**	18	5	2	**24**	**0**

a) no cardanols were present by HNMR

Natural Indian CNSL has been reported to contain more cardols than others, but this assertion was not based on extensive studies,[9] and was not confirmed in our experiments. The concentration of anacardic acids by HPLC matched well that found by HNMR. Both HPLC and NMR can therefore be used as methods for determining the composition of both natural and technical CNSL.

[1] The relative molar response factor (RMR) was calculated with the formula:

$(RMR)_A / (RMR)_B = (\text{peak area in HPLC})_A/(\text{mol})_A/(\text{peak area in HPLC})_B/(\text{mol})_B$.

3.2.Technical CNSL - Screening separation procedures

Having characterized the crude oils, the next objective was to separate them into their basic constituents, i.e. cardols from the cardanols in CNSL, anacardic acids from cardols in natural CNSL. Because Technical CNSL is the most available oil it was the focus of attention. The first approach was to test a range of procedures based on different physical-chemical properties, to select a method that could not only afford the oil constituents but could be scaled-up at a relatively low cost. To obtain standards for the characterisation of the fractions obtained in the different processes to be tested CNSL was separated by column chromatography on silicagel with pentane-ethyl acetate-acetic acid (gradient elution). It afforded cardanol and cardol, the spectra of which have been reported. (see Figure 2-2, and 2-3).

3.2.1.Base treatment

The purpose of this series of experiments was to separate cardanols from cardols on the basis of their different acidities.

CNSL Bras (10 % solution in petrol) was treated with dilute aqueous NaOH (1-1.3 equivalents relative to cardols). The aqueous layer was acidified with HCl and re-extracted (with ether). Both layers afforded a mixture of cardanols and cardols, showing that no enrichment of cardols could be obtained. Furthermore mass recovery was only around 60 %. The pKa values of phenol and resorcinol are very similar. If these values are also similar for cardanol and cardol, separation using alkaline treatment would be impossible.[157] The experimental determination of the pH of a sample of CNSL diluted in methanol to which was added aqueous NaOH, showed that there was no step change that would allow a separation of the compounds via base treatment, so this procedure was not further investigated. Similar titration of CNSL in methanol with ammonia did not give a step change, and so it was concluded that there was no obvious procedure to separate cardanols from cardols using acid base extraction.

3.2.2.Adsorption

Partition phase chromatography

This is currently used to separate steroids on an industrial scale.[158] The use of this technique (introduction of CNSL into a column of silicagel treated with methanol, and then elution with petrol) allowed cardanol (pure by NMR) to be obtained as a pale yellow oil; however

the yield was low (4.5 %), even with a high ratio of solvent (3 litres of petrol/ 1g of CNSL) and so this method was not further investigated.

Filtration on silica

An alternative approach was to adsorb CNSL on silica and then desorb it by washing with petrol (at ambient temperature or under reflux), or with solvents with increasing polarity. Using this method, cardanol was obtained as a clear yellow oil, but with low yields, as shown in Table 2-5. Small increases in the polarity of the washing solvent led to elution of a mixture of cardanol and cardol, so this process was abandoned.

TABLE 2 - 5: Selective desorption of cardanol on silica

Solvent	cardanol (by ^{1}H NMR) (%))
Petrol	5
Petrol with reflux	8
Petrol toluene (9-0.5)	Cardanol impure

3.2.3. Complex formation

(i) The Sharpless method

This allows the resolution of hydroxy-derivatives by selective complexation with calcium chloride.[159] A range of mixtures (geraniol/citronellol, p-cresol/o-cresol, etc.) have been successfully separated using this technique. Sharpless reported competition between pairs of monohydroxy alcohols and monohydroxyphenols for complex formation with the calcium salt; phenols, as a class, form poorer complexes than alcohols of comparable melting point, perhaps because the ability to form complexes may be related with basicity - phenols are weaker bases than comparable alcohols. A plausible hypothesis would therefore be that resorcinolic compounds (like cardols) would complex more strongly than monohydroxyphenols (like cardanols). However the technique remains empirical, and only a trial-and-error approach allows its suitability to separate cardanols from cardols to be determined.

A petroleum solution of CNSL (10 %) was therefore mixed with ground calcium chloride (1.4 mols per mol of cardol) and a catalytic amount of absolute ethanol (1 % mol/mol CNSL). Complexation of cardol with calcium chloride (followed by TLC) was very slow (completion took 36 h). At the end of the reaction, the heterogeneous mixture was filtered, to afford pure cardanols (35 % of the initial CNSL) after removal of the solvent. Increasing the

amount of calcium chloride reduced the reaction time but also the amount of cardanols recovered, while reduction of the amount of the halide salt didn't provide pure alcohol. Change of solvent (toluene, instead of petrol) didn't provide any improvement in yields or reaction time. Attempts to recover the complexed cardanol and cardol from the solid calcium chloride by hydrolysis in methanol/acetone were unfruitful, and the use of calcium chloride was abandoned.

TABLE 2 - 6: Separation of CNSL by alkylresorcinols complexation

Reagents	**Yield of cardanol** (pure by NMR) (%)
Calcium chloride	35
Aluminium chloride	15
Calcium sulfate	Not selective
Molecular sieves	Not selective
Boron oxide (B_2O_3)	12

Using the same basic procedure, the behaviour of other reagents (see Table 2-6) that might complex the OH group (Lewis acids and drying agents) was analysed. As this didn't allow the yield of cardanols to be improved, the use of selective complexation to separate cardanols from cardols was not investigated further.

(ii) Urea complexes

Two methods were tested to generate these complexes, by percolation on a urea column with petrol and by dissolving a solution of cardanol with a small amount of methanol in an aqueous solution of urea (6 M). Neither of these methods gave any selectivity toward cardols or cardanols, or to any of their unsaturated components.

3.2.4. Petrol-Diol partition

(i) Comparison of diols

In a standard set of experiments, CNSL (1.00 g) was distributed between petrol (10 ml) and one of the diols (10 ml) indicated in the Table 2-7. In each case, the non-polar layer contained cardanols, which were pure by NMR. Due to its relatively high boiling point,[i] the diol was very difficult to eliminate by vacuum distillation, as indicated in the original

[i] Ethylene glycol boiling point is 245 °C.

procedure,[133] and so the polar layer was diluted with water and re-extracted with ethyl acetate, to give the yields reported in Table.

TABLE 2 - 7: Separation of CNSL by petrol-diol partition

Polar solvent	**Non-polar layer Yield of cardanol** (pure by NMR) **(%)**	**Polar layer Yield of cardanols + cardols** [a] **(%)**
Ethylene glycol	8	81
1,3-propanediol	8	81
1,4-butanediol	11	78
1,2-butanediol	7.3	80
1,5-pentanediol	6.5	82

a) the NMR spectrum was similar to that of the initial CNSL

These yields are somewhat different from the ones reported, [133] but clearly confirm that it is possible to obtain pure cardanols. Due to this, CNSL (1.00 g) was partitioned between petrol (10 ml) and 1,4- butanediol (10 ml). After separation of the immiscible layers, the polar layer was re-extracted with petrol (2 x 10 ml). Elimination of the non-polar layer afforded cardanols (11 %, pure by HNMR), while the polar layer afforded a mixture of cardanols-cardols (78 %, HNMR similar to the starting material). The same experiment, using 1,2 butanediol afforded cardanols (7 %, pure by NMR), and a mixture of cardols-cardanols (80 %, HNMR similar to the starting material).

(ii) Continuous extraction

As multiple and repeated extractions did not provide a cardol-rich fraction, two consecutive continuous extractions of CNSL, first from a solution in butanediol and then from pentanediol, were carried out using petrol, and gave the yields shown in Figure 2 - 9.

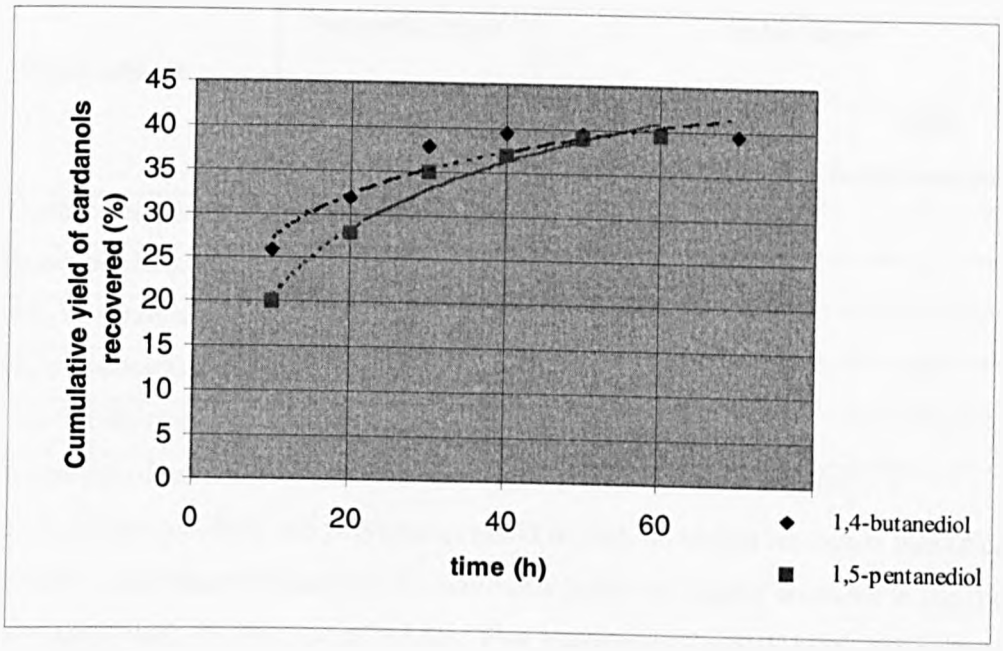


FIGURE 2 - 9: CONTINUOUS EXTRACTION OF CNSL

Even after 60 h it was not possible to remove more than 4 g of cardanol (pure by NMR) from 10 g of CNSL. The residue contained cardanol and cardol in a proportion ca 10 :1 (by NMR).

3.2.5.Partition with non-diol solvent systems

(i) A study of amino-derivatives

Because of the difficulty in obtaining pure cardols the previous results were not considered satisfactory, and a search of solvents that could improve selectivity was the next target. Particularly interesting was to analyse the behaviour of solvents with two polar groups (like the glycols) as it was expected that they would exert dipole-dipole and hydrogen bonding forces selectively with cardols.

Therefore CNSL (1.00 g) was mixed with petrol (10 ml) and one of the polar solvents indicated in Table 2-8. After separation of the two layers, the petrol layer was evaporated. The amine layer was diluted with water, was acidified and re-extracted with ethyl acetate, to give the yields reported in the Table 2-8 .

TABLE 2 - 8: EXTRACTION USING AMINOALCOHOLS AND POLYAMINE SOLVENTS.

Polar solvent	Non-polar layer	Polar layer	
	Yield of cardanol (%)	Yield of cardol + cardanol (%)	Ratio cardol/cardanol
Diethanolamine	9[a])	58	[b])
Monoethanolamine	6	65	[b])
Diethylenetetramine	13	75	[b])
Diethylenetriamine	8	68	[b])
tert-Butylamine	No separation	No separation	----------

a) some traces of cardols b) HNMR very similar with the one of CNSL

Like diols, amino-alcohols and polyamines could be used to obtain cardanols free of cardols. Additionally, in all these separations the non-polar layer was lightly coloured while the polar layer remained dark. In the case of the first four experiments, a dark black flocculate (1-3% of the original CNSL) separated; this was more accentuated with diethylenetetramine. Acidification and re-extraction of the polar layer was a laborious process. A large amount of water used in this step, and the relatively high aqueous solubility of cardanols/cardols may be the cause of the poor total mass recovery, a major drawback of this method. This also suggested that a process that could use a polar solvent with a low boiling point that could be eliminated by distillation would reduce the losses.

(ii) Kamlet-Taft qualitative approach to solvent screening

As the previous results did not allow pure cardols to be obtained and led to high mass losses, they were considered unsatisfactory. However the petrol-diol and petrol-amino-derivative partitions are particular cases of a general case; this led to the analysis of other solvent systems. A theoretical framework was used to reduce the number of experiments in a search of an optimal solution, based on the concept that the behaviour of a solvent is a function of several descriptors: the Hildebrand parameter (δ_h), dipolarity/polarizability (II), hydrogen bonding acidity (α), hydrogen bonding basicity (β)), δ a "polarizability correction term", and ζ a coordinate covalency measure.[160, 147] The Kamlet-Taft methodology, has been described earlier (page 22). In the present case the system was used as an heuristic guide. Experiments providing information on the variation of selectivity towards cardols with solvents having different parameters were then performed. A preliminary search was restricted to readily available solvents and using published information on the parameters. Therefore CNSL-Braz (1.00 g) was mixed with petrol (10 ml) and one of the polar solvents indicated in the Table 2-9.

TABLE 2 - 9: CNSL EXTRACTION USING NON-DIOLS, NON-AMINO SOLVENTS

Polar solvent	Non-polar layer	Polar layer	
	Yield of cardanol (%)	Yield of cardol + cardanol (%)	Ratio cardol/cardanol
Methanol	No separation	No separation	[b]
Dimethylformamide	15.2 [a]	62	[b]
Acetonitrile	19 [c]	64	0.10
Trifluoroethanol	93 [a]	4	0.5

[a] Cardanols with traces of cardols by NMR [b] values were similar to CNSL [c] Pure by NMR

After separation of the two layers, the petrol layer was evaporated. With DMF, the products were diluted with water, and re-extracted with petroleum, which was removed to give the yields reported in the Table 2-9. Methanol,[i] acetonitrile, and TFE layers were simply evaporated to give the yields reported. Methanol gave no separation as with another monosubstituted compound previously tested (butylamine).

When the polar solvent could be removed by distillation, the procedure afforded a high mass recovery (losses were less than 0.5 %), but in addition to the fractions recovered from the solvents, a dark resinous flocculate was obtained. The amount of this increased from trifluoroethanol to acetonitrile. Trifluoroethanol gave higher yields of cardanol but with lower purity by NMR (there were clear traces of cardol in the petrol extract).

To use Kamlet-Taft methodology to correlate and rationalize the multiple interacting solvent-solute interactions in a qualitative manner, a graphical representation was needed. Because this allowed a maximum of three variables, and Equation 1 has six variables, the correction factor (δ), the coordinate co-valency measure (ζ) and the Hildebrand parameter (δ_h) were not represented. In the solvents used in this work, both δ and ζ were always zero, except that in the case of tert-butylamine ζ is 0.5. Experimental values of the Kamlet- Taft parameters were used to represent solvents in a ternary plot. [160, 161] In addition to solvents indicated in Table 2-10, data obtained from previous experiments (Table 2 - 7 , Table 2 - 8) were plotted. Some solvents were not represented because parameters were not available, and because the ones provided allow a prediction of how selectivity could be improved. Additionally ethyl acetate, chloroform, dichloromethane and THF were included. These later solvents do not provide any separation as they are totally soluble in petrol.

[i] Because the mixture petrol:methanol (10:10) was totally homogeneous, CNSL was dissolved in a mixture petrol:methanol (7:3).

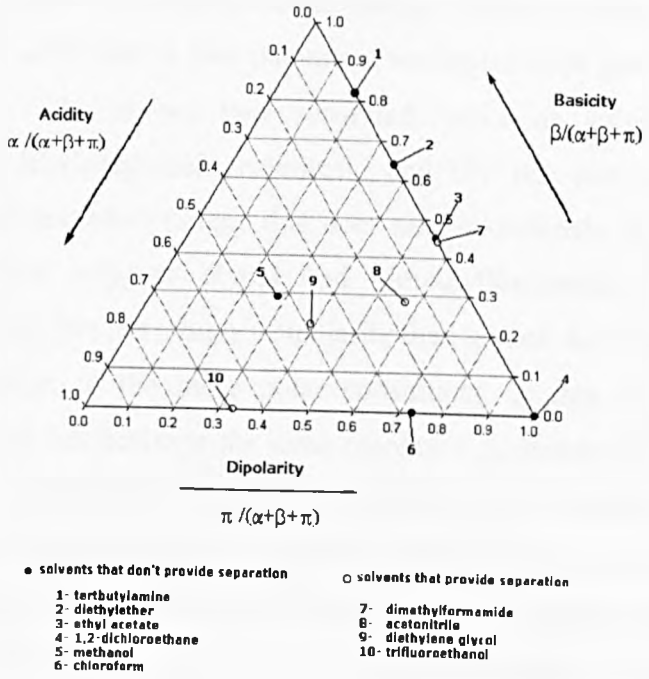


FIGURE 2 - 10: SOLVENT INTERACTION PLOT PRELIMINARY TESTING

No clear correlation could be seen. There is a clear overlap between point 3 for ethyl acetate, and point 7 for dimethylformamide. To clarify the representation, all solvents with Hildebrand parameter lower than 100 kcal dm^{-3} were eliminated.[i] This afforded the plot represented in the Figure 2-11.

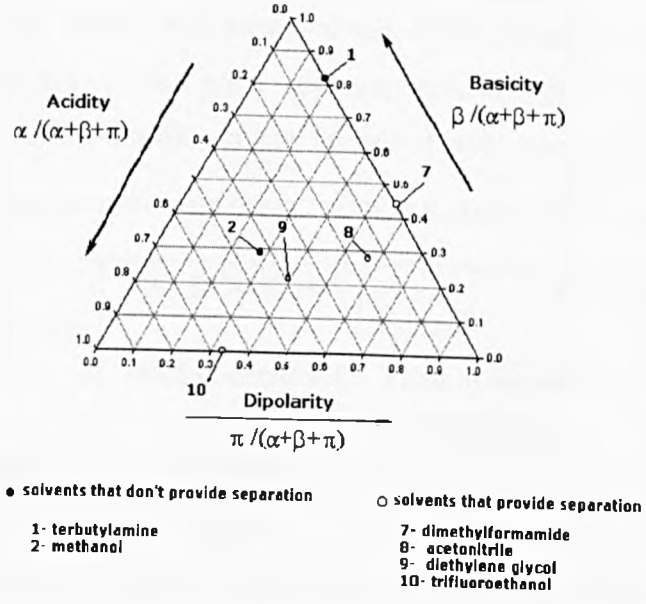


FIGURE 2 - 11: SOLVENTS WITH HILDEBRAND PARAMETER HIGHER THAN 100 KCAL DM^{-3}

[i] Hildebrand parameter (in kcal dm^{-3}) of ethylene glycol is 274.0, methanol 205.2, trifluoroethanol 137.1 acetonitrile 137.8, dimethylformamide 138.9, diethylether 56.2, ethyl acetate 79.2, 1,2-dichloroethane 98.3, chloroform 84.2 (data from ref. 165, 167).

The Hildebrand parameter is a measure of the energy needed to separate two molecules of solvent. Solvents with such a low parameter solubilize both petrol, cardanols, and cardols. Figure 2 - 11 shows two separated areas of solvents: one around dimethylformamide, ethyleneglycol, acetonitrile, and TFE that provides separation and one around methanol and t-butylamine that does not. Acetonitrile (point 8) provided a better separation than ethylene glycol and dimethylformamide (points 9 & 7). Acetonitrile is less acid, but has a higher dipolarity than glycol. An increase in dipolarity would favour attraction to the more polar constituent, in this case cardols versus cardanols.[i] Acetonitrile has however the same dipolarity as dimethylformamide but also a higher acidity. As both factors contribute to the attraction to cardols, acetonitrile was expected to be better. Methanol and t-butylamine (points 5 & 1) do not provide enough dipolarity to provide a selective attraction towards cardols. The fluorinated compound is less dipolar than acetonitrile and even than dimethylformamide, but provides better selectivity to cardol, because its hydrogen donor acidity parameter is higher than the one of acetonitrile, but so is the case of ethyleneglycol versus acetonitrile. In recent papers, both Platts[162] and Kiss[163] suggested that in this case, the Taft-Hamlet equation should contain an additional parameter, associated with its fluorinated character. The Kamlet-Taft published coefficients show a number of solvents that would fit in the region of the plot shown to provide separation. To test the validity of this model two additional solvents were tested: DMSO and nitromethane. CNSL-Braz (1.00 g) was mixed with petrol (10 ml) and one of the polar solvents indicated in the Table 2 - 10. After separation of the two non-miscible layers, the petrol layer was evaporated.

TABLE 2 - 10: EXTRACTIONS PERFORMED TO TEST KAMLET-TAFT MODEL PREDICTIONS

Polar solvent	**Non-polar layer**	**Polar layer**	
	Yield of cardanol (%)	**Yield of cardol + cardanol (%)**	**Ratio cardol/cardanol**
Dimethylsulfoxide	14[a)]	65	[b)]
Nitromethane	23[c)]	62	0.12

[a)] Cardanols with traces of cardols by NMR [b)] values were similar to that from CNSL [c)] Pure by NMR

With DMSO, the polar layer were diluted with water, and re-extracted with petroleum, which was removed, while with nitromethane, distillation under vacuum provided the yield indicated in the Table. Cardanols obtained using petrol-nitromethane partition were

[i] This statement is derived by comparison with phenol and resorcinol which have partition coefficients (@ChemDraw property database) log K_{cw} in cyclohexane/water of -0.720 and -3.790 respectively.

a pale straw yellow colour (the lightest colour of all cardanols obtained by CNSL solvent partition in this work). The yields of cardanols obtained in these last two experiments could have been forecast by the model as demonstrated by the relative position of solvents that have provided separation in the ternary plot in Figure 2-11. DMF, point 7, overlaps point 11, DMSO; yields of cardanols using these two solvents are similar, while the yield of cardanols obtained using acetonitrile (point 8) is slightly smaller than the one obtained using nitromethane (point 12).

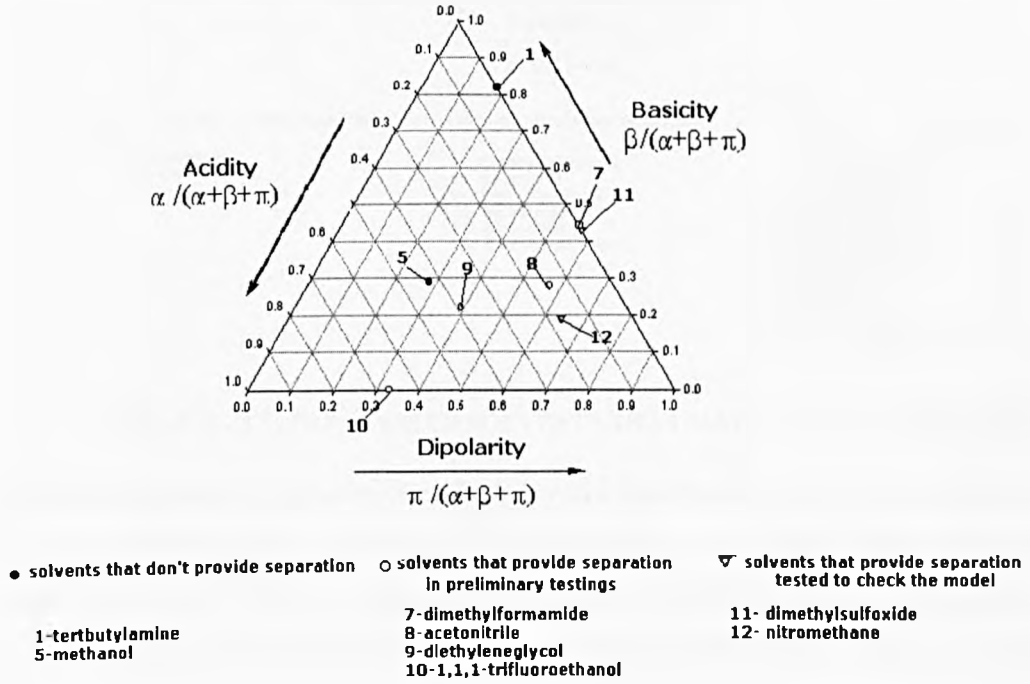
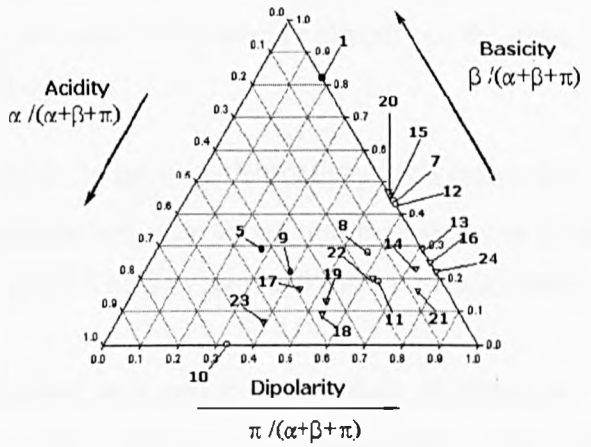


FIGURE 2 - 12: SOLVENT USED TO CHECK THE MODEL

Present results have eliminated the need to test others compounds indicated in Figure 2-13 , as their expected selectivity would not overcome other disadvantages. Other nitro compounds and cyano derivatives are more costly and also have higher boiling points than their smaller homologues. Extraction with N-methylpyrolidone, a solvent with low volatility, was anticipated to lead to high mass losses. Fluorophenols were not tested because of their high boiling point (178 - 185 °C). Hexafluoro-2-propanol, predicted to behave similarly to trifluoroethanol,[1] was not tested because of its cost (around £ 5 /g) which would limit its use on large scale.

[1] Hexafluoropropanol, with a cohesive energy density 30 kcal dm^{-3} lower than trifluoroethanol, would be expected to solubilize more cardol.



• solvents that don't provide separation

1- tertbutylamine
5- methanol

○ solvents that provide separation

7- dimethylformamide
8- acetonitrile
9- diethylene glycol
10- trifluoroethanol
11- nitromethane
12- dimethylsulfoxide

▽solvents that may provide separation

13- cyanopropane
14- nitroethane
15- N-methylpyrrolidinone
16- benzonitrile
17- 2-fluorophenol
18- 3-fluorophenol
19- 4-fluorophenol
20- fluroxene
21- enflurane
22- isoflurane
23-hexafluoropropanol
24-methoxyflurane

FIGURE 2 - 13: NON-TESTED SOLVENTS THAT MAY PROVIDE SEPARATION

This new approach to optimise the selectivity in a liquid extraction process uses the Kamlet-Taft solvent parameters qualitatively. It allows, with a very small number of solvents, the analysis of which "interaction-mix" provides the best separation. In addition the method provides a rational basis for interpreting experimental results. Three groups of solvents were found to provide high selectivity to cardols, nitriles and cyano compounds and a fluorinated alcohol. The approach is expected to be less laborious and more fruitful than the previously used, trial and error analysis. However its reliability still needs to be checked with others pairs of compounds to be separated; as the present study shows, fluorinated compounds imply a new dimension in this space. Higher numbers of cheap, non-toxic, and non-flammable solvents, and more detailed parameter databases may be expected to be provided in the future, allowing a bigger range of solvents to be analysed.

(ii) The black resinous solid

The addition of either TFE or acetonitrile to a 10 % CNSL solution in petroleum (even under a nitrogen atmosphere), led to flocculation of a black resinous material. With TFE, 0.09 g of resinous material was obtained per gram of CNSL, with $R_f = 0$ in methanol. This material didn't have the same R_f as the polymeric material from CNSL reported in the literature,[164] which was a mixture with different R_f values in chloroform-ethyl acetate. In the present case the material showed a broad NMR spectrum. The mass spectrum was very similar to that of pure cardanol but gave an additional very small peak at m/z 352 (this corresponds to the

addition of two oxygen atoms to cardol (15:0)). The IR spectrum was similar to that of CNSL, but showed a reduction in the relative intensity of the three peaks for the unsaturated bonds at 988, 945 and 910 cm^{-1}.

(iii) Cardol recovery with the petrol-trifluoroethanol solvent system

Because selective solvents had been found, the next step was to develop a method to use them to obtain pure cardol. The first approach was to test trifluoroethanol.

Back extraction

While it was not possible in a one-step extraction, to obtain pure cardanol with petrol-trifluoroethanol (TFE) (see Table 2 - 9), the latter was a quite extraordinary solvent. Not only was it possible to remove it by mild distillation (b.p. 76 °C), but also it showed a *high selectivity* toward cardol. Unfortunately it also had a *very low capacity.*

A solution of 1.00 g of CNSL diluted in 1ml of heptane, after 40 successive extractions with 1 ml 1,1,1-trifluoroethanol gave 0.57 g of cardanols (pure by HNMR) in the petroleum layer, and 0.23 g of a mixture rich in cardol in the fluoroalcohol layer; 20 re-extractions of the polar layer with 1 ml of heptane gave cardol, without any trace of cardanols (by ^{1}HNMR) but with TFE (ca.0.5 g) indicating that 10 % of the original cardol could be recovered.[i] This is the first solvent system that allowed pure cardols to be obtained, but the huge volume of solvent used, and the low recovery meant that this procedure needed to be improved.

(iv) Cardol recovery with Petrol-Acetonitrile; Back extraction

Despite its lower selectivity towards cardols than TFE, acetonitrile[ii] can dissolve large quantities of CNSL/cardols or cardanols; petrol-acetonitrile (P-ACN (10:10)) was therefore seen as a possibility to overcome the lack of capacity of TFE. This was checked using a multistep back extraction, and a continuous extraction. CNSL (10.00 g) was dissolved in 1:1 petrol-ACN (200 ml). Separation of the layers, provided, from the non-polar layer cardanols (1.95 g), while the polar layer provided a mixture of cardols and cardanols (5.90 g). The balance was a sticky material (2.01 g) that flocculated. The acetonitrile fraction was redissolved in ACN (100 ml) and re-extracted with petrol. This was repeated four times and the results are indicated in the table.

[i] Because of the low capacity of this solvent to dissolve CNSL constituents, continuous extraction with TFE of a 10 % CNSL solution in petrol was carried out. This gave a two-phase solution in the receiver, a TFE solution rich in cardol, and a layer of cardanol mixed with methylcardol and cardol. Due to this, this procedure was abandoned.

[ii] Nitromethane was a slightly better solvent than acetonitrile, but the latter was used, as representative of this group of solvents. (Nitromethane costs roughly four times more than acetonitrile)

TABLE 2 - 11: Petroleum- ACN multistep extraction

Re-extraction	Petroleum layer			ACN layer		
	Weight (g)	Cardanol (%)	Cardol (%)	Weight (g)	Cardanols (%)	Cardols (%)
0	1.95	100	0	5.9	91	9
1	1.02	100	0	4.90	87	13
2	0.70	99.4	0.6	4.20	82	18
3	0.52	na	na	3.6	na	na
4	0.35	98.5	1.5	3.2	75	25

Multiple back extraction of acetonitrile also yield cardanols essentially free of cardols, and 3.20 g of a solution with 25 % cardols relatively simply from 10.00 g CNSL.

In conclusion, using the multistep back extraction, the petrol-acetonitrile system allows pure cardanols (ca. 30 % of the original CNSL) to be obtained. Obtaining pure cardols is difficult, as a solution with only 25 % cardols has been obtained. The performance of the solvent were therefore tested using continuous extraction.

Continuous extraction

CNSL (20.00 g) dissolved in 1:1 petrol-ACN (400 ml), gave cardanols (5.53 g) after separation of the petrol layer, an enriched mixture of cardols (8.3 g) in the acetonitrile layer and 5.6 g of a sticky material that flocculated in the flask. The fraction from the acetonitrile layer was redissolved in ACN (100 ml), and continuously extracted over 36 h. Fractions collected from the petroleum layer contained mainly cardanol (Table 2.12).

TABLE 2 - 12 CONTINUOUS EXTRACTION WITH PETROL OF AN ACETONITRILE SOLUTION OF CNSL

		Amount		Cardol/cardanol (by ^{1}H NMR)
		g	% a)	
First petroleum layer	Cardanols	5.53	27.65	0
Petroleum layer b)	Cardanols-cardols	7.4	37	0.1
Residual acetonitrile layer b)	Cardols rich	**1.2**	**6.0**	**1.87**
Flocculated mat.		5.76	28.8	-----
Time of extraction (h)		36		

a) of the CNSL sample b) from continuous extraction c) Amount of CNSL 20 g.

Petrol-ACN partition was a cheap and fast method to obtain cardanols free of cardols and of the black fraction that flocculated. Continuous extraction for 36 h afforded a solution rich in cardols (6.0 % (wt), unfortunately not pure cardols). These results essentially confirm the preceding experiment, which shows that this solvent is not selective enough to obtain pure cardols in a small number of stages.

3.3.Technical CNSL Liquid-Liquid extraction

3.3.1.General

As obtaining cardanols in a relatively high yield by liquid – liquid extraction was simple and cheap, this procedure was considered the most suitable method to separate the oil. At this stage, it was also shown that a mixture gradually depleted in cardanols could be recycled, providing in each cycle a mixture richer in cardols. However, to be scaled up, the solvent system needed to be improved (since it is reported that a maximum of 7 re-extractions is economically feasible).[165]Important solvent properties, to be considered were:[166]

a) The *selectivity* (measured as a ratio between the concentration of the two compounds to be separated in the extract-rich phase).
b) The *capacity* (measured as a ratio of the solute concentration between the raffinate[i] and the extract phase).
c) S*olvent losses* (which are a function of the solubility of the extracting solvent in the raffinate phase).

3.3.2.TFE with co-solvents

(i) Analysis of co-solvents

The use of continuous extraction with TFE failed due to its low capacity as a solvent (see page 47). In order to get around this, the use co-solvents was examined. Five were tested: dichloromethane, methanol, acetone, nitromethane and acetonitrile. All are polar solvents and have lower boiling points than TFE. Both nitromethane and acetonitrile were selective to cardol (see page 42, and 43) and a synergic effect was expected when one of them was mixed with TFE. Samples of CNSL in petrol (0.1 : 1), were mixed with TFE with increasing concentrations of the co-solvents. Even at very small concentrations, around 1 %, acetone did not lead to a clear separation between the non-polar and polar layers, and so this solvent was discarded. Dichloromethane gave results very similar to those for methanol which are described below. The relative concentration of cardols vs. cardanols, in the TFE layer, is plotted versus the concentration of the co-solvent, (see Figure 2-14). Surprisingly, a maximum for the cardol-cardanol ratio was observed; this could be related with a change in the cohesivity of the TFE layer.[153] Another significant difference between the solvents miscible/immiscible in petrol is that, even with 0.5 % methanol there was no flocculation of

[i] In an extraction process solvent is mixed with the feed and provide an extract and a raffinate.[156]

the black solid, while with acetonitrile-TFE (or nitromethane-TFE), not only did the solid flocculate but the cardol rich layer was straw yellow colour rather than black.

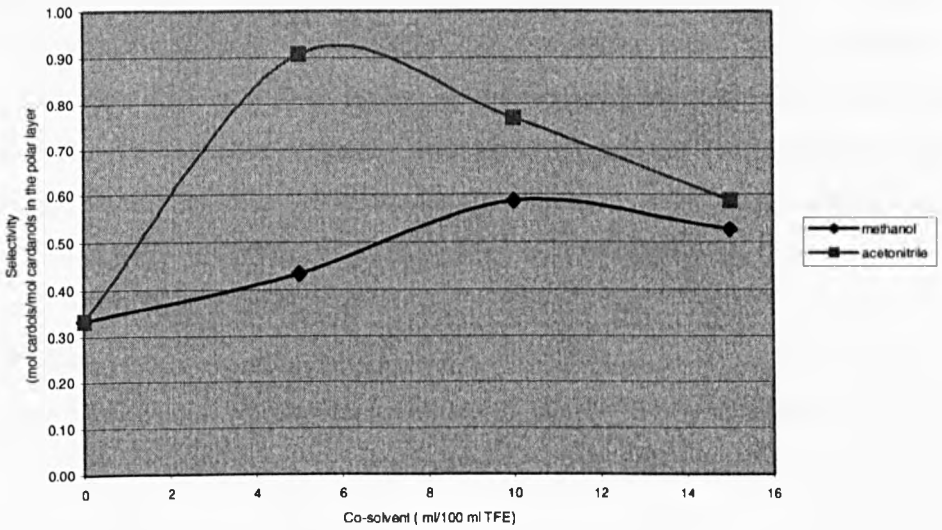


FIGURE 2 - 14: SELECTIVITY IN CNSL EXTRACTION WITH P:TFE:COSOLVENT.

This maximum, obtained more significantly with co-solvents that are also immiscible with petrol, (indicating that selectivity is higher with a mixture TFE: co-solvent than with TFE alone), suggests that in multiple step back extraction, pure "cardols" can be obtained in fewer steps than using pure solvents. Before testing this, the possibility to use P:TFE: co-solvent to obtain "pure cardanols", was analysed.

(ii) Could P: TFE: co-solvent be used to obtain "pure" cardanol ?

In a separate experiment, when a petroleum solution of CNSL (1 : 0.1) was extracted twice with TFE-methanol (1 : 0.05), all the cardol was removed. Back extraction of the TFE layer with petrol removed only a very small part of cardanols, and the use of this system was discontinued. This suggests that because methanol is not selective it dissolves both cardanols and cardols in the polar phase, and therefore it is going to be difficult to remove cardanols from this phase. When a petroleum sample of CNSL (1 : 0.1) was extracted three times with TFE- acetonitrile (10 : 1), no cardols remained in the petrol layer. Evaporation of the solvent from this layer gave 62 % of cardanols (with no cardols by NMR). The polar layer gave 28 % of an equimolar mixture of cardol and cardanols (by NMR). In addition, 8 % of black solid, with a broad NMR spectrum similar to that of CNSL, was recovered. The TFE-10 % acetonitrile solvent mix has a relatively low boiling point and was recovered easily by a vacuum distillation. Similar

results were obtained when instead of acetonitrile, nitromethane was used as a solvent modifier.

Thus repeated extraction of the petroleum layer with TFE:modifier afforded cardanols (pure by HNMR) without cardols. But because the procedure using TFE:cosolvent is more laborious and more expensive than using acetonitrile, using the latter is recommended on a laboratory scale to obtain pure cardanol. Yields are higher using TFE: cosolvents, but CNSL is very cheap, so this is not a crucial factor for laboratory work. However, as can be seen later, only TFE:cosolvent allows cardols to be obtained in high purity.

3.3.3.Cardol recovery - extraction of the polar layer

To check the best method to re-extract the cardols, petrol-TFE acetonitrile (1 : 1 : 0.05) was tested.

(i) Multistep back extraction with petrol-TFE-ACN systems

CNSL (1.000 g) dissolved in a mixture of petrol-TFE- ACN (10:10:0.5), gave cardanols (560 mg) in the petrol layer, a mixture of cardols-cardanols (151 mg, 1:2 by HNMR) in the TFE-ACN layer, and a sticky material (300 mg with some solvent) that flocculated. The polar layer was redissolved in TFE-ACN (10:0.5, 10.5 ml) and re-extracted with petrol (4 x 10 ml). The petrol layers gave a cardol/cardanol mixture (130 mg, 5:95 by HNMR) and the final TFE-ACN layer gave a cardol rich mixture (20 mg, 4:1, by HNMR). This procedure was applied to all CNSL samples available to the study (see page 26) with similar results.

(ii) Continuous extraction with Petrol-TFE-ACN systems

CNSL (4.0 g) dissolved in a mixture of petrol-TFE-ACN (10:10:0.5), gave cardanols (2.0 g) in the petrol layer, a cardol rich fraction (0.97 g) in the TFE-ACN layer, and a sticky material-containing some solvent (2.1 g) that flocculated.

TABLE 2 - 13: CONTINUOUS EXTRACTIONS WITH PETROL OF A TFE-ACN (10:0.05) SOLUTION OF CNSL

		Amount		cardol/cardanol (by HNMR)
		g	% a)	
First petroleum layer	Cardanol	2.02	50.5	0.05
Petroleum layer b)	Cardanol-cardol	0.68	17.0	0.1
Residual acetonitrile layer b)	Cardol rich	**0.24**	**6.1**	**1.87**
Flocculated mat.		1.06	26.5	-----
Time of extraction (h)		6		

a) of the CNSL sample b) from continuous extraction

The polar fraction was redissolved in TFE-ACN (10:0.5, 42 ml) , and continuously extracted with petrol over 6 h. Hourly samples of the petroleum layer, and the final TFE-ACN layer samples were analysed and results are presented in the Table 2-13.

These two results confirm that the use of this solvent system allows a solution richer in cardol (60 % for the continuous extraction, and 80 % for the back extraction) to be obtained. Present data don't preclude however the possibility of obtaining higher purity in continuous extraction (eg., by increasing the extraction time).

(iii) Comparison between solvents systems

As it has been proved that both P-ACN and P-TFE-ACN (5 %) are selective toward cardols, with the capacity to dissolve CNSL constituents, it was important to compare them. Table 2 - 14 summarised results obtained in previous two continuous extraction.

TABLE 2 - 14: MASS BALANCE IN BOTH CONTINUOUS EXTRACTIONS

Solvent system		P- TFE-ACN (5%)		P-ACN	
		Mass used in the experiment (g)	% of starting material	Mass used in the experiment (g)	% of starting material
Starting material	CNSL Braz	4	100	20	100
Petroleum extracted fraction 1 [(b)]	Cardanols	2.02 [(a)]	50.5 [(a)]	5.53	27.65
Petroleum extracted fraction 2 [(c)]	Cardanols-cardols	0.68	17.0	7.4	37
Residue liquid fraction 1 [(c)]	Cardols rich	**0.24**	**6.1**	**1.2**	**6.0**
Residue fraction 2	Flocculated mat.	1.06	26.5	5.76	28.8
	Time of extraction (hrs)	6		36	

(a) not pure by ^{1}HNMR (b) extraction performed before the continuous extraction (c) fraction from the continuous extraction

Because the P-TFE –ACN (10 : 10 : 0.5) system shows a higher selectivity to cardols than P-ACN (10 : 10), the time of extraction was much reduced. The purity of cardols obtained in these two experiments (around 60 %) is equivalent. The purity of cardanols by P-ACN extraction was higher, but it has been shown in previous experiments that extracting CNSL Braz in Petrol with TFE-5 % ACN gave cardanols with no cardols detectable by NMR .

3.3.4. Equilibrium data in a Petroleum-Trifluoroethanol-Acetonitrile extraction

In the case of non-miscible solvent systems, basic solvent extraction theory gives a relationship between parameters of the process (the solvent ratio, number of extraction steps, concentrations in each layer) and the partition coefficient, deduced on the basis of a material

balance and equilibrium equations. Establishing such a relationship in the case of CNSL partition with Petrol-TFE-ACN would therefore allow how "pure cardol" could be obtained to be predicted if the parameters of the extraction changed. Equilibrium data (Figure 2-11) of the separation of cardanols/cardols were obtained dissolving CNSL (10.00 g) in petrol (100 ml) TFE (100 ml) and ACN (5 ml), weighing both extracts, and measuring the concentration in each phase by HPLC. The vacuum dried polar layer was then repartitioned in P-TFE-ACN (10 : 10 : 0.5), and weights and concentrations of cardols and cardanols in both fractions were determined as above. The operation was repeated re-extracting the polar layer up to six times. Data obtained were plotted in the Figure 2 –15.

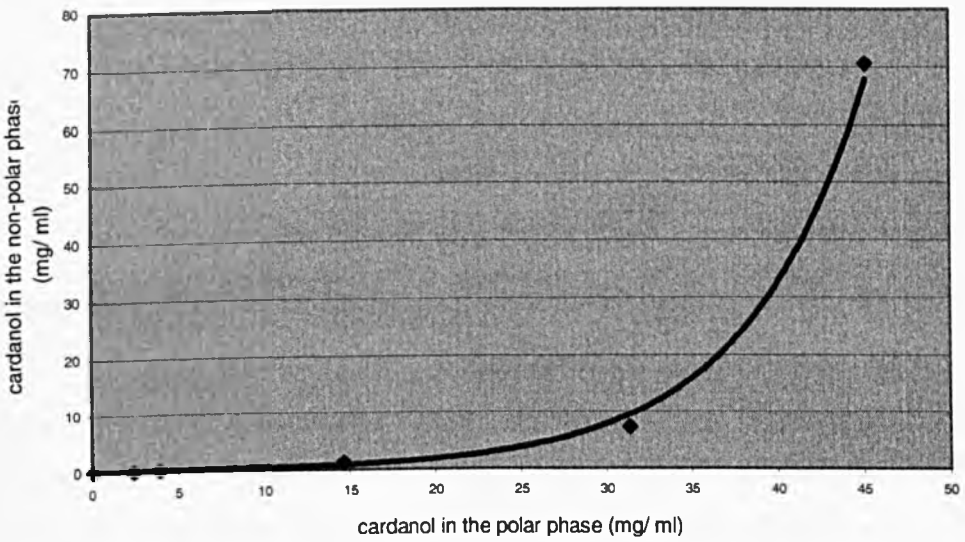


FIGURE 2 - 15: EQUILIBRIUM DATA FOR TECHNICAL CNSL EXTRACTION WITH P:TFE:ACN (5%)

A relationship between the parameters of the process can be obtained using the McCabe-Thiele graphical method (details in **Appendix 2**). In the case of a co-current system the concentration of cardanols in the both polar and non-polar phase after each re-extraction, can be estimated as a function of the ratio of polar solvent to non-polar solvent, use of this technique is presented in the Figure 2-16.

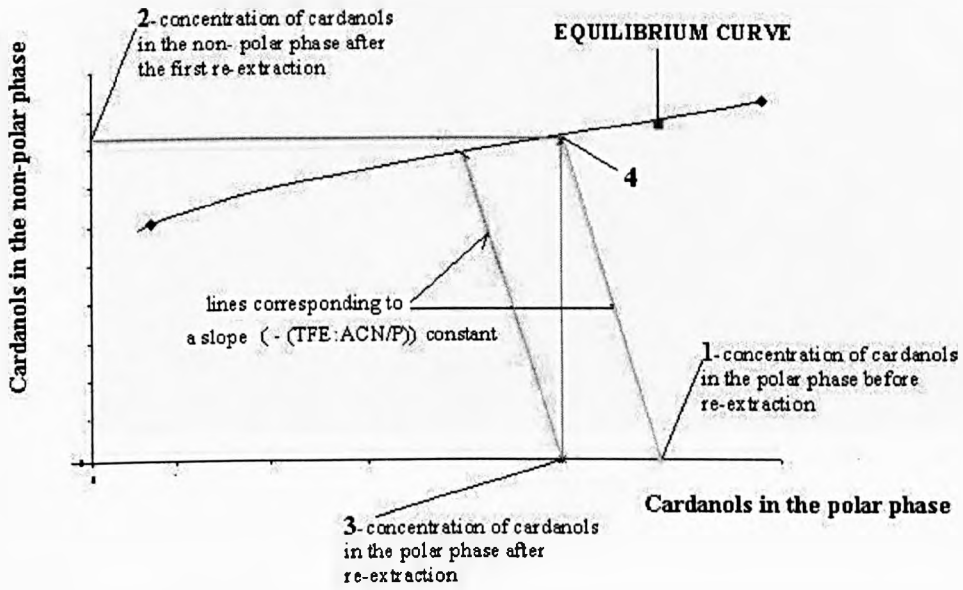
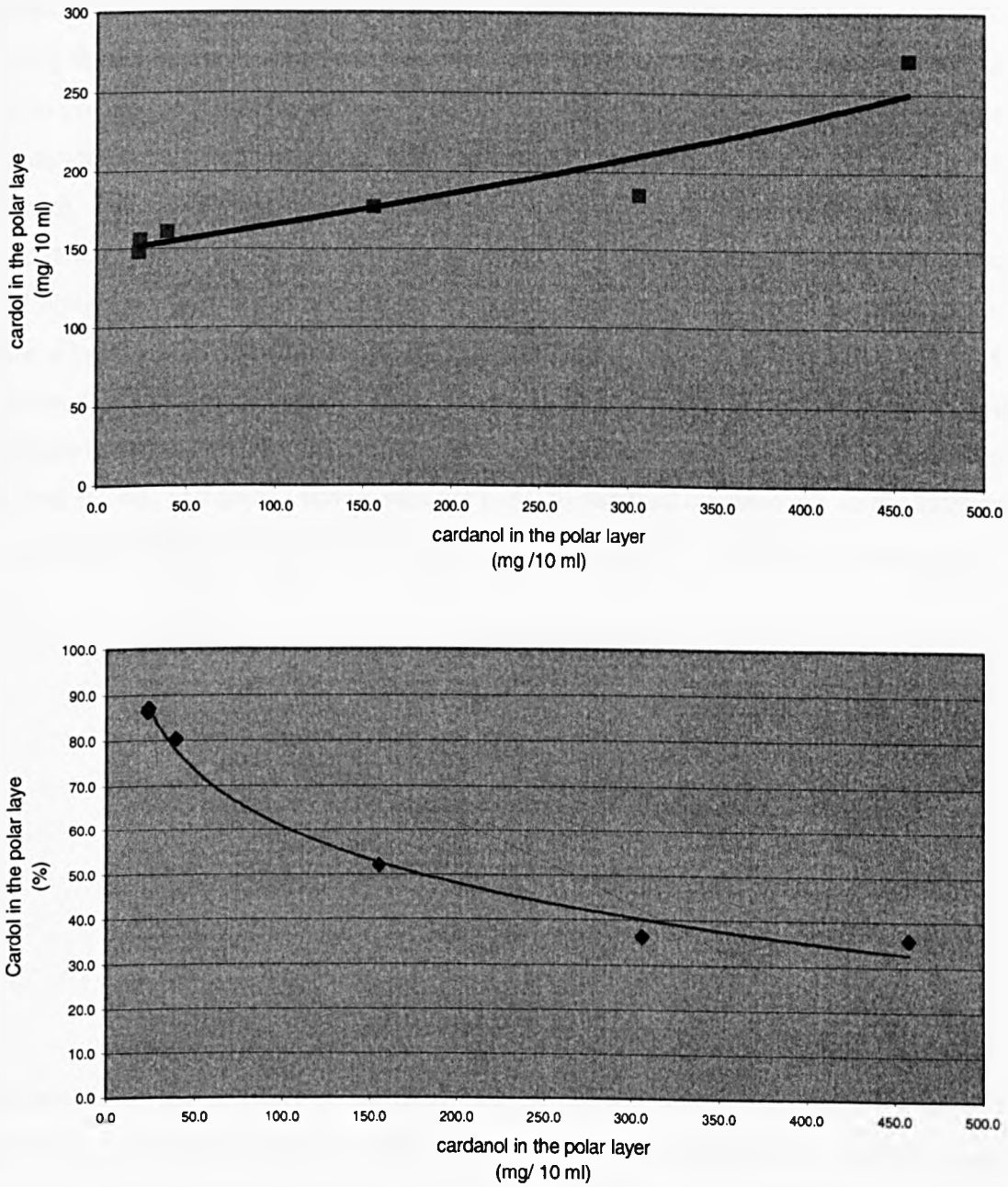


FIGURE 2 - 16- CORRELATIONS BETWEEN CARDANOLS IN BOTH PHASES BEFORE AND AFTER RE-EXTRACTION

When a TFE:ACN solution of a mixture of cardanol-cardol is re-extracted with petroleum, the concentration of cardanols in the resulting two phases corresponds to point (4) . This point is at the intersection of the equilibrium curve and of a line, the slope of which is – (volume of polar solvent/ volume of non-polar solvent), and passes through point (1) (which abscissa is the concentration of cardanol in the polar layer before extraction, and ordinate is 0). The operation could be repeated n-times to determine the concentration of cardanols in both phases after n extractions, or a similar operation could be performed for other solvent ratios, or for a different composition of the mixture cardanols-cardol to be separated. The corresponding concentration of cardols could be found from the graphs provided in Figure 2-17. Both were obtained from experimental data used to draw the equilibrium curve presented in Figure 2-15.



a) there are only five point because there is an overlap between the first point (cardol 87%) and the second one (cardol 86.4 %).

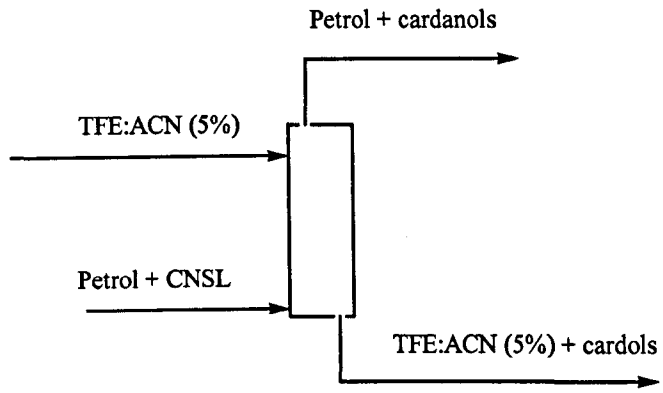
FIGURE 2 - 17: CARDOLS IN THE POLAR PHASE IN TECHNICAL CNSL EXTRACTION WITH P:TFE:ACN (5 %)

When the concentration of cardanol in the polar phase decreases, the concentration of cardols in the same phase, expressed as a percentage (shown on the y-axis) increases until 87 %, corresponding to a concentration of 14.8 mg/ml.

The data show that the amount of both solvents could therefore be reduced at the expense of increasing the number of extraction steps, or inversely that with a higher ratio of solvent, (TFE:ACN: P 30:1.5:10), a solution of 80 % cardols (purity) could be obtained with just one re-extraction.

3.3.5. Possibility of large scale separation in a counter-current system

Having shown that the method could be applied to CNSL on a laboratory scale, the next step was to predict the feasibility of the separation of cardols from cardanols, using a continuous counter-current extraction column. This specialised equipment was not available for this research, but the experimental data collected above allow its required dimensions to be estimated. (more details are provided in Appendix 2). In the co-current system of extraction, used until now, three fractions are recovered after the extraction: cardanols (with the non-polar solvent), a middle fraction (mixture of cardanols-cardol in petrol) and a cardol rich fraction (in TFE- cosolvent). The advantage of a counter current extraction is the elimination of the "middle fraction" as could be understood from Scheme 2-1 which shows the feed (CNSL and petrol) and solvent (TFE-ACN) supplied continuously to the extraction column, and cardanols and petrol, and cardols with TFE-ACN simultaneously removed.



SCHEME 2 - 1 COUNTER-CURRENT EXTRACTION SYSTEM

The answer to the problem of feasibility lies in defining the operational conditions (i.e. purity of cardanols and cardols at the outlet of the column and ratio of solvents), and in using the equilibrium data previously deduced (see Figure 2-15) to establish the number of theoretical plates (see Appendix 2 for such calculation). This parameter is then used in empirical correlations provided by equipment manufacturers to estimate the dimensions of the extraction column. The technical feasibility could then be estimated, for example if the counter-current column is 50 m high it is not feasible.[i] (Appendix 2).

Experimental work reported in this thesis shows that P-TFE-co-solvent could be used in a counter-current system to separate cardanols from cardols (obtaining cardanols pure, and cardols 87 %) (Figure 2-17). As an example, an unit providing 3.75 kg/h cardols operating at

[i] These dimensions have been estimated by ***Koch Modular Process Systems, LLC. Extraction Technology Group*** *(45 Eisenhower Drive Paramus, NJ 07652 Tel: (201) 368-2929 Fax: (201) 368-8989)* a company manufacturing liquid extractions columns, on basis of Figs 2-15 and 2-17b), however it is recommended to perform pilot plant studies before commissioning a plant. The dimensions indicated are roughly the same as those estimated using the relations provided by Walas, S.M. [126]

a ratio of solvents P:TFE:ACN (10:5:0.25) would need to be 1.72 m high, and 0.27 m in diameter. An increase of capacity to 20 kg/h would correspond to a column of 2.4 m height and 0.6 m in diameter. These separation units are obviously technically feasible.[i]

3.3.6.Conclusions: What is the method of choice to separate cardanols/cardols/solid ?

There are a number of answers to this question.

1) If the purpose is to obtain a sample of cardanols (with a reduced amount of solid/ and no cardols) in the laboratory, the solution is to dissolve technical CNSL in acetonitrile (1 : 10) and to extract with petrol (2 x 10); removal of the petrol would afford cardanols (pure by NMR), ca. 30 % of the original CNSL sample.

2) If the purpose is to obtain cardols (purity 100 %) from Technical CNSL the single method that was developed is to extract a petroleum solution of the oil using TFE. However the procedure is laborious, recovery is very low, and not suitable for larger scale use because of the amount of solvent involved.

3) If the purpose is to recover cardols from cardanols, a faster method, that would provide cardols (purity ~85 %) would be to mix CNSL-petrol-TFE-ACN (0.1 : 1:1 : 0.05). Washing the petrol layer with petrol-TFE-ACN (1:1:0.05) would afford cardanols (pure by HNMR), corresponding to 50 % of the initial CNSL. Re-extraction the polar layer with petrol would afford the above indicated cardols (purity 87 %) in 1.8 % yield of the initial CNSL (see Figure 2-17). The re-extracted fraction, contains a mixture of cardanols-cardols that could be separated with the next batch of CNSL. The volume of solvents, number of re-extractions could be modified as indicated in Section 3.3.4. using the methodology for co-current extraction and equilibrium data obtained.

4) If the purpose is to obtain cardols and cardanols in a continuous system, this work indicates that the use of the counter current extraction system using petrol-TFE-ACN should be feasible on an industrial scale. The possibility of recycling solvents by distillation, and the low flammability and toxicity of TFE-ACN suggest that this process would be environmentally sound.

[i] An extraction process using Petrol-TFE system, using the procedure indicated previously would correspond to two columns, one of at least 18 m to obtain a cardol rich extract and one of 9 m to obtain cardols 100 % pure.

3.4.Additional information collected in the development of the T-CNSL separation procedure

3.4.1.Analysis of a published solvent extraction procedure

A recent study, reported a separation of CNSL (with 63.% anacardic acids, 11 % cardanols, 22 % cardols) in a two-step procedure.[167] Anacardic acids separation was performed on the basis of the non-solubility of its calcium salt (using methanol as solvent). Separation of cardanols from cardols was then performed using the partition between a non-polar and a polar layer. However as the solvent system chosen (petrol - methanol with ammonia (25 %)) has very low capacity to remove cardanols (lower than petrol-butanediol), it was modified with ethyl acetate. Ethyl acetate is a non-selective modifier (some cardols migrate to the non-polar layer); the work in this thesis suggests that selective modifiers must be immiscible in the non-polar phase.[i] To eliminate these cardols from the petrol layer, the literature procedure washed this layer with dilute sodium hydroxide. This led to losses in the aqueous layer. To recover the cardols from the polar layer a new approach was to extract it from the methanol-ammonia layer with ethyl acetate. It was claimed that it was possible to obtain cardols (100 % purity by HPLC), in high yield. This later concept was therefore tested by dissolving cardols in methanolic ammonia and adding in a separating funnel ethyl acetate in amounts indicated in the paper. This gave an homogeneous solution which separated only on adding 4 times more ethyl acetate. Recovery of cardols from the ethyl acetate was only 45 %.

After a discussion with the author of this thesis, the same group published a modified version of this procedure, using just petrol-ammonia-methanol to separate technical CNSL and claimed to obtain cardanols (100 % pure by HPLC) and cardols (100 % pure by HPLC) with 100 % recovery. With both CNSL Bras, and CNSL VMSRF[ii] these results were irreproducible, as it was only possible to obtain pure cardanols in low yields, and a mixture of cardanols-cardol, as in the petrol-diol and petrol-amine experiments reported in this thesis. [168]

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[i] See more details in page 49, analysis of TFE-co-solvents.

[ii] CNSL supplied by VMRF- Villa Maya Research Foundation is also the research centre where the authors of the above paper are based.

3.4.2.A new procedure to obtain technical cardanols

In the separation of Technical CNSL using petrol-diol partition it has been reported that a fraction of CNSL (identified as a black "polymeric" fraction) stays mainly in the non-polar phase with cardanols, but that some cardanol migrates to the polar phase. [133]. Assuming that this phenomenon is common to any immiscible solvent partition of Technical CNSL, it could be hypothesized that increasing the quantity of polar solvent would extract most of the cardanols to the polar layer, leaving the "polymeric" fraction in the non-polar layer. As, with the range of solvents tested, nitromethane provided most flocculation of the solid, petrol-nitromethane was used to check the hypothesis, both with cardanols obtained from a previous acetonitrile-petrol partition and directly from CNSL. Cardanol obtained from a CNSL-acetonitrile-petrol (1 : 10 : 10) partition, was dissolved in petrol and washed with nitromethane; the nitromethane layer provided clear reddish cardanols (69 %), while the petrol layer gave black-brown cardanols (30 %). CNSL-Braz was submitted to the same procedure and provided of a mixture of cardanols-cardols (66 %) and a black brown sludge (34 %). Both procedures were scaled up to provide enough material to measure the viscosity with a U tube. The treated cardanols gives 65.5 cps while the treated CNSL gives 73.1 cps. These two products could be considered as equivalent to "commercial", singly distilled cardanols (see Table 1-4, p. 10). The double distilled cardanols have a pale yellow straw colour, and a lower viscosity.

The possibility of removing the high molecular weight fraction without distillation and obtaining directly a solution that could be further processed could reduce the cost of production of fine chemicals obtained from technical cardanols. This was illustrated in the epoxidation of cardanols with hydrogen peroxide (see later).

3.5.Natural CNSL separation

3.5.1.Base treatment of natural CNSL

As the main literature method to obtain anacardic acid, was based on precipitation of the acid with lead hydroxide (a toxic compound),[43] a new method using cheap and safe reagents was clearly needed. Anacardic acid and cardol were therefore separated by column chromatography to provide standards for the separation study.

The acid group present only in anacardic acids led to a search for alternative bases that could react selectively with it. Old patent literature refers to separation using sodium hydroxide,[142] and calcium hydroxide.[140]The use of sodium hydroxide was not tested as it had been shown previously that this base could react easily with cardols.

Preliminary attempts to extract selectively anacardic acid with aqueous sodium bicarbonate failed to separate the acid, so attention focussed on possible use of calcium hydroxide. As reported in the patent it was possible to obtain anacardic acid as a precipitated calcium salt, which was regenerated with hydrochloric acid (72 % of the original oil was recovered as anacardic acid with 98 % purity), while cardols were recovered pure (7 % of the original oil). One of the factors causing the high mass loss (21 %) could be the high volume of water used. Acetone, instead of methanol used in the patent, was used as solvent, and anacardic acids yields and purity were similar (the patent however did not discriminate between the yield of cardols and losses). This procedure could therefore be applied to acetone-extracted CNSL. The procedure did not work when petrol was used as solvent.

3.5.2.Solvent partition of natural CNSL

(i) Liquid-liquid extraction using petrol- ACN

A petrol-diol extraction was reported to have been used to separate anacardic acid from Natural CNSL. To check the possibility of using other systems, Natural CNSL (10 g) was partitioned between petrol and ACN. The petroleum layer gave a brown oil (20 %) (pure anacardic acid by NMR), while the ACN layer gave also a brown oil (80 %) (a mixture of anacardic acid/cardol ratio by NMR : 2.1 mol/mol). Because it was a very easy and cheap procedure this method was used to obtain "pure anacardic acid" in the remaining part of the work. The acetonitrile layer was separated using the methodology explained later (page 64).

(ii) Liquid-liquid extraction using petrol-TFE-ACN

a) Determination of the optimal ratio

The Petrol-TFE-ACN system with different amounts of ACN in the TFE layer was then investigated using the same technique. The data obtained (Figure 2 - 18) show that maximum selectivity was obtained with P:TFE:ACN (10 : 10 : 0.5).

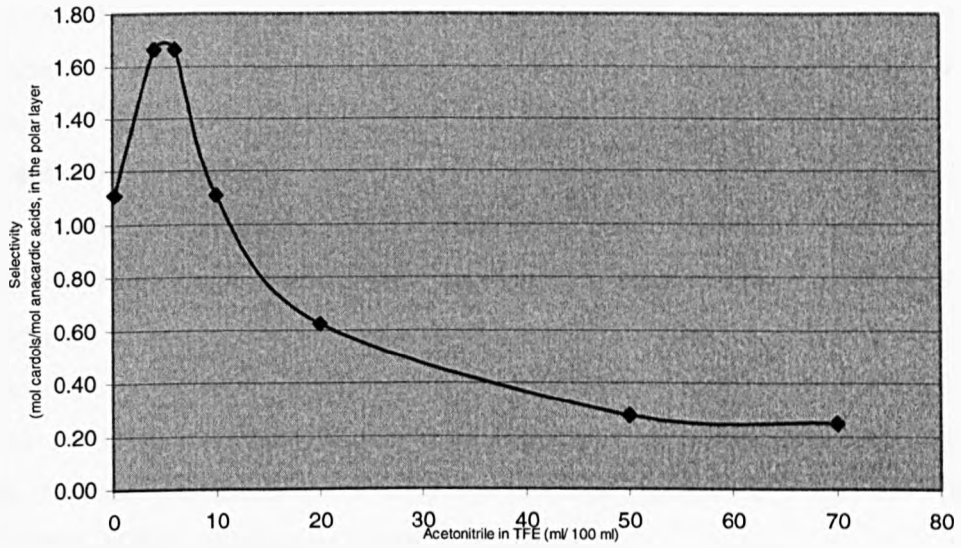

FIGURE 2 - 18: OPTIMUM AMOUNT OF ACN IN TFE LAYER IN NATURAL CNSL EXTRACTION WITH PETROL-ACN-TFE

Like in the extraction of Technical CNSL, in the Natural CNSL extraction, TFE with 5% ACN showed a high selectivity to cardols and therefore this solvent system was used to determine the possibility of obtaining pure cardols.

b) Multistep back extraction to obtain pure anacardic acids and cardols

Natural CNSL was then partitioned between Petrol and TFE-ACN using the ratio from (a) that gave the highest selectivity. The non-polar layer gave anacardic acid with some cardol, but when re-extracted with TFE-ACN it gave, in the non-polar layer, anacardic acid (purity 100 % by NMR, 43 % of the original oil).The first polar layer give a mixture rich in cardol (corresponding to the maximum of the Figure 2-18). Repeated extractions of this with petrol gave cardol (5 % of the original oil) with no trace of anacardic acid. The two remaining fractions (a mixture of anacardic acids and cardols) obtained in the re-extraction of both layers were mixed (to obtain a "middle fraction") and added to Natural CNSL to be re-extracted in the next batch. This methodology is explained later (see page 64).Because it was very simple, cardol used in the remaining part of the work was obtained using partitioning of Natural CNSL between petrol and TFE-ACN.

3.5.3. Equilibrium data of a mixture of anacardic acids/ cardols in TFE-ACN

In the partitioning of natural CNSL between petrol and TFE-ACN (5 %), equilibrium data were determined using the same technique as used in the separation of Technical CNSL (see Section 3.3.4):

a) To establish a relationship between ratio of solvents and purity of cardol. Because preliminary experiments (section 3.5.2) showed that it was easier to obtain pure cardol with natural CNSL than with Technical CNSL, partitioning of anacardic acid- cardol with P-TFE-ACN was seen to be the best method to obtain cardol in future laboratory work. As after each extraction, a different "middle fraction" would be mixed with the original natural CNSL for recycling, oil with different compositions of anacardic acid- cardol would be available. A procedure similar to the method outlined in Figure 2-16, would allow the ratio of petrol/ TFE-ACN to obtain pure cardol to be predicted.

b) To estimate the feasibility of a counter current extraction, allowing pure anacardic acid and cardol to be recovered in a continuous system.

So natural CNSL (10 g) was partitioned between petrol (100 ml), TFE (100 ml) and ACN (5 ml). The concentration in each phase was measured by HPLC. The polar extract was then repartitioned in P-TFE-ACN (10: 10: 0.5), and weights and concentrations of cardols and anacardic acid in both fractions were determined as above. The operation was repeated re-extracting the polar layer up to four times. Data collected were used to plot Figures 2-19, 2-20 and 2-21.

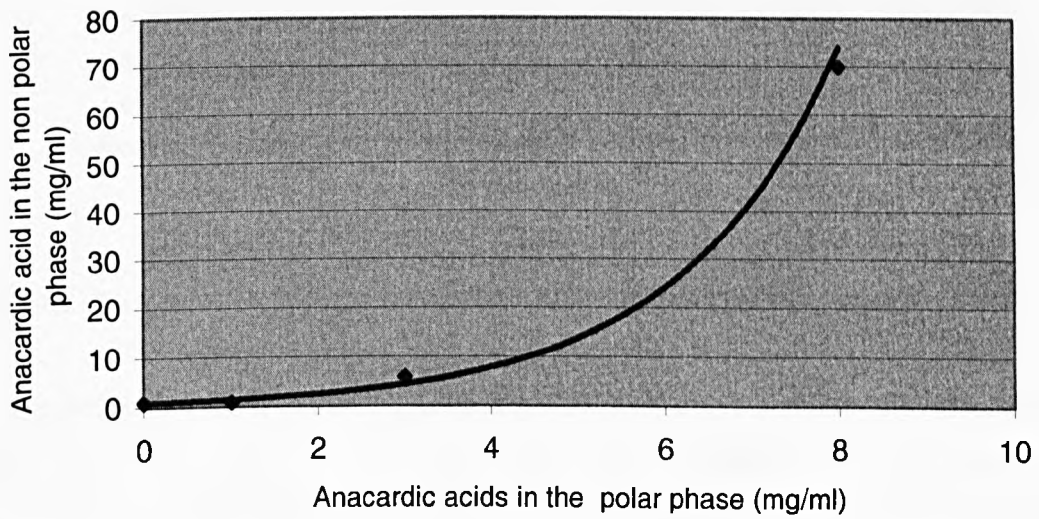

FIGURE 2 - 19: EQUILIBRIUM DATA IN NATURAL CNSL EXTRACTION WITH P:TFE: ACN

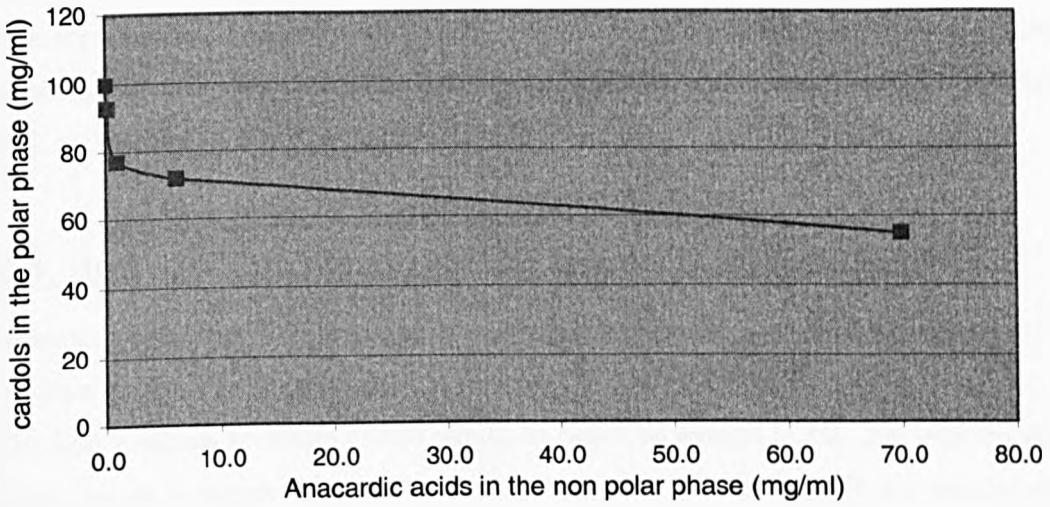

FIGURE 2 - 20: CARDOLS IN THE POLAR PHASE IN NATURAL CNSL EXTRACTION WITH P:TFE:ACN

These plots, and the general method outlined in Figure 2-16, were reliably used to recover cardol (from different anacardic acid-cardol mixtures)[i] in the rest of this work.

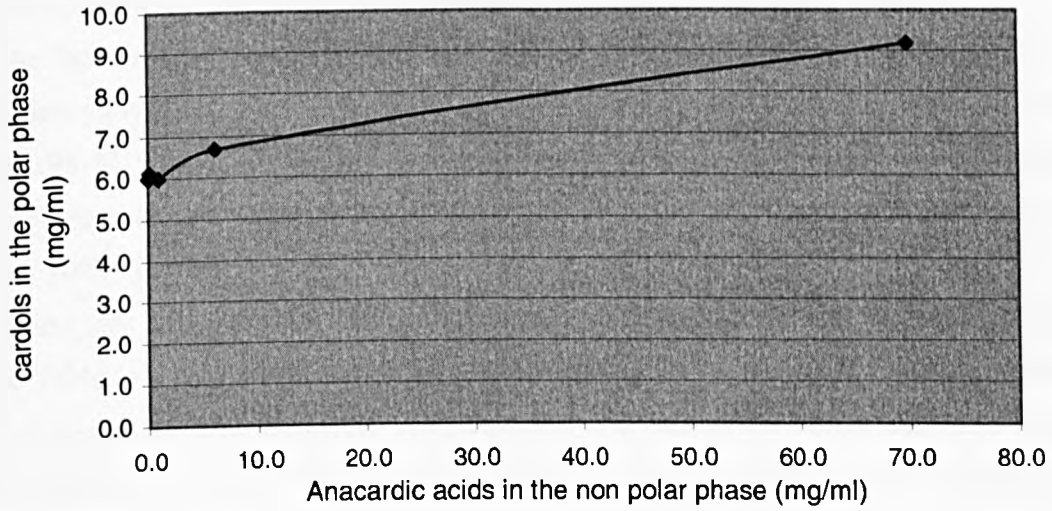

FIGURE 2 - 21: CARDOLS IN THE POLAR PHASE IN NATURAL CNSL EXTRACTION WITH P:TFE:ACN

A comparison of these plots (Figure 2-19, 2-20 and 2-21) and the ones obtained with technical CNSL (Figure 2-15 and 2-17) confirm, that to obtain cardol (in a given purity), from a mixture with a given concentration of non-cardol [cardanol (in a mixture cardanol-

[i] In the last chapter of this thesis reactions involving anacardic acid are described. This was obtained by Petrol-Acetonitrile partition as described in 3.5.2. The acetonitrile layer was then mixed with some original natural CNSL. This provided a significant amount of anacardic-acid –cardol mixture, in addition to the one obtained by recycling the "middle fraction".

cardol), or anacardic acid, (in a mixture anacardic acid-cardol)] and with the a constant ratio of solvents, the number of extraction steps is smaller in the second case. This also implies that a separation of anacardic acid-cardol using a counter current column would need less stages than the one used to separate Technical CNSL. As separation of cardol from technical CNSL is feasible, so it is from natural CNSL.

3.5.4. How to obtain pure cardanol, anacardic acid and cardol

A preliminary answer to this question was given before (Section 3.3.6), but there are now more data to give a better answer.

1.The best methods to obtain cardol would be based on natural CNSL, not only because its cardol content is higher than in Technical CNSL, but also because it is easier to remove anacardic acid than cardanol from cardol. Extraction of CNSL using acetone, followed by precipitation of anacardic acid with calcium hydroxide provided cardol (100 % purity, 7 % of the original oil). Partition based on Petrol-ACN-TFE afforded cardol in 100 % purity and 5 % yield based on CNSL. As a laboratory method the latter is a method of choice because of its simplicity, and the possibility of recycling the middle fraction. In a continuous extraction unit the yield would be increased as no "middle" fraction is obtained

2.The best method to obtain anacardic acid is solvent partition of natural CNSL. For laboratory purposes, petrol-acetonitrile affords a cheap and fast method to provide anacardic acid (98 % purity, 72 % yield based in natural CNSL). On a larger scale, continuous counter-current extraction, using petrol-TFE-ACN would afford anacardic acid and cardol (both 100 % purity).

3.In the case of the cashew shell oil obtained by other methods than the hot-bath method (see Table 1-1, p 3) where only a partial decarboxylation of anacardic acid takes place, the oil typically contains anacardic acid, cardanol and cardol. To obtain each one of the 3 compounds, a combination of two methods (solvent partition with TFE-ACN, and precipitation using calcium hydroxide) is suggested. However due to its lack of availability this technology has not been tested.

3.6.Estimation of anacardic acid in kernels

The main process of shelling nuts involves heating them to remove the oil by diffusion. It was now hypothesized that part of the oil could migrate to the kernel.

As the kernels are edible products with no apparent toxic side effects, the anacardic acid /cardol content of commercial kernels could be considered as an indicator of its non-toxicity for humans.

Kernels were extracted in a soxlhet with petroleum to afford a pale yellow oil (38 %). The amount of oil was less than the 45 - 48 % usually reported,[169] maybe due to the fact that the kernels were a snack already fried and salted. The oil had an NMR with a multiplet characteristic of the backbone of the triglycerides, a multiplet corresponding to olefinic protons, but no trace of aromatics.

To analyse the oil by HPLC, the sample was gradually concentrated until detection of signals in the chromatogram was possible at 312 nm. To identify the peaks the sample was spiked with pure "anacardic acids". The content of anacardic acids in the kernels, calculated as a function of the area of the corresponding peaks, was estimated as 160 ppm. This value may be a very low mark, as it has been shown that cashew apple juice[i] sold in the US contain 500 ppm AA.[80] The data obtained in this work raise however a question on the safety issues pertaining to anacardic acid. The maximum legal concentration of anacardic acids as constituents of a popular medicinal plant, *Ginkgoa Biloba Lin* is only 5 ppm (in Europe), and costly methods are used to remove anacardic acid from Ginkgo formulations (Ginkocer and preparation thereof),[170] but no adverse effects have yet been related to cashew kernel/cashew apple juice consumption, suggesting that data on oral toxicity of anacardic acid should be reanalysed.

3.7.Separation/Identification of Semecarpus Oil constituents

3.7.1.Cold extraction of the pericarp

A sample of *Semecarpus Anacardium* nuts, similar to the one described in "Indian trees"[171] was supplied by an Indian company, *Apurva Organics Ltd.*

Most of the previous compositional studies on the oil did not provide details about how it was extracted from the nuts, and/or involve distillation to purify the oil. As some constituents may be thermosensitive, the extraction and analysis used in this work avoided the use of heat.

An aliquot of seeds was cut transversally and the kernel separated manually from the shells. These where then milled in a coffee mill. The powdered shell was extracted with methanol-ethyl acetate-dichloromethane. The extraction was repeated three times, until no more oil (yield 30.5 %) was obtained when the solvents where removed under vacuum.

The IR of the oil shown a characteristic signal for the out of plane deformation of the aromatic C-H at 740 and 770 cm^{-1} and the complete absence of bands between 800 and 840 cm^{-1}, which are characteristic of a substituted aromatic ring.

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[i] Because at this range of concentration, anacardic acids could control *helicobacter pylori* (considered to cause gastritis) it has been suggested that cashew juice could be useful constituents of an healthy diet.

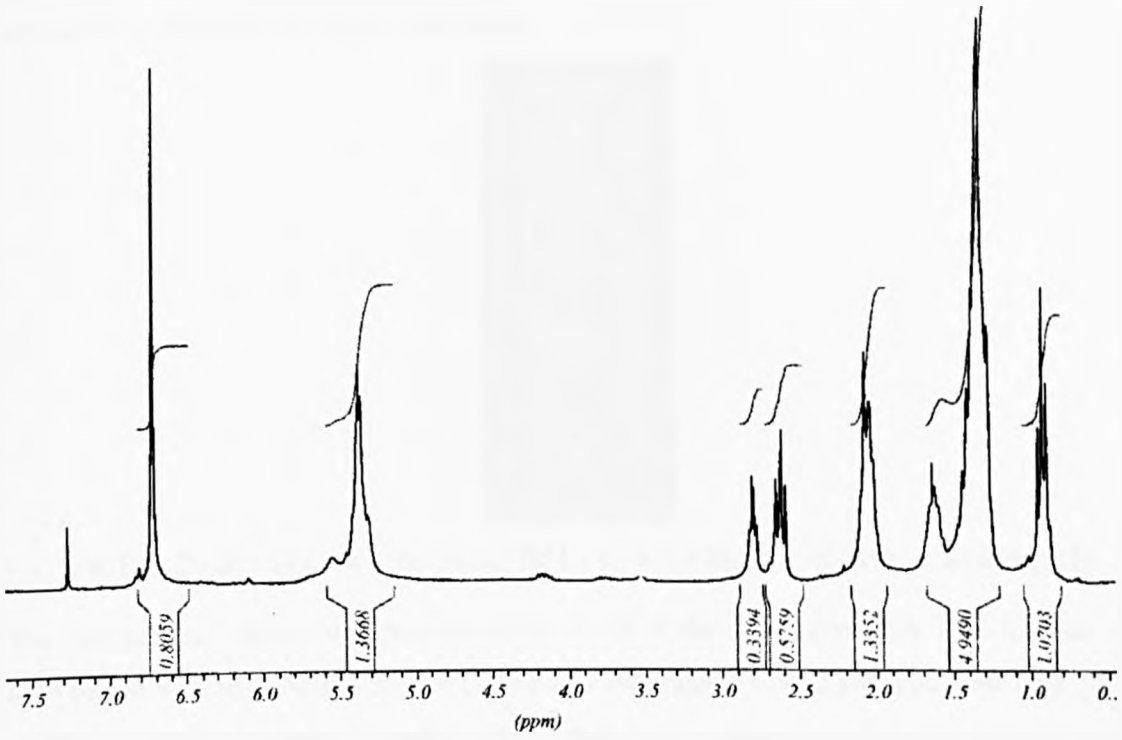


FIGURE 2 - 22: ^{1}H NMR OF BILHAWAN SHELL LIQUID.

The NMR of the pericarp oil (Figure 2-22) shows a singlet at δ 6.7 corresponding to the aromatic protons of the catechols; a multiplet at δ 5.4 for the protons in the double bonds, the remaining part of the spectrum being similar to the one of CNSL; triplets at δ 2.8 and 2.6 corresponding to skip allylic and benzylic protons, multiplets at δ 2.07 and at δ1.65 to the protons α to the double bond and to the benzylic groups, multiplets at δ1.35 to the protons of the alkyl chain and a triplet at δ 0.93 to the terminal methyl group. Assuming that the aromatic protons were mainly from catechol derivatives, and that the olefinic protons were from the chain, this would correspond to 2.6 double bonds for each catechol derivative, a fact that could not be explained by any of the previous studies. The number of protons in the benzylic position, match well with the ones from the terminal methyl in a ratio 2/3. Expansion of the double bond region showed what looked like a doublet of triplet. No trace of anacardic acid could be detected.

TLC analysis

Elution of the crude oil on a silicagel plate with petrol-ethyl acetate (5:2) gave one major spot, a middle spot and three minors ones. A sample of oil was separated by column chromatography, with gradient elution with petrol-ethyl acetate-acetic acid. The compound corresponding to the first (minor) spot at the top of the plate could not been separated and

both the second (the major one) and the fifth (the middle) spots gave NMR spectra that could not be assigned as single compounds

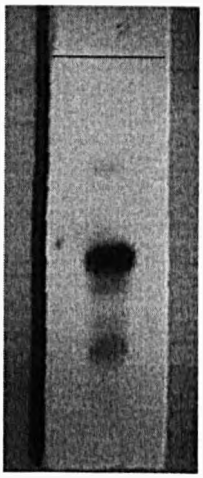


FIGURE 2 - 23: TLC OF THE CRUDE BSL OIL WITH PETROL-ETHYL ACETATE (5:2)

The second (and major) spot accounted for 76 % of the semecarpus oil. This fraction was then eluted with petrol-ethyl acetate (1:1) on a silver nitrate coated silicagel plate (see Figure 2-24) and gave 3 spots (2 major and a small one), suggesting that this fraction might correspond to unsaturated congeners of the same chemical family.

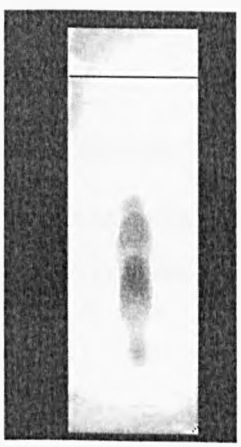


FIGURE 2 - 24: SILVER NITRATE TLC PLATE OF BSL MAJOR COMPOUND

HPLC assay

HPLC confirmed the complexity of the mixture as the chromatogram obtained using water-acetonitrile-acetic acid (40-60-10) and a detector at 292 nm (maximum UV absorption of the sample) showed 18 peaks. The first (major) fraction accounted for the first major 3 peaks and 74 % of the area. Hydrogenation of the corresponding fraction obtained by column chromatography, afforded a white powder, (corresponding to one peak in the HPLC assay)

identified as 3-pentadecylcatechol, indicating that the other peaks probably corresponded to unsaturated homologues.

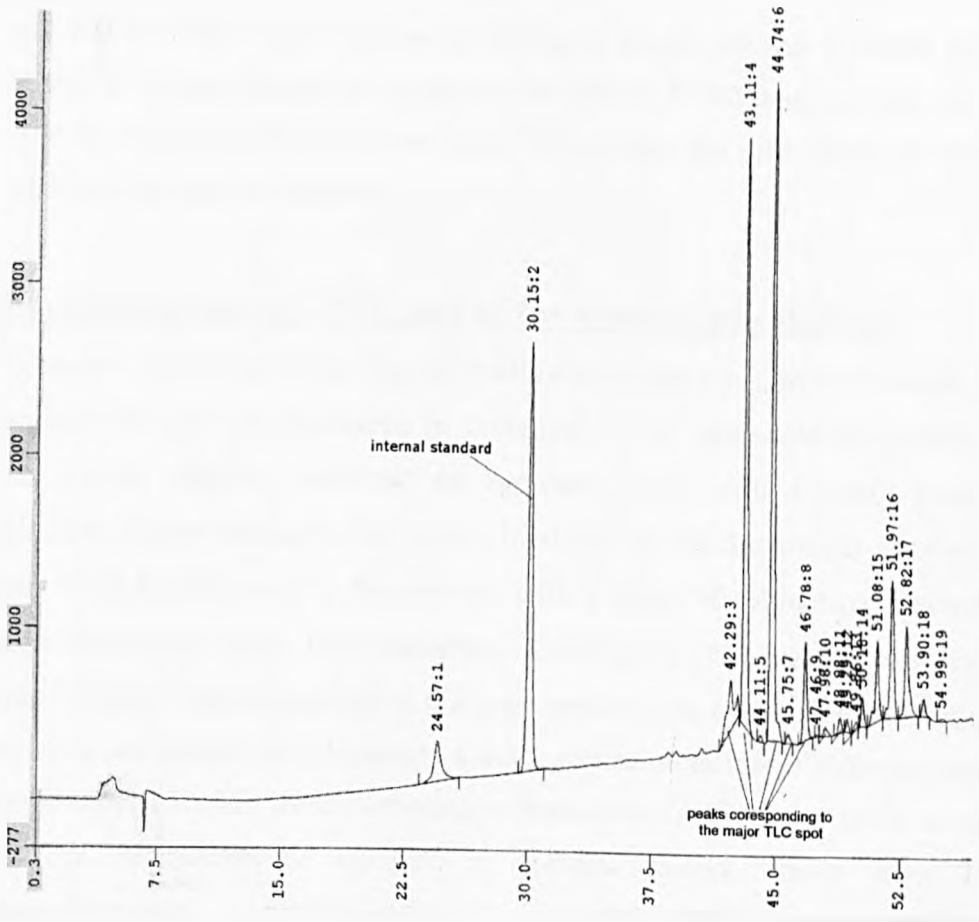


FIGURE 2 - 25 : HPLC CHROMATOGRAM OF THE SEMECARPUS SHELL OIL.

HPLC using the detector at 313 nm (maximum absorbtion for anacardic acid), using hexylresorcinol as internal standard, did not show anacardic acids as suggested in the literature (see section 1.5.2, p 15).

Semecarpus analysis-conclusions

As suggested by previous work, the data presented indicate that semecarpus shell oil, also called BSL, is mainly a mixture of pentadecenylcatechols. However, in addition to the two previously identified compounds, the data suggest that the oil also contains a third pentadecenylcatechol, and a minor amount of unidentified compounds. These pentadecylcatechols accounted for 76 % of the oil sample that was investigated.

No trace of anacardic acids C15 could be found.

Total identification of the main individual constituents, and of the minor fraction was not performed because the author of this thesis contracted a severe allergy to the oil.

4. CONCLUSIONS

4.1.General

This work has provided a new and fast technique to search solvents in liquid extraction methods, which allowed a system to separate cardol (purity 87 %) from cardanol, and cardol (purity 100 %) from anacardic acid to be found. This system has been shown by calculation to be technically suitable for scale up.

4.2.Characterisation of CNSL and of the semecarpus shell oil.

Both Technical and Natural CNSL from different origins were analysed in this work. Beside the two major families of constituents in Technical CNSL: cardanols and cardols, some Technical CNSL samples contained an aggregate (with salts (mainly potassium), cardanols and a minor amount of an unidentified high molecular weight fraction). This aggregate could be removed by flocculation with a range of solvents or destroyed by refluxing with mineral acids. The composition of both kinds of oil has been determined by HPLC and ^{1}HNMR. Results provided by the latter method were found to be accurate enough to characterise the sample and to provide a quick technique to assess different separation methods developed in this work. Semecarpus Anacardium was shown to be a complex mixture, but as previously thought, it contains mainly (more than 74 %) pentadecenylcatechols.

4.3.Separation methods

In the case of both kinds of CNSL, despite the difference between the samples, new methods to separate them into their main families of constituents have been developed and shown to be reproducible:

(i) Liquid-liquid extraction with immiscible solvent systems

A petrol-diol mixture has been previously shown to partition both Technical and Natural CNSL into their constituents. To find a more selective solvent system, a new and fast technique has been developed, which uses a qualitative approach to the Kamlet-Taft relationship. Solvent system properties have been then improved by the use of phase modifiers. Fluorinated systems, Petrol-TFE-ACN or P-TFE-NM could be used to partition both kinds of CNSL, but with several advantages over previously investigated systems: they have much higher selectivity and could be used in a minimum of extraction steps to obtain both cardols and cardanols solutions. Solvents could be recycled by distillation. These facts

should allow the separation of cardanols and cardols or anacardic acids and cardols on a larger scale. Equilibrium data and a method of calculation to provide a relationship between the ratio of solvents and the purity/ and amount of the cardols/ anacardic acids or cardols/cardanols have been provided. These data could allow the design of a bigger installation; a Reciprocating Plate Extraction system has been suggested. On technical grounds, as a raw-material, natural CNSL is preferred, both because of its higher content of cardols, and because it has been possible to obtain a fraction with 100 % purity; however present commercial availability of the natural oil is scarce, so a large scale manufacture of cardols may use technical CNSL. As a fast laboratory procedure (when the recovery of pure cardols does not matter) a simplified system could be used. Washing a petroleum solution of Technical CNSL with an immiscible polar solvent system (ACN, NM) gave a high yield (30 % of the oil) of cardanols , with a purity of 100 % (by HPLC). An equivalent of the commercially available "technical cardanols"/"distilled CNSL" could also be obtained by flocculating the above mentioned aggregate with petrol-ACN or petrol-NM.

(ii) Calcium hydroxide

From Natural CNSL, cardols can also be obtained in high yields and purity by treatment of the CNSL with calcium hydroxide to remove anacardic acids, which could then be recovered. Despite the fact that this method uses cheaper reagents, liquid-liquid extraction is an interesting alternative because it allows higher recovery of both compounds, is faster, require less manpower and the reagents can be recycled. It is unfortunate that in this work, samples of CNSL obtained by steam extraction (see page 3 for more data on this unusual cashew shell oil) that contained both anacardic acid, cardanol and cardol, have not been investigated. However, experimental work done in this thesis suggests that to separate this kind of mixture would need both techniques, one to separate cardols from anacardic acid and cardanols, and the other to purify anacardic acid, or eventually one to separate anacardic acid, from cardanol-cardol, and the other the separate the latter two compounds.

(iii) Others methods

In the case of Technical CNSL, a range of others methods (alkaline extraction, complexes with solids, partition phase chromatography, filtration on silica) have been shown to be non-competitive with the former procedure as they provide cardanols in lower yields. A single previously published method, that could eventually be scaled up, fractional crystallization (see details section 1.2.2, page 21) could provide, in the case of steam extracted CNSL, cardols in high purity. Energy is a major cost constituent in separation processes, and this technique requires more energy than the liquid-liquid extraction process.

4.3.Anacardic acids in kernels

The fact that anacardic acids could be found in cashew kernels, presently consumed by millions of people suggests that in a certain range of concentration, they could have low mammalian toxicity. Because anacardic acids have known beneficial biological activities (see Section 1.4.3), this implies that it could be useful constituent of an healthy diet. Additionally, because our new method of separation allows anacardic acid to be produced on a large scale, new uses, in which it could come into contact with humans could be developed.

4.4.Recommendations for further studies

1. The present methods to search solvents for liquid extraction are based on empirical or semi-empirical methods, (trial and error, the "Kortum und Buchholz-Meisenheimer classification" (page 29), or group additivity methods like UNIFAC or NRTL). One important limitation of the group additivity methods is that they cannot differentiate between isomers, and this problem has been addressed with additional empirical relationship. The new approach presented in this work does not have such limitations, but still needs to be tested with other pairs of compounds to be separated. The fact that the coefficients of the Kamlet-Taft model could be calculated, and that existing mathematical methods could optimise calculation of the distribution coefficients based in Equation 1 suggests that the approach could be used in designing a new computerized system which would find an optimum system of separation based on the chemical structure of the compounds to be separated.

2. The fact that cardol could be obtained with simpler methods than the ones used previously to synthesize 5-alkylresorcinol, opens the way to use it at low cost not only for chemical research, but in biological studies aimed at its large-scale use.

3. Continuous extraction technology (suggested for large scale separation) still requires that pilot plant studies should be performed when markets for pure cardol, anacardic acid or cardanol are developed.

CHAPTER 3 - SHORT CHAIN PHENOLS BY PYROLYSIS

1. INTRODUCTION

1.1.Short-chain phenols

m-Alkyl-phenols are commonly found in many biologically active substances such as pyrethroids,[172] and a range of drugs showing anti-tumour, analgesic, and cardiovascular activity (see Figure 3-1).

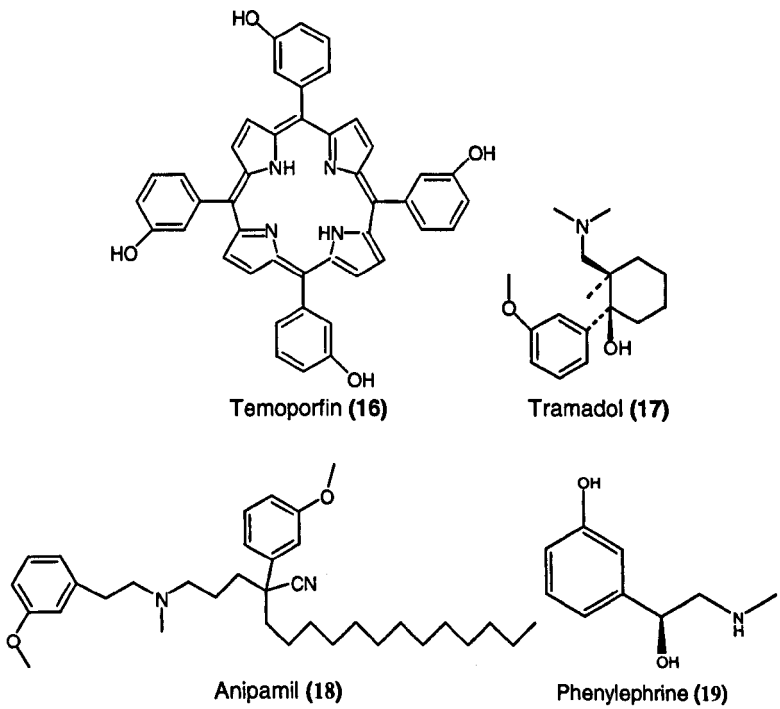


FIGURE 3 - 1: SOME COMMERCIALLY IMPORTANT META-ALKYLPHENOLS

Temoporfin (16) (Foscan-PDT) is a new and powerful antitumour agent introduced recently by Scotia Pharmaceuticals.[173] Tramadol (17) is a post-operative analgesic.[174] Anipamil (18) is a cardiovascular agent and Phenylephrine (19), a monohydroxy epinefrin analogue, is used to treat many illnesses, from acute hypotension to eye disorders, in nasal decongestants, and local anaesthetics for ear, nose and oropharyngeal uses.[175] It is currently produced in 7-8 steps with an overall yield of 8 - 20 %.

1.1.1.Vinylphenols

Meta-substituted phenols are more costly to obtain than other alkylphenols because alkylation of phenol (or hydroxylation of an alkylbenzene) at the meta-position is not favoured.

The potential of CNSL to produce compounds such as m-vinylphenol (MVP) (**20**) that could be used, e.g., to synthesize phenylefrine in higher yield was considered.

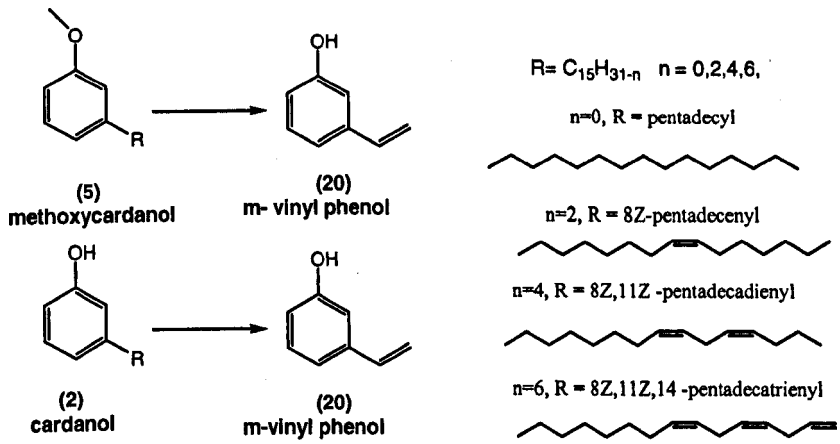
At present, the two most important applications of poly(vinylphenol)s are as photoresist materials for the DRAM (dynamic random access memory)[176,177,178] and in the formulation of engineering thermoplastics (PEEK, and PAEK),[179] as short-chain m-substituted phenols introduce more plasticity and lower the extrusion/injection temperature. Vinylphenols have strong anti-nematocidal properties.[254] p-Vinylphenol is currently manufactured via decomposition of bisphenol ethane, or via dehydrogenation of p-ethylphenol.[271]

1.1.2.Propylphenol

m-Propylphenol (MPP), a constituent of cow urine, is used as the main constituent of attractants to catch the tse-tse (*Glossinidae*)[180] and the stable fly (*Muscidae*).[181] Tse-tse flies are a major plague in the African continent as they carry a protozoan parasite that causes sleeping sickness in both humans and cattle.[182] The current price of MPP is £1600 per kilogram.[183] Due to its common structural feature with cardanol, it looks an attractive target if it could be obtained at a competitive price.

1.1.3. Short chain phenols from CNSL

m-Vinylphenol (MVP) (**20**) can be obtained from cashew nut shell liquid, cardanols (**2**) and methoxycardanols (**5**), by pyrolysis in the gas phase at 500 - 800 °C.



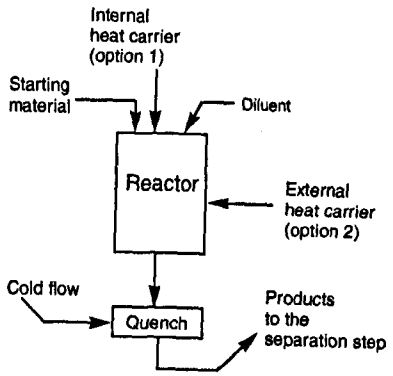
SCHEME 3 - 1: MVP FROM METHOXYCARDANOLS AND CARDANOLS

This claim was first made in 1950 by Evans, in a British patent[184, 185] and recently in 1996, by Bending in two German patents.[186, 187] CNSL pyrolysis was also investigated by Khan and co-workers[188, 189] who cracked CNSL at 500 - 550 °C at atmospheric pressure, but used the resulting phenolic fraction to manufacture resins without identification of its individual components.

1.2.Pyrolysis

1.2.1.The principle

Pyrolysis is basically the thermal decomposition of a molecule in the absence of air, or oxygen.



SCHEME 3 - 2: PYROLYSIS PROCESS

An illustrative scheme of a typical pyrolysis process is represented in Scheme 3-2. The starting material, sometimes mixed with a diluent (usually steam), is introduced into the reactor, where it is heated as quickly as possible to the temperature of the reaction, using an internal heat carrier, or by external heating of the reactor. At the outlet of the reactor and to stop the reaction, the hydrocarbon mixture is quenched, by mixing with a cold flow (which can be inert or the starting material itself, or a fraction of the cooled product), and then the cooled material goes to the separation step. The reaction can be performed in a batch ('destructive distillation') or a continuous system.

1.2.2.Pyrolysis mechanisms

The total number of elementary reactions which can occur during pyrolysis, can be very high even for a simple molecule. It is generally agreed that pyrolysis often proceeds by a radical chain mechanism. This was proposed by Rice-Herzfeld (1930)[190,191,192] and slightly modified later,[193] and seems to give qualitative coherence to most experimental data. Retro Diels Alder reactions,[194] pericylic reactions,[195,267] and reactions involving nitrene,[196] or carbene,[197] intermediates have also been proposed to explain complex mechanisms of certain pyrolysis reactions.

1.2.3.Parameters

The main parameters that control the process are not only the classic parameters of a chemical reaction (partial pressure, temperature and residence time in the reactor) but also the heating rate, the quench, and coksification of the reactor.

Heating/quenching rate

In the pyrolysis of tar[198] and more recently in biomass studies,[199,200] the heating rate was proved to be important. Slow heating, and extended reaction times are more likely to increase the yield of char. The quenching time/temperature is also important in determining the product distribution. If high temperature kinetics and equilibrium favour the formation of desired end products, these can be meta- stable at these temperatures and so can undergo secondary transformations at the time of cooling.

Coke/Tar

Coke/tar formation is a major concern in pyrolysis units. The techniques commonly used to reduce coke formation are based on the use of a range of additives,[i] the design of the reactor, and more important, on the use of steam, which besides reducing the partial pressure of the reactants, gives the water-gas shift reaction:

$$C + H_2O \longrightarrow CO + H_2$$

Coke is formed by at least three mechanisms.[201,202] First, through polymerisation/condensation and agglomerating in the gas phase. The condensation into tar droplets is followed by adsorption on surfaces that lead to dehydrogenation into coke. This generally results in film or globular coke formation. Coke precursors include ethylene, propylene, butadiene, acetylene and benzene, all of which are produced to some extent during most pyrolysis reactions. [203,214,204] Secondly, coke can grow directly through the reactions of small gas phase species with sites on the coke surface. These species are likely to be olefins and free radicals such as methyl, ethyl, vinyl, phenyl or benzyl. This mechanism is favoured by higher temperatures and higher concentrations of reactive species (see for example, Mauss[205] for surface growth mechanisms of soot-like particles).The metallic surface of a reactor is reported to catalyse the growth of a filamentary type of coke, which contains metal granules and is magnetic in character; these metals granules are derived from the surface of the reactors constructed of high alloy steels. Such coke occurs, for example, on the surface of nickel-chromium-iron alloys used in commercial reactors but not on glass surfaces.[206, 207, 208]

[i] Including salts of alkali metals or alkali-earth metals at ppm levels, which are believed to promote coke gasification by steam. In addition, the use of organic polysiloxane compounds in ppm quantities reduces the adhesion of coke to the walls. Sulfur compounds have also been used widely to suppress coke formation, especially early on in the pyrolysis process, by deactivating metal surfaces.[(275)]

1.2.4.Laboratory techniques

Chemists have used many techniques to perform pyrolytic reactions for both kinetic studies and preparative chemistry. These can be classified into three major groups:

1- Low temperature, slow heating and static systems

These batch systems are used,[225] at low temperature (25 - 550 °C) and low conversion; an example is represented in the Figure 3-2 where pyrolysis occurs at reflux temperature, the product being more volatile than the starting material.

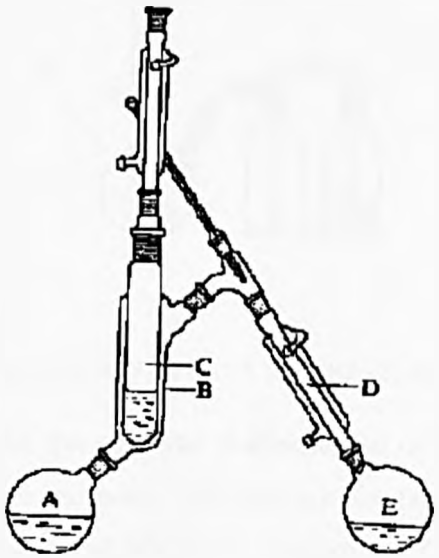


FIGURE 3 - 2: STATIC SYSTEM OF PYROLYSIS

The reactant is heated in flask A. The vapour (product and reactant) passes to chamber B, when the undecomposed reactant condenses on the finger C and returns to A, while the product passes to the condensor D and is collected in receiver flask E. This technique was used by Khan in his CNSL pyrolysis study.[188, 189]

Medium to high temperature - gas carrier & flow reactor systems

Studies with continuous tubular flow reactors were historically associated with medium to high temperature (300 - 600 °C), high partial pressure, residence times of 1 - 30 sec, at atmospheric pressure. An example is given in Figure 3-3.

The reactant is dropped at a constant rate from funnel A into the reactor B, which may contain glass beads as heat transfer carriers; a T-connection provides an inlet to add a diluent if required. Products are collected in flask D, which is cooled to a temperature at which it condenses and no reaction continues.

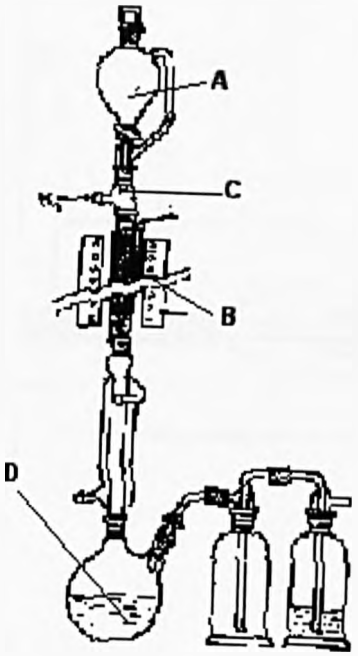


FIGURE 3 - 3: A CONTINUOUS MEDIUM TEMPERATURE PYROLYSIS SYSTEM

This apparatus is suitable for the pyrolytic β-elimination of esters, which happens in the range of 300 - 600 °C, where secondary products are not favoured.[209] A reactor following this principle was used by Evans and Whitney in their study of CNSL pyrolysis.[184]

Fast reactions & Flash Vacuum Pyrolysis (FVP)

In pyrolysis reactions which employ high temperature (650 – 1800 °C), secondary (mainly bimolecular) reactions become inevitable and therefore need to be inhibited; however previously reported methods show this to be difficult to control.[209] FVP[i] techniques are ideal for these systems, where the principle is to flow a gas at very low pressure into a compartment at high temperature where the molecules decompose (unimolecularly). A typical installation is shown in Figure 3-4.

[i] Curie point pyrolysis technique can also be used to study very fast pyrolysis reactions (in this case the thermal energy is supplied by a high frequency induction field, giving rise to a temperature profile from room temperature to 300 - 900 °C in less than 0.1 sec). However this is only an analytical technique.

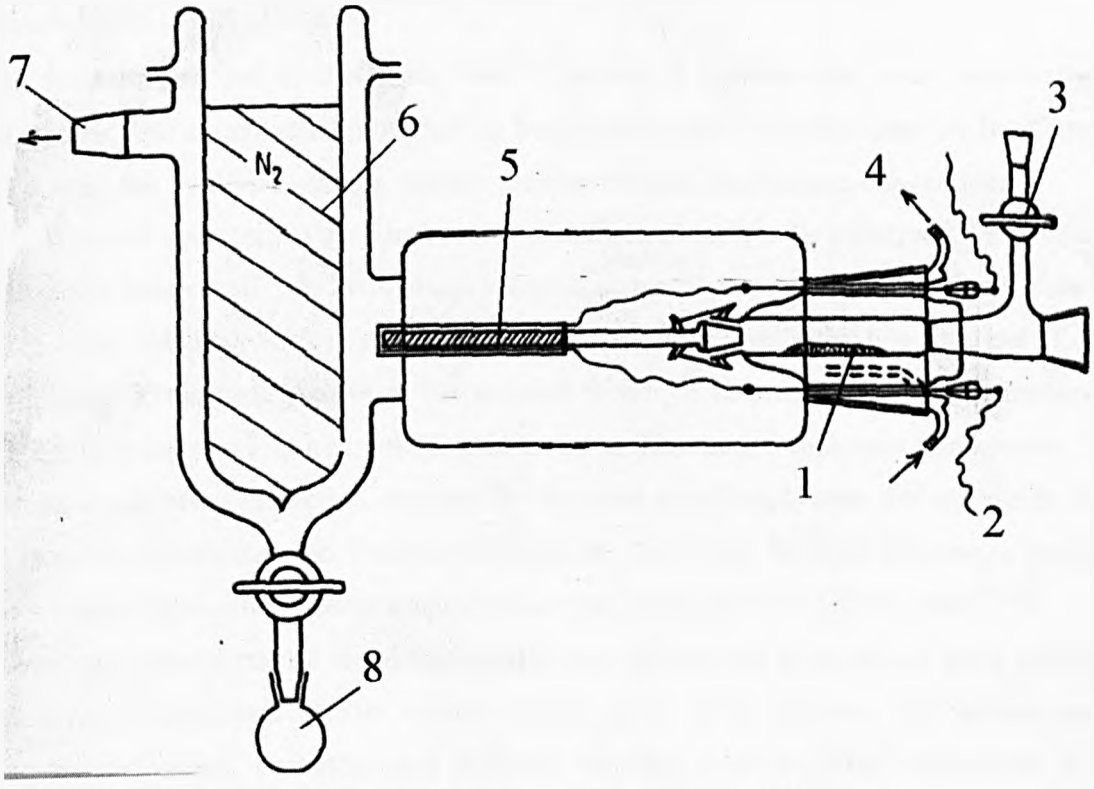


FIGURE 3 - 4: TYPICAL FVP SCHEME [211]

The solid sample to be pyrolysed is introduced in the sublimation chamber (1) where it is volatilised by heating with an electric resistance (2) in an inert gas atmosphere, continuously introduced through the tap (3). The volatiles flow to the reaction chamber (5). The mixture is then quickly cooled using a liquid nitrogen cold finger (6) connected to a high vacuum pump (7). The product of the reaction is collected in the receiver (8). A typical residence time is in order of a millisecond.

In the case of pyrolytic reactions at very low pressure (less than 0.1 mm Hg) the thermal excitation of molecules occurs mainly by molecule–wall collisions. The residence time has been calculated to be a function of molecular velocity (an intrinsic property of the molecule) and reactor geometry, and is independent of the pressure and the addition rate of the substance.[210] If the compound to be pyrolysed is carried into the reactor in a stream of inert gas at pressure of at least 10 mm Hg, the thermal excitation occurs mainly by molecule-molecule collisions. In this case residence time is a function of the pressure drop in the reactor and of the viscosity of the gas.[211]

FVP has been used not only for mechanistic investigations but also for preparative organic synthesis, such as the preparation of highly reactive intermediates[212] and fullerene fragments.[213]

1.2.5.Industrial reactors

Because the purpose of this work was to develop a method that could potentially be developed into an industrial procedure, it was important to know that there are two families of continuous pyrolysis reactors, namely the conventional and the non-conventional.

Conventional reactors are tubular furnaces where compounds to be pyrolysed flow inside an externally heated coil. The main disadvantage is that, with time, the reaction forms a deposit of coke on the inner surface of the tube, which reduces not only the flow rate but also the efficiency of the heat transfer to the reaction media. If conversion is to be maintained a higher heat input is required, resulting in a rise in the external tube skin temperature. This increase reaches a maximum imposed by the tube metallurgy, then the run needs to be stopped to decoke the tube. Despite this question, more than 80 % of ethylene is produced by a multibillion-dollar industrial pyrolysis process using tubular oven reactors.[214,215]

Non-conventional reactor technologies have been introduced to minimize these problems. They have direct heat transfer systems, using gas or solid carriers. Gas carriers can be superheated steam, or oxygenated products resulting from a partial combustion of the feedstock. Solid heat carriers are used in reactors where the solids are in movement (most use fluidised bed, or riser technologies). In this case the coke is deposited on the solids which are then removed from the reactor, regenerated by burning the coke and reintroduced in the reactor. The main disadvantage is the need for costly and complex engineering to ensure correct recycling of the solid heat carriers.[216]

1.3.Yields from published CNSL pyrolysis procedures.

1.3.1.Pyrolysis in a batch reactor

Khan [188,189] cracked CNSL at 500 - 550 °C, in a batch reactor, using atmospheric pressure. They fractionated the product by distillation and alkali separation obtaining phenols substituted with a hydrocarbon chain varying between C_4 and C_6 length (9 % weight of CNSL). Subsequent research, using an alumina-silica-zirconia solid catalyst, afforded an increased yield of 23 % of low molecular phenols. The fraction was used to give non-flexible phenolic resins, and was not separated and characterised in terms of its individual components.

1.3.2.Pyrolysis in tubular reactors

All the CNSL pyrolysis experiments performed in tubular reactors and reported in patents (See Table 3-1) gave m-vinylphenol in low to medium yields (12 - 27 %).

TABLE 3 - 1: LITERATURE DATA ON CNSL PYROLYSIS

Reference:	Starting material	Temp (°C)	Liquid product (g)	Yield of MVP (%)	Observations
BP 669 074/ USP 2698868/	1600 g Cardanols + 2070 g superheated steam @ 360 °C	580	977	13	Residence time 0.146 sec . Process gave 597 g of high boiling compounds
BP 669 074/ USP 2698868/	5000 g Cardanols + 11428 g superheated steam @ 360 °C	600	6500 a)	26.4	Process gave 520 g of high boiling compounds
BP 669 074/ USP 2698868/	900 g cardanyl methyl ether + 1658 g superheated steam @ 350 °C	650	440	12.4	----------
BP 669 074/ USP 2698868/	550 g p-hexylphenol+ 3606 g superheated steam @ 350 °C	580	380	47 b)	90 g of high boiling compounds
DE 196 45 287 A1 (1996)	10 g technical CNSL	400	----------	12	Fixed bed reactor Catalyst H Mordenite
DE 196 45 287 A2 (1996)	Cardanols (unknown amount)	550	----------	69	Fluidised bed reactor

a)This include both the organic and the aqueous phase; b) vinylphenol obtained in this case was p-vinylphenol

1.3.3.Pyrolysis in a fluidised bed reactor

The last German patent DE 196 45 287 A2 (1996) reported in Table 3-1 used a fluidised bed reactor, which is a reactor in which the reactant in the gas phase is in a fluid-like state over a solid catalyst. Although the figures are not absolutely clear, it appears that at least 27 %[i] of the cardanols are transformed into coke, which if left would eventually deactivate the catalyst.

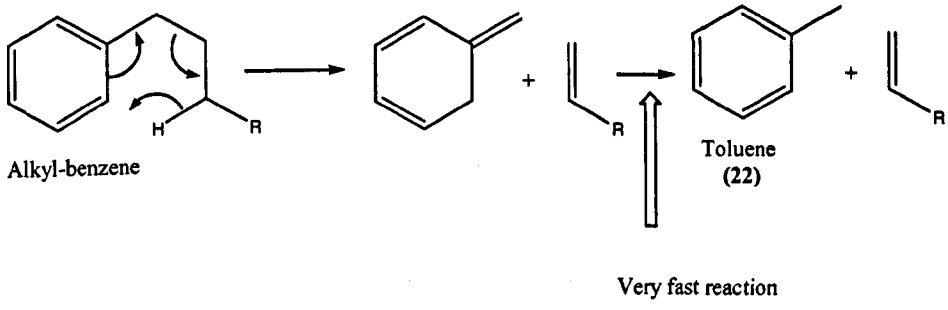
1.4.Understanding CNSL FVP with model compounds studies

1.4.1. Aromatics vs linear carbon chain

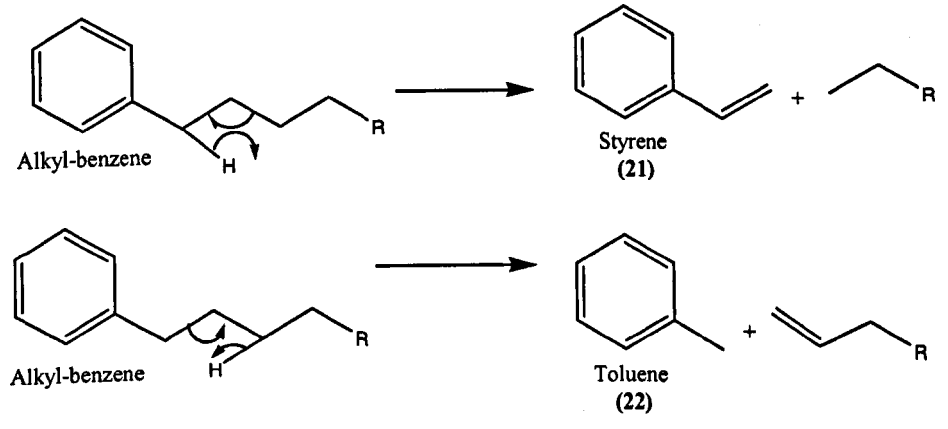
Previous studies have recorded the conversion of aromatics and alkanes at 800 °C; benzene yields 4 - 18 % of scission products using residence times of 0.27 - 2.07 seconds, while n-decane gives conversions of 64 - 99 % with 8 - 29 milliseconds. [217,218] Therefore side chain cracking is the dominant process in the pyrolysis of alkyl-aromatics (e.g. ethyl,[219,220

[i] In the case of DE 196 45 287 A2(1996) it is reported that 50 % of the products are phenols (35 % MVP, 10 % EP, 3 % meta-cresol, and 2 % phenol), and the remaining are gases. To produce 50 g of phenols will need at least: (35/120 + 10/122+ 3/ 108 +2 / 96) 304 = 127 g of cardanols, because the remaining 50 g are gases and gases, meaning that 27 g remaining of the lateral linear chain of cardanols are transformed in tar and coke, which would quickly deactivate the catalyst.

propyl,[221] butyl,[222] dodecyl,[223]and tetradecyl/pentadecyl benzene[224]). Performing the reaction under two experimental conditions: (e.g. low temperature (400 ^{0}C) and high residence time (15 to 180 minutes) in a batch reactor and very high temperature (800 °C) and very small residence time (a fraction of a second, in a plug-flow reactor) affords in either case, toluene and styrene as the main products. Retro-ene and a 4-centre pericyclic mechanisms[225] were proposed to explain the appearance of styrene (**21**) and toluene (**22**), but these explanations were dismissed, on the basis of deuterium labelling studies, in favour of a radical mechanism.[224]

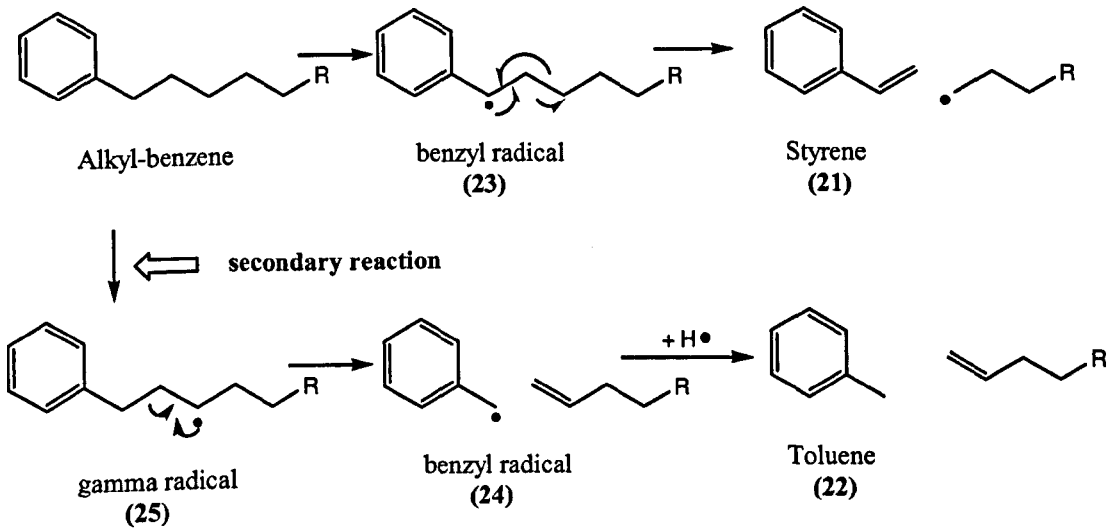


SCHEME 3 - 3: PROPOSED RETRO-ENE MECHANISM



SCHEME 3 - 4 :PROPOSED PERICYCLIC MECHANISM

A possible radical mechanism is described in Scheme 3 - 5 , where in the propagation step, a benzyl radical (**23**) is formed though hydrogen atom abstraction.



SCHEME 3 - 5: PROPOSED RADICAL MECHANISM

The stability of the resonance stabilised benzylic radical is higher than the corresponding primary or secondary radical, and the benzylic carbon-hydrogen bond is 40 kJ weaker than a secondary carbon- hydrogen bond.[240, 226] The radical formed then undergoes a homolytic cleavage at the ß position of the chain giving styrene.

Researchers have postulated that in the propagation step, an alternative mechanism could be followed, in which a γ radical induces a ß cleavage, followed by abstraction of an hydrogen, to yield toluene. The γ radical is thought to be very reactive, since upon ß scission, it forms a resonance stabilized benzylic radical.[222, 224] Other radicals, generated by the abstraction of hydrogen on any other carbon in the chain, would also undergo successive cleavage by ß scission. Because the concentration of the γ radical would be small compared with the benzyl radical (**23**), and the models could not justify the amount of toluene (**22**) obtained experimentally, Freund pointed out that initiation by a carbon-carbon homolytic cleavage could give directly the benzyl radical (**24**) which after hydrogen abstraction would give (**22**).[i]

The apparent rate of cracking increases with side chain length (effect more pronounced when the side chain contains less than five carbon atoms); this was explained as a function of the hydrogen abstractable steps in the alkyl chain.[227]

Styrene has also been obtained by pyrolysis of phenylethylamine, dibenzylpropane and dibenzylbutane.[228,229,258] Toluene has been shown to be stable in pyrolytic conditions approaching 750 °C.[230] Pyrolysis of duodecylbenzene, at low temperatures (320 - 420 °C)

[i] In the case of the butyl-benzene pyrolysis, Freund developed a complex model (with 60 equations), matched well for overall conversion and selectivity for the major products. (See reference 222)

using extended reactions times (up to 90 h) (mimicking geological reactions), gives toluene as the major product, and a large fraction of ethylbenzene appears through reductive processes.[223]

1.4.2.Role of the hydroxyl group in pyrolysis of alkyl aromatics

Due to a weak effect of stabilisation of the benzyl radical, the hydroxyl group in the aromatic ring has a very small weakening effect on the bond energy $C_{\alpha \text{ to the ring}}$-$C_{\beta \text{ to the ring}}$.[231] Compared with ethylbenzene, the bond strength of ethylphenol is reported to be 2.9 kJ/mol weaker.[232] Individual cresols (methyl-phenols) have also been subjected to thermal cracking, with many data showing that m-cresol is the more stable isomer. At 816 °C, using a ratio of steam/hydrocarbon 10/1, and a residence time of .05 sec the conversion of the m-isomer is only 5 % while it is 15 % for o-cresol, and 13 % for p-cresol.[233] Braekman carried out the pyrolysis of a phenolic fraction of a tar at a temperature of 700 to 800 °C and a residence time of 2 sec in a plug flow reactor. A maximum yield of m-cresol was obtained at 775 °C. The phenol, cresols, and the xylols were virtually non-existent at 800 °C. The existence of vinylphenol in the product was not indicated explicitly, but a "non identified phenols fraction" varied from 30 % at 700 °C to more or less zero at 800 °C.[234] o-Ethylphenol was also subjected to pyrolysis at 750 °C and the main products were phenol and o-hydroxystyrene. Ethyl-phenol inhibited the rate of cracking of dodecane, but dodecane accelerated the cracking of phenol.[235] Under pyrolytic conditions phenol is stable until 780 °C but undergoes total conversion at 889 °C with residence times smaller than 180 sec giving as the major products carbon monoxide, cyclopentadiene and benzene.[236,237,238] There are no studies reporting the existence of a 1,3-dihydroxybenzylic radical that could be expected from the alkenylresorcinolic species present in CNSL.

1.4.3. Potential behaviour of an allylic chain in pyrolytic conditions

The effect of the unsaturated linear carbon chain of the CNSL constituents is not so straightforward. Among the different steps in pyrolysis reactions (initiation, propagation, and terminations), initiations reactions are the slowest, as they have higher activation energy. For example for alkane cracking, Alara[239] reports 355 kJ/mol for initiation, 125 kJ/mol for C-C cleavage of a radical, and 50 - 62 kJ/mol for hydrogen transfer, the two main reactions in the propagation step, and 0 kJ/mol for the termination step. The rate of initiation determines the global rate of the reaction and therefore overall conversion of the starting material. Initiation reactions are homolytic carbon-carbon bond cleavage, as the C-C bond dissociation energy is lower than the corresponding C-H.[240] The most important constituents

of the technical CNSL are represented in the Figure 3 - 5 with the C-C bonds susceptible to cleave in the initiation step labelled.

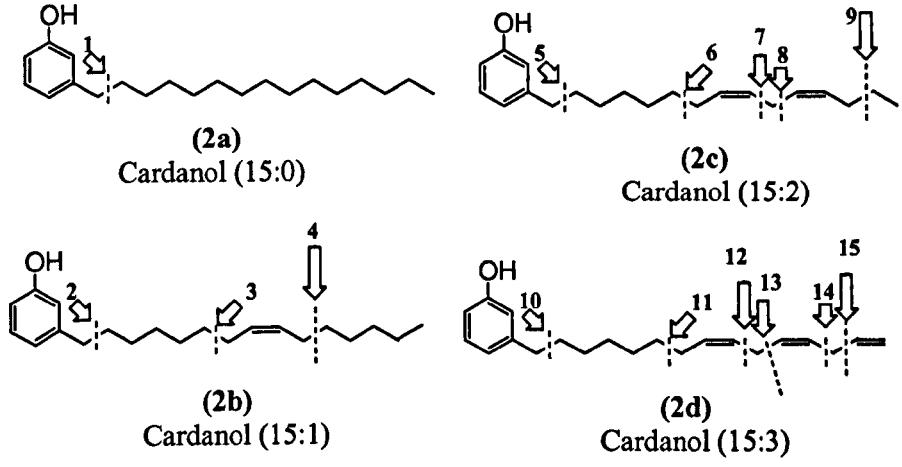


FIGURE 3 - 5 :REACTIVE BONDS IN INITIATION STEP

Cleavage on the bonds 3, 4, 6, 9, 11 would generate allyl radicals.[241,242]

The energies necessary for these cleavages, in pyrolytic conditions, have been suggested to be roughly similar to those for the dissociation of the bonds 1, 2, 5 or 10 which would give benzylic radicals.[243] Once generated, these radicals could follow the classic Rice mechanism (see on page 74). The energy required to cleave the bonds 7, 8, 12, 13, 14, and 15 is unknown. No experimental measurement of the C-C bond dissociation energy of a double allylic compound is reported, but based on a semi-empirical model, Luo[244] stated that in the case of 1,4 pentadiene it would be 40 kJ/mol lower than the benzylic energy.

The possible involvement of allylic radicals in the production of tar is less useful, from a synthetic point of view. Cycloaddition of an allylic radical to an olefinic bond is a basic reaction for formation of C_5 cyclic compounds.[201] These compounds dehydrogenate in pyrolytic conditions to give aromatics and ultimately polycondensed aromatics, which lead to the tar formation.[245]

1.4.4. Expected secondary reactions

Light gases like acetylene, butadiene (which could result from the cracking of the phenolic ring),[238] ethylene and vinyl aromatics have also been characterised as tar precursors.[201] A mechanism (*i.e* radical addition reactions of C_2-C_5 hydrocarbons with aromatic rings) has been postulated for polyaromatics/soot formation and growth.[246]

1.4.5. MS considerations

The primary pyrolytic products could be estimated on the basis of thermochemistry or using a correlation with the mass fragmentation of the same molecule. The latter approach relies

on the fact that mass spectral (by EI) and pyrolytic fragmentations appear to be closely parallel. This looks strange as the reactive species are different (a radical in most pyrolysis and a radical cation in MS-EI). More suspicious is that there are no references about this correlation in standard MS books, and the huge (and easily available) body of MS information is not systematically used today to justify/ extend the validity of the new pyrolysis reactions reported. But this approach has been (and is still) used in pyrolysis papers, and a first approach to the theoretical basis[247] of this correlation was developed using a perturbation molecular approach to the interpretation of mass spectrometry and its relation with photolytic/thermolytic reactions, and was supported by Ian Fleming, a leading chemist in the field.

The MS of individual cardanols (15 : 0), (15 : 1), (15 : 2) and (15 : 3) show a base peak at M = 108 while MS of cardol (15 : 0), (15 : 1), (13 : 3), (16 : 3) show it at M=124, indicating the presence of a resonance –stabilized hydroxy benzyl ion or of the respective dihydroxy species. The intensity of the remaining peaks between the molecular peak ion and the base peaks is very small indeed.

This suggests that the most likely first intermediate in a FVP of both most important CNSL constituents would be the corresponding benzylic radicals. However while the existence of 3-hydroxybenzylic radical has been reported in the literature, the existence of the dihydroxybenzylic congener is unknown.

1.4.6. Conclusions

From the evidence collected it appears that vinylphenol could be obtain from CNSL. Its main constituent, cardanol – a mixture of alk(en)yl phenols, could in FVP conditions, generate radicals by unimolecular decomposition of the most labile bonds, which will undergo reactions similar to the ones shown in the Scheme 3 - 5 giving m-vinylphenol. The fact that anisole[248] afforded phenol under pyrolytic conditions at 640 °C and atmospheric pressure may also explain why methoxycardanols (in Evans pyrolysis of cardanols derivatives) also yielded the same range of products as cardanols.

The formation of the dihydroxybenzylic radical or the possible formation of vinylresorcinol from cardol have not yet been reported, but its existence has been suggested by EI-MS. The place of C-C bond scission in the initiation step, which creates the first radical, is predicted differently based on two different approaches. The first one, a "bond dissociation energy" approach, suggests strongly that it will be in a bond which is in a position α to one double

bond and vinyl to another double bond,[i] while the second one, based on EI-MS analysis suggests that the benzylic position would be predominant. It is also unclear what kind of role the aliphatic chain of CNSL constituents and the possible vinylaromatics and others olefin generated in the reaction could have in the genesis of tar–like compounds or if suitable manipulation of the process could inhibit or minimize these unwanted products.

2. METHODOLOGY

The purpose of this study was to evaluate the possibility of using CNSL to produce MVP in high yield through a pyrolysis process without the use of solid catalysts that need to be continuously regenerated. Not only is the design of the equipment expected to be much simpler but also the capital and operational cost of this kind of installation are expected to be lower.

From the literature, it could be hypothesised that decomposition of CNSL would be favoured in FVP conditions operating at:

a) Low pressure (intramolecular radical reactions are favoured, it also inhibits aromatic condensations).
b) Short reaction time (the likelihood of secondary reactions is reduced).
c) Temperatures between 650 - 850 °C (allowing the cracking of the olefinic and saturated chain, but reducing the possibility of cracking of the aromatic ring).
d) High heating rate.
e) Fast cooling rate.

Despite the fact that most conventional pyrolytic reactors (used in industry) operate at atmospheric pressure, and the partial pressure of the reactant is reduced by the introduction of steam, the main reasons for using flash vacuum techniques are:

- The fact that the vaporisation of CNSL is more likely to occur at low pressure. Previous researchers agree that minimum polymerisation occurs in CNSL distillation when it is carried at reduced pressure.[249,250]
- The elimination of products generated by contact of steam with the phenolic residue.

One of the main arguments against the use vacuum in industrial conditions has been the cost of the overall heat transfer in vacuum conditions, but recent studies have shown that when using a vacuum of 0.5 atm, the heat transfer coefficient is 90 % of the value at atmospheric pressure.[251]

The potential deliverables using this approach would be:

a) data about mechanistic pathways,

[i] Positions 7,8,12,13,14 or 15 in the Figure 3-5

b) the effects of the reaction conditions on the yields, but also

c) an examination of the feasibility of scale up of such a process

3. RESULTS AND DISCUSSION

3.1.CNSL Flash Vacuum Pyrolysis in a small diameter reactor

3.1.1.Apparatus and preliminary experiments

The first approach was to use a slight modification of the FVP equipment used by Trahanovsky.[252] As the starting material was a liquid, the sublimation unit was eliminated to give the apparatus shown schematically in Figure 3-6. The reaction chamber was a quartz tube (0.75 cm wide x 30 cm long) (A) mounted 30° to the horizontal in an electrical tube furnace (B) fitted with alumina end plugs. The quartz tube was connected to a collector flask (F), a liquid nitrogen cooled trap connected to a vacuum pump (G) of 0.1 - 5 mm Hg.

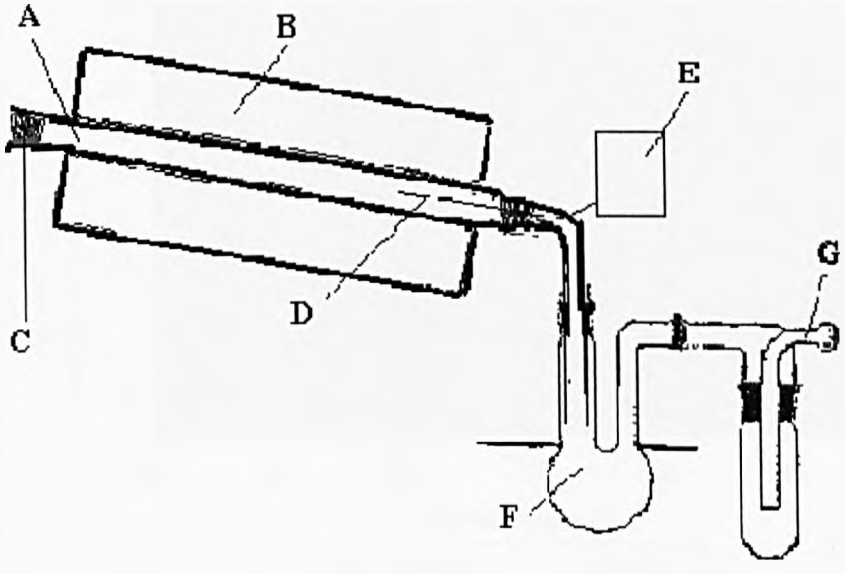


FIGURE 3 - 6: FLASH VACUUM PYROLYSIS LABORATORY APPARATUS

The CNSL was introduced through a septum (C), using a 250 µl GC syringe, where it was rapidly vaporised and transported to the reaction zone and cracked. In a typical run 1 ml of compound was fed over 5-6 hr using 250 microliter aliquots. In the first runs, the temperature was measured continuously during the reaction by a probe (D) introduced in the reactor. In a typical run fluctuations of 1 - 3 °C were observed. As the temperature recorded by the probe was similar to the one displayed by the control system in the oven, subsequent runs only used the oven display. The products and unconverted starting oil were trapped in a

flask (F). In a typical experiment, 15 minutes after the last injection of CNSL, the vacuum was broken, the crude sample was brought at room temperature, weighed, dissolved in deuterated chloroform, and filtered through cotton wool into an NMR tube to provide NMR spectra and GC of the mixture for characterisation. At the end of each run, the apparatus was dismantled, and the reactor tube was cleaned.

3.1.2. Crude yields & qualitative identification of the products

(i)General

In order to understand the optimum conditions, a range of temperatures (600 - 850 °C) was investigated. For each temperature, the experiment was done twice to ensure reproducibility. The precision of the data can be inferred from the figure where the crude yields obtained at a range of temperatures are plotted. In general, these data exhibit acceptably low scatter at higher temperatures.

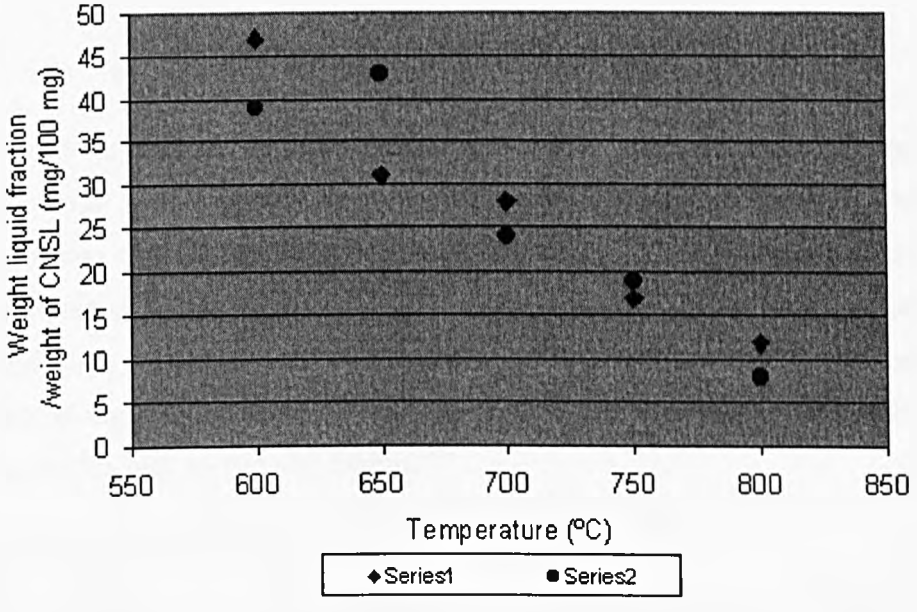


FIGURE 3 - 7: CRUDE YIELDS FUNCTION OF TEMPERATURE

(ii) Tar deposits

In each run, a significant amount of tar was deposited at the inlet and outlet of the apparatus. Other parts of the reactor remained clean. At 750 °C, the amount of tar recovered was around 30 % of the mass of CNSL injected. In an attempt to reduce tar formation, emulsions of water-CNSL (0.2 : 1, 0.5 : 1, 1 : 1, and 2 : 1) were injected at 750 °C; however no clear improvement in the tar reduction or in the yield of the products could be noted.

(iii) GC of the crude product mixture

Analysing the mixtures obtained at 650 and 730 °C by DI-MS suggested the presence of cresol, 3-ethylphenol, 3-propylphenol, and 3-vinylphenol. This was confirmed by comparison of the pure compounds using GC. The GC analysis (see a typical trace in Figure 3 - 8) shows four prominent peaks in addition to cardanols.

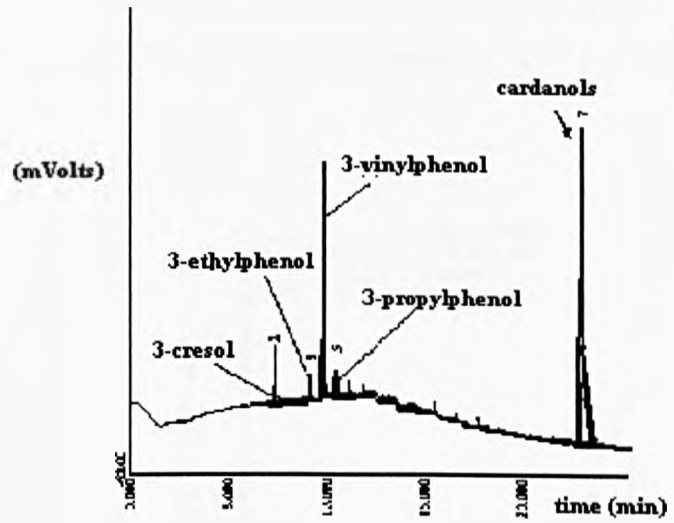
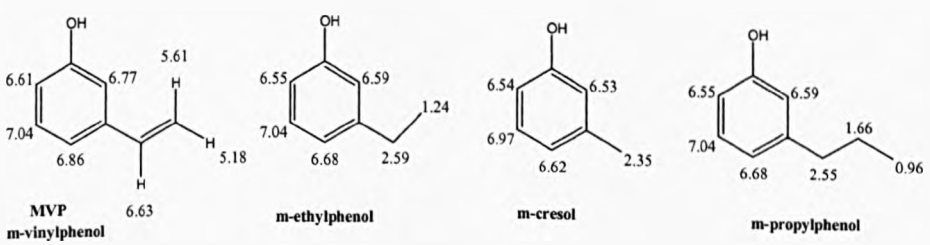


FIGURE 3 - 8: GC SPECTRA OF FVP PRODUCTS AT 600 °C

3-Cresol and 3-ethylphenol were obtained from Aldrich. Because they were commercially unavailable, both 3-propylphenol and 3-vinylphenol were obtained through synthesis. 3-propylphenol was obtained, using a published method, in 67 % yield, through a Grignard reaction between 3-hydroxybenzaldehyde and ethyl magnesium bromide, followed by a catalytic reduction using hydrogen and palladium.[253] 3-Vinylphenol was obtained in 45 % yield by the Wittig reaction using 3-hydroxybenzaldehyde with triphenylmethylbromide in the presence of 2.5 mol eq. of butyl lithium.[254]

(iv) HNMR analysis of the crude product

HNMR chemical shifts of the four phenols detected by GC are presented in Figure 3 -9.



Numbers refer to the chemical shift in ppm in $CDCl_3$

FIGURE 3 - 9: CHEMICAL SHIFTS OF THE MAIN PHENOLS IN CNSL FVP

Examination of the crude HNMR spectrum of the crude pyrolysis products of CNSL at 750 °C (see **Figure 3-10)** clearly indicates the formation of a vinylic signal with a coupling pattern corresponding to a monosubstituted vinylic structure at δ 5.3 and 5.8. HNMR spectroscopy thus clearly confirmed the presence of MVP fraction and the loss of many long chain methylene resonances when compared with CNSL. The HNMR spectrum was highly complicated, showing overlapping patterns. GC/GC-MS results showed no trace of starting material could be observed, but did show the presence of MVP and MPP.

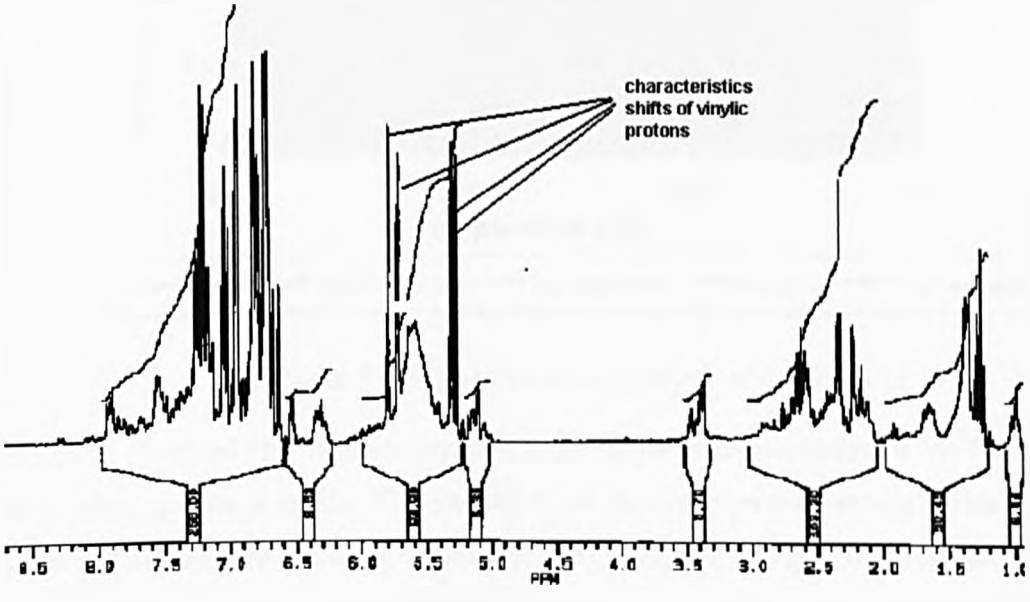


FIGURE 3 - 10: ^{1}H NMR SPECTRUM OF CRUDE PRODUCTS OF FVP AT 750 °C

3.1.3.Quantitative analysis of the condensable fraction

The Figure 3-11 shows the relative mass percentage of the phenols detected by GC in the crude reaction mixture when Brazilian CNSL was pyrolysed, at a range of temperatures.

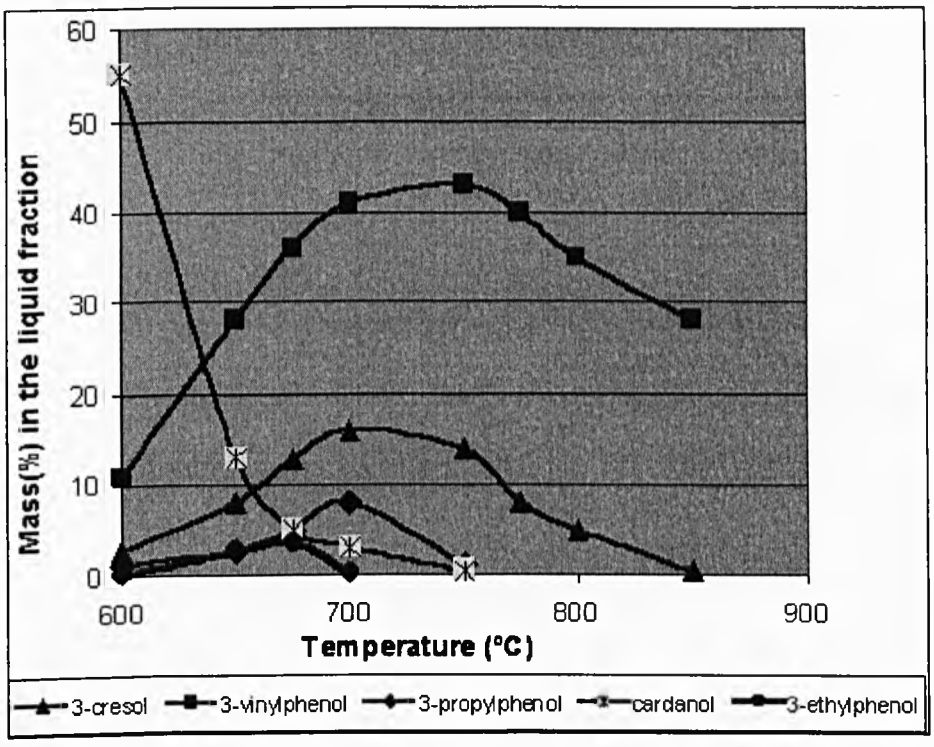
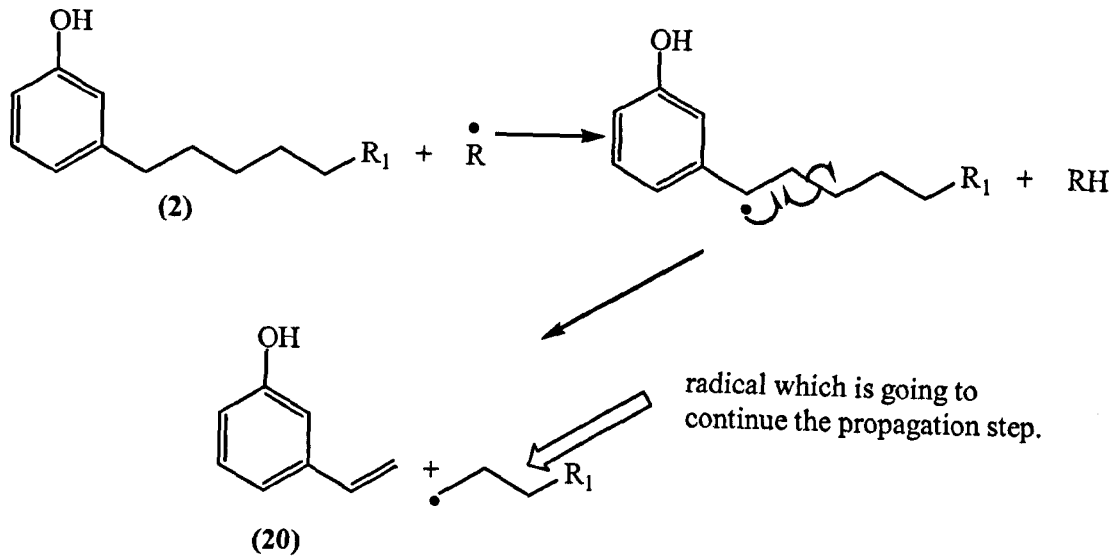


FIGURE 3 - 11:Flash vacuum pyrolysis of CNSL-Braz

It can be observed that the concentration in the crude product mixture of MVP is far greater than others products at 750 °C being 42 % of the crude product mixture. However at this temperature the liquid fraction recovered was only 192 mg/g CNSL (containing approx. 91 % cardanols); this corresponds to an overall 21 % yield (yield being defined as the number of moles of MVP/number of moles of cardanols). The main products of CNSL pyrolysis under the conditions of these preliminary experiments, besides coke are MVP, MC, MEP and MPP.

In the light of literature information, it is reasonable to propose that once radicals have been formed in the initiation step, they produce a benzyl radical by hydrogen abstraction from cardanols, which would give vinylphenol (**20**) and a radical by β-scission. This new radical would also abstract a hydrogen atom continuing the propagation step.



SCHEME 3 - 6: MVP FROM CARDANOLS

Hydrogen abstraction from other position on the chain would create other radicals; these by successive β-scissions would generate the small-chain alkylphenols obtained.

3.1.4.Preliminary conclusions

Preliminary data demonstrated that both MVP, MPP could be obtained from CNSL using FVP at a range of temperatures. Disappointingly, the best yields were low (*i.e.* 21 % for MVP at 750 °C, and 9 % for MPP at 700 °C). Neither these experiments, nor literature information, allow an estimate of how much additional vinylphenol could have been produced at the expense of tar, by modification of the parameters of the process. The answer to this important question was the focus of the next piece of work. Another unclear question was the fact that no products with di-hydroxyaromatic structure could be isolated, so it was unclear if cardols follow the same pattern as cardanols.

3.2.Cardanol pyrolysis in medium sized quartz reactors

Before additional work could be done on pyrolysis it was important to reduce or at least understand how tar was being produced. Obtaining 50 % of the starting mass as tar at the entrance and exit of the furnace is a problem reported in a recent study of FVP of other phenols,[258] and no solution to this problem was found. In order to simplify the factors involved in the production of tar, cardanols was used instead of CNSL. The potential advantage of this option was to eliminate both the aggregate and the cardols/methylcardols component of the oil. The aggregate contains metallic salts and no compounds with cardols/methylcardols structure could be found in the products of preliminary pyrolysis

experiments. Furthermore, previous work at the BioComposites Centre suggested that cardols were not stable at more than 400 °C.[183]

In order to obtain larger quantities of products, the diameter of the quartz tube reactor was increased to 0.5 cm id, the remaining part of the laboratory equipment being the same. An additional modification was, however, that at the end of the reaction, the vacuum was not broken immediately, Now the reaction tube was cooled gradually (20 °C/min) under vacuum and when the room temperature was reached, the vacuum was broken and the receiver flask removed from the system. This new procedure was introduced to reduce the thermal shock and had an additional advantage: the tar in the hot reactor did not now burn in hot air, and could be collected for analysis.

3.2.1.Reactant vaporisation and tube flow

The first critical step in any FVP is the vaporisation or sublimation of the starting material. As the characteristics of the reactor (and so how much heat could be transmitted from the oven) could not be changed, the parameters that could be modified to ensure that all the reactant was smoothly vaporised were:

- The geometry of the reactor,
- The point of injection of the reactant
- The injection rate of the reactant

To study these questions, a known amount of cardanol was injected at different rates (2 ml/min, 3 ml/min) into a quartz wool pad located in the hot zone of the reactor 10 cm from the inlet. The apparatus was connected to a high vacuum pump (0.01 mm Hg). The oven was heated to 450 °C (100 °C above their known boiling points). The resulting gas was condensed in a flask, cooled in the liquid nitrogen bath. Five minutes after the injection, the tube was quickly cooled and the collector flask weighed to see how much starting material was recovered.

When the reactor was horizontal, no distillate was recovered in the collector flask; however visual analysis of the tube showed a small amount of coke in the quartz wool pad and a large amount of an oil partially coked in the junction between the reactor tube and the nitrogen trap. The remaining tube was clear. When the tube was inclined at 15°, the fraction collected in the nitrogen trap came to 40 % of the cardanols injected. In the previous experiments (see page87) when CNSL was injected in the reactor, part of the compound remained in the inlet as a tar. With cardanols, in smaller measure, it was possible to observe the same phenomenon. When injected, it was possible to see, in the inlet of the tube, some whitish clouds corresponding to a back flow of the cardanols during the injection. A change of the point of injection, to 10 cm from the inlet, using a long needle increased the recovery to 60

%. Cardanols with 3 % hydroquinone (a polymerisation inhibitor) were then injected as suggested Mahanwar.[249] No improvement in the yield was noted. More efficient heat transfer was accomplished when the reactor tube was filled with 30 quartz rings (with a total an external surface of 230 mm^2). Injection led to a further increase to 87 - 92 % cardanol recovery. It was not possible to improve more the recovery further either by increasing the angle of the pipe reactor or the number of quartz rings. Attempts to use aluminium foil at the outlet of the reactor to eliminate condensation before the collecting flask, and heating this area with a heat gun didn't improve the recovery. Therefore unless otherwise stated, the next experiments refer to reactions performed when the reactants were injected with a 1 ml syringe 10 cm from the inlet, directly in the hot zone of the reactor inclined at 30° (30° was used instead of 15° to be absolutely sure that any liquid flowed into the reactor).

3.2.2. FVP on a clean quartz ring filled tube reactor

(i) Procedure

In a series of pyrolysis reactions at 740 °C, cardanols (1.000 g) were injected into the hot zone of the reactor as previously described.[i] At the end of the reaction, a visual observation showed the first 20 or so quartz rings to be slightly covered with black coke, also at the outlet of the reactor, mainly in the elbow just before the cold receiver, a small amount of tar was evident on the internal wall of the tube. In 8 runs, with identical parameters (pressure, time of injection, temperature) the mass of the liquid fraction recovered varied between 206 +/- 44 mg while the tar collected in the outlet of the reactor varied between 18 +/- 13 mg. TLC analysis of both two fractions were consistent from run to run, as the tar gave two major spots near the base line, while the liquid product showed four spots, two with very similar R_f.

[i] . The temperature indicated in the text is the one on the oven display, which is higher than that in the reactor. The temperature in the hot zone of the reactor, measured with a type K thermocouple, on the inside wall of the quartz reactor under vacuum, was 3-6 °C lower. The radial temperature gradient was unknown. At both extremities of the tube the temperature was 370-400 °C lower than in the centre.

(ii) Condensable fraction characterisation

Indication that MVP is a major compound from the liquid fraction recovered on the condensing flask, was suggested by ^{1}HNMR, as shown in Figure 3-12.

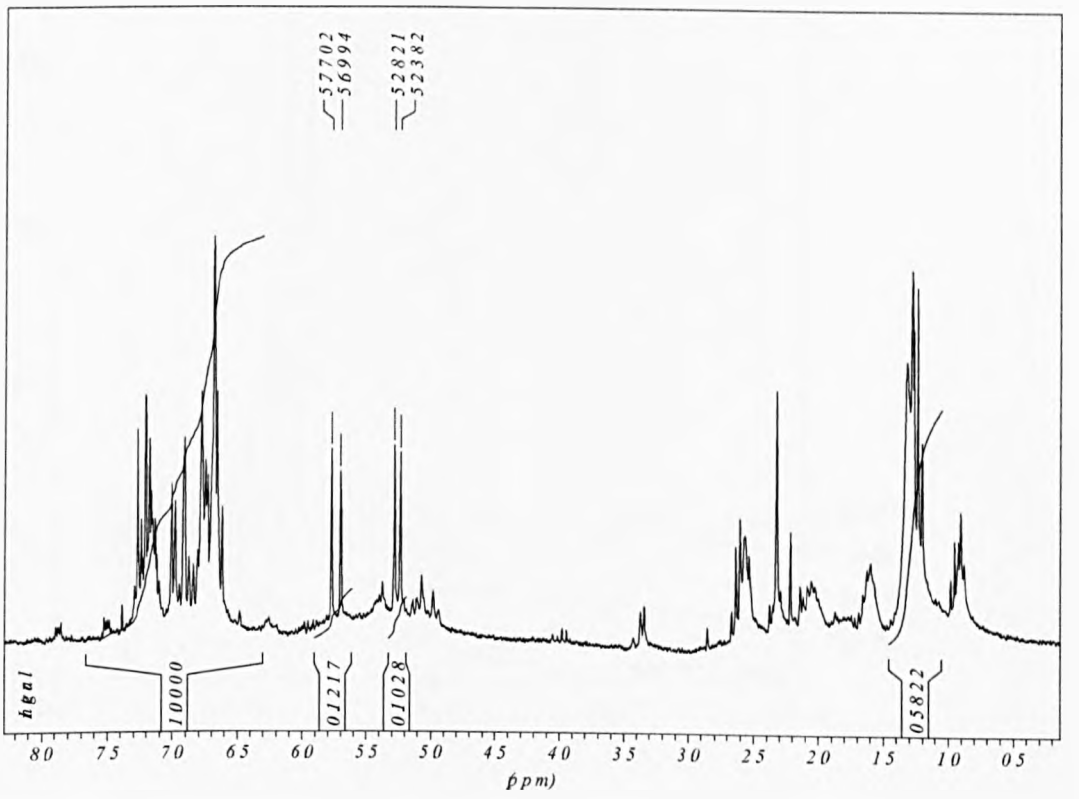


FIGURE 3 - 12: ^{1}H NMR SPECTRUM OF CARDANOLS REACTED IN A CLEAN QUARTZ REACTOR AT 750 °C , 0.1 MM HG.

Because the viscosity of the samples was very high and they were dark black, chromatographic analysis was performed by HPLC. The pyrolytic products did not have UV absorption at 290 nm (the wavelength used for aromatics like CNSL, cardanols and cardols), but showed a maximum at 204 nm like 3-vinylphenol. Figure 3 - 13 shows an overlap of different HPLC chromatograms corresponding to samples of cardanol pyrolysed at different temperatures. It indicates a maximum yield of MVP at 760 - 780 °C.

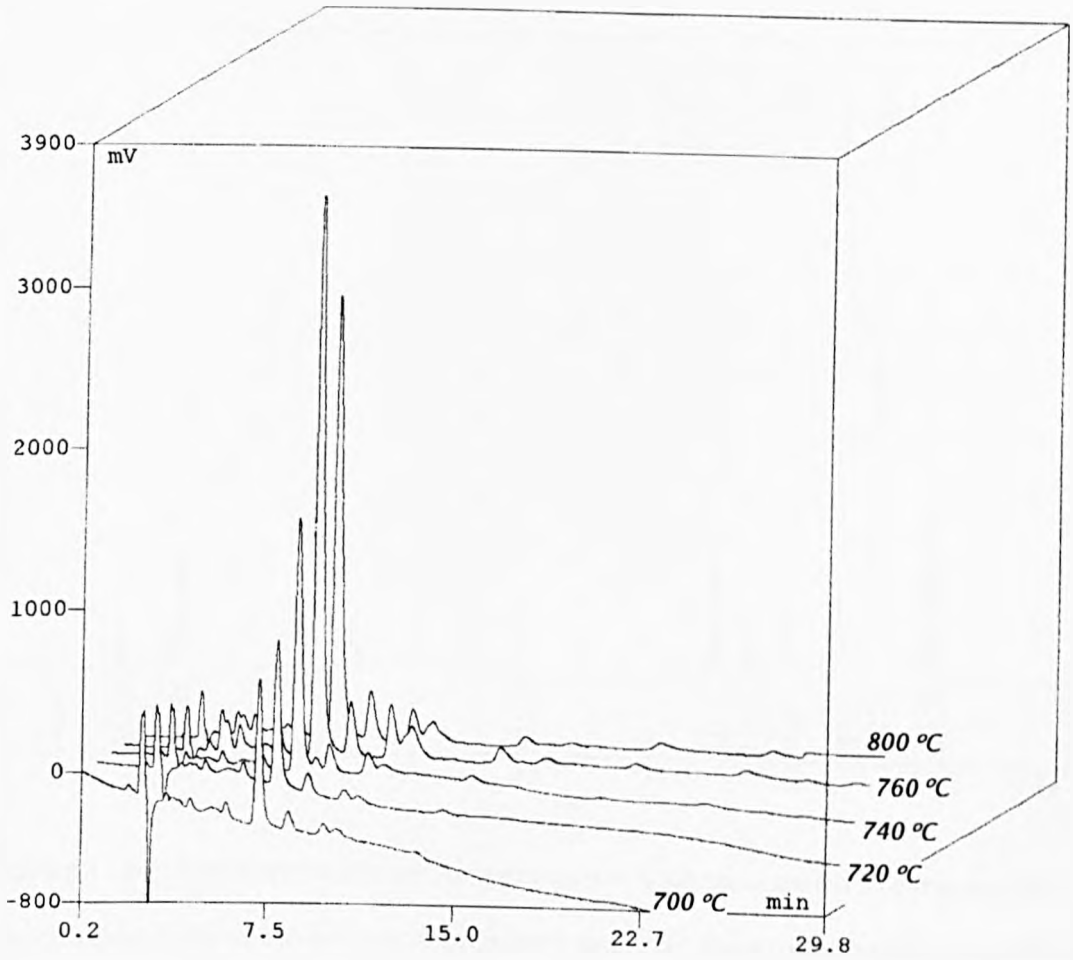


FIGURE 3 - 13: HPLC CHROMATOGRAMS OF CONDENSABLE FRACTIONS OF CARDANOL FVP ON A CLEAN QUARTZ REACTOR, DETECTED AT 204 NM.

The major peak was identified as MVP by co-injection with a pure a sample. In this system the maximum yield of MVP was 32 % at 760 °C.

(iii) Tar characterisation

The HNMR analysis of the tar (Figure 3-14) provided a spectrum that was very different from the one of that of fraction, but similar to the HNMR of starting material, though with smaller olefinic signals and some minor additional signals.

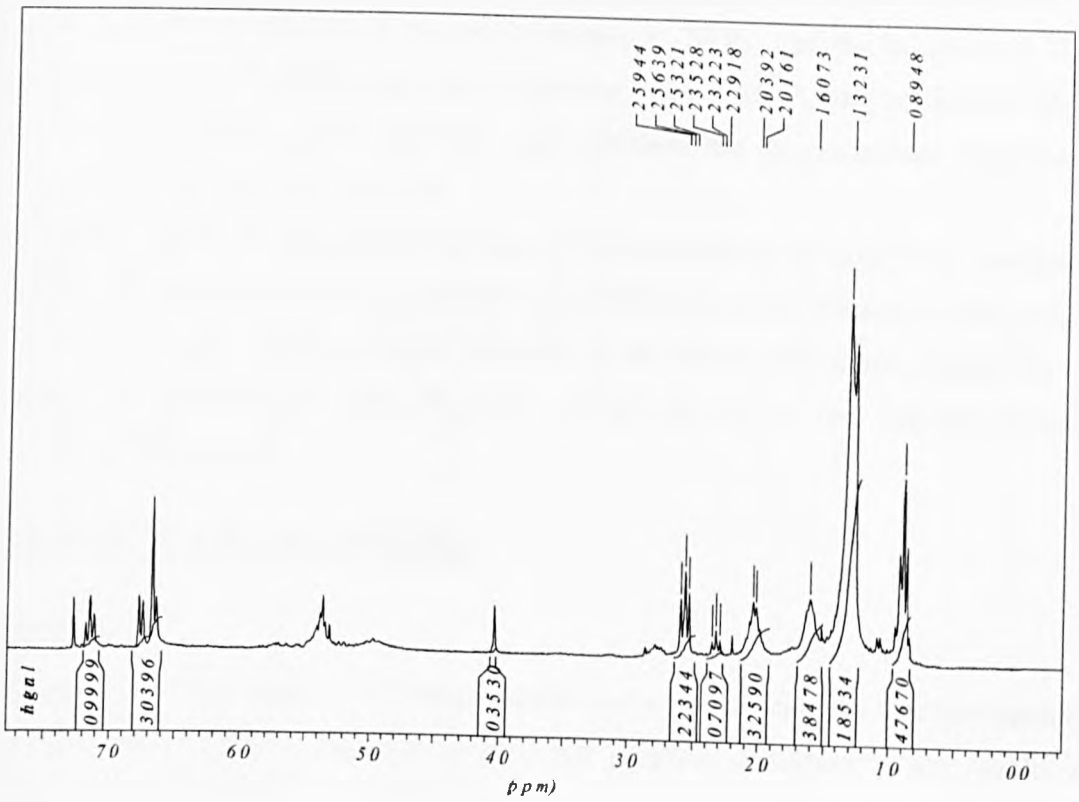


FIGURE 3 - 14: ^{1}H NMR SPECTRUM OF THE TAR –LIKE FRACTION COLLECTED AT THE OUTLET OF THE REACTOR.

The chemical shifts in the aromatic region were similar to those of cardanols, suggesting that this fraction consisted mainly of meta substituted alkylphenols. The remaining part of the spectrum also showed others signals that could be attributed to a meta-alkenyl-substituted aromatic, the benzylic triplet at δ 2.55, the doublet of triplet at δ 2.0 for protons α to the double bond, and a broad signal at δ 1.6 corresponding to the proton α to the benzyl group. The disappearance of the signal for the protons α to two double bonds confirmed that this position is very reactive, and is one of the first to react in FVP conditions.

The sample inside the reactor, between the point of injection and the outlet was mostly a black solid, which was washed with $CDCl_3$ and filtered over a cotton pad. The filtrate gave a HNMR spectrum very similar to that discussed above, but with the signals at δ 2.3 and the singlet at δ 3.98 as the only sharp features, the remaining signals being broad.

Despite the fact that HNMR could not be assigned, it is clear that the aromatic ring remains untouched, and that apparently no new polyaromatic species have been formed.

(iv) Conclusions

FVP of cardanols in a clean quartz reactor affords a tar –like fraction and an MVP rich fraction. An important conclusion that the ^{1}HNMR analysis provided, was the absence, in the tar-like fraction, of significant amounts of polyaromatics. In comparison with the

preliminary set of experiments (where CNSL was injected in the inlet of the reactor), the present system with the use of cardanols instead of CNSL, and the injection of CNSL directly in the hot zone of the reactor, the maximum yield of MVP, was increased to 32 % at 760 °C, being slightly better than the yield obtained the in preliminary experiments. However mass recovery was variable.

One possible cause of the non-repeatability of the experiments is secondary reactions of radicals on the reactor surface such as hydrogen transfer reactions which have been reported in FVP.[255,256] As this would generates instability in the system, this could explain the high variation of mass recovery also observed. It was decided to test this hypothesis by passivation of the surface.

3.2.3. FVP in a deactivated tube

(i) General

In the case of FVP reactions,[257,252] only unimolecular scissions and very fast heterogeneous reactions occur. Catalytic reactions in very fast pyrolysis conditions[210] are usually not important as they are typically slow, they have low pre-exponential factors and moderate activation energies, compared with desorption which has a very high pre-exponential factor and a lower activation energy. However recent experimental evidence has shown that silica reactors can have catalytic sites activated at high temperature.[258] Barton[259] was able to obtain reproducible kinetics for the decomposition of t-butyl chloride to isobutene only after conditioning the reactor by 40 previous pyrolytic runs.

(ii) Liquid fraction analysis

Cardanols obtained by the petrol/TFE (5 % ACN) extraction of CNSL were injected at 700 °C, to cover the tube with a carbonaceous layer. Cardanols were then injected first at constant temperature (740 °C), and then at a range of temperature (720 - 800 °C). Between runs, a black resinous fraction like-tar that was deposited in the reaction tube was washed with dichloromethane (see more details on page 119-section (iii)). Mass recovery was higher than using a clean apparatus, but variation was in the same range (for 850 mg of cardanols injected, recovery was 485 +/-38 mg) and the yield of MVP (estimated from NMR) was lower than the one obtained in a clean apparatus, as can be seen in Figure 3-15.

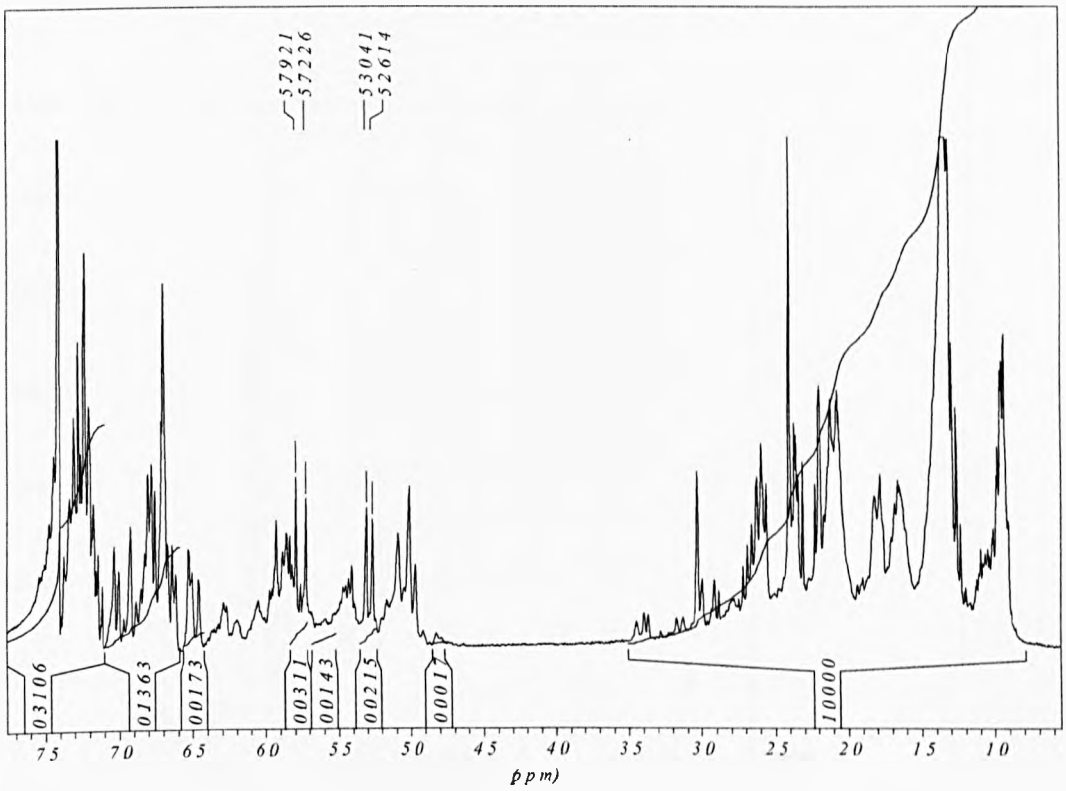


FIGURE 3 - 15: ^{1}H NMR SPECTRUM OF THE CONDENSATE OF FVP IN A DEACTIVATED QUARTZ REACTOR

TLC analysis of the products obtained at 740 °C, gave seven spots, some with very similar R_f values. HPLC showed a marked difference when clean apparatus was employed. A range of products with higher retention time appeared as the temperature was increased, but conversely the yield of MVP decreased with temperature as shown in the Figure 3- 16.

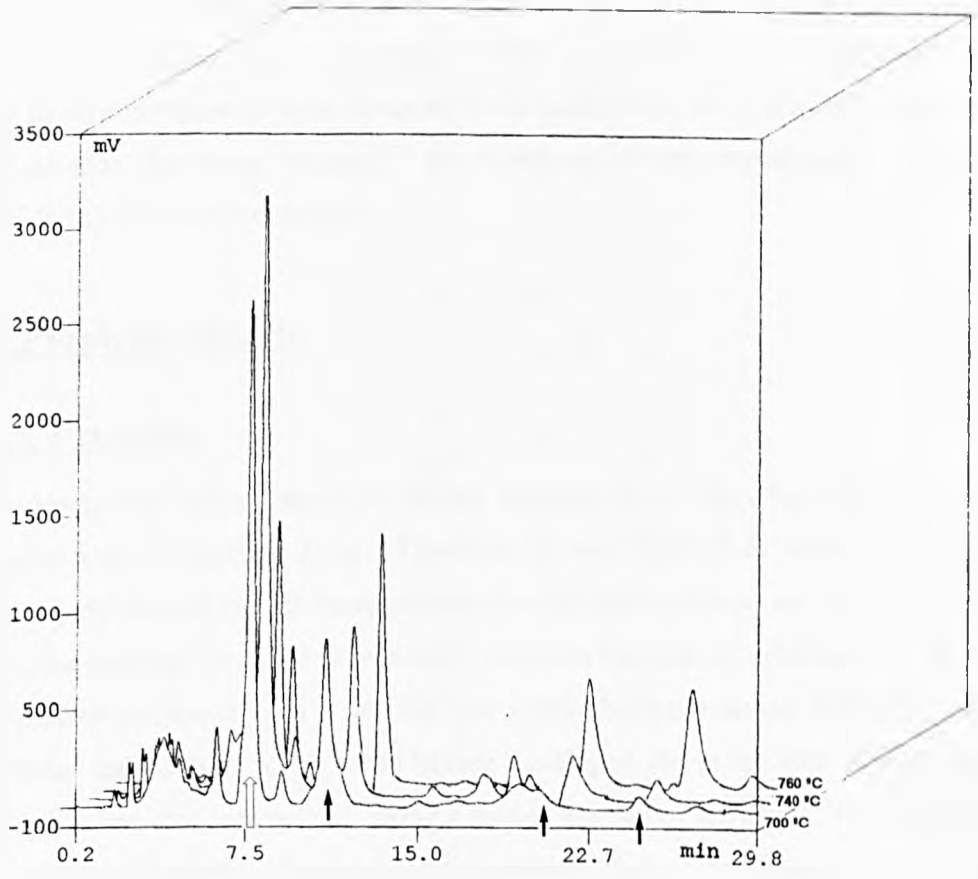


FIGURE 3 - 16: HPLC CHROMATOGRAMS OF THE CONDENSATE OBTAINED BY CARDANOL FVP ON A DEACTIVATED TUBE , AT DIFFERENT TEMPERATURE, AT 204 NM

The appearance of new products that were undetected in a clean reactor, could be due to fast catalytic reactions on the black coke. Poor yields of MVP, and corresponding higher yields of secondary compounds were observed and therefore this approach was not studied further.

(iii) Tar analysis

An HNMR analysis of the tar produced in deactivated tube showed some peaks corresponding to cardanol, and many unidentified peaks in the high field region of the spectrum.

(iv) Conclusions

Using a coating technique was expected to deactivate the reactor, reducing secondary reactions. However the selectivity of the FVP of cardanols decreased.

Another possible explanation is connected with heat transfer, as it is known that black bodies transmit more heat by radiation than others, and radiation is one of the dominant forms of heat transfer in vacuum pyrolysis at high temperature. It could be hypothesized that results obtained (in the case of previous research) by the so-called passivation could be due

to a better heat transfer because of the existence of a black body. This would also explain why we could have a high conversion to MVP in a small diameter black coated pipe, and a very small conversion in large diameter black coated pipe, as in this second case insufficient heat transfer (due to the vacuum,[260] which reduces the heat transferred by convection) was provided to the reaction medium.

3.3.Pyrolysis with air

3.3.1 Principle

The deactivated reactor approach did not improve MVP yield, but it did suggest that heat transfer was a dominant factor. Therefore, it was decided to study alternative ways to improve the heating rate of the reactant at the pyrolysis temperature. The literature suggested that slow heating rates induce secondary reactions that mainly produce coke /tar and change the reactor surface in such a way that the system becomes erratic. Dow Chemicals, Union Carbide, and Kellogs all reported having developed the production of ethylene in higher yield than conventional reactors using a minute amount of oxygen.[201] The oxygen burns with a very small fraction of the reactant providing part of the energy for the endothermic reaction. Also (and potentially more important) a better heating rate was anticipated, in addition to the elimination of residual coke. As a result, the liquid fraction was expected to contain less secondary products.

3.3.2.Procedure

In a typical experiment, cardanols (0.800 g, 0.25 mmols) were co-injected simultaneously with air (20 ml) (*ca.* 0.16 mmols of oxygen/mol cardanols), into a reactor filled with quartz rings at temperature ranging 650 to 726 °C. After injection temperature readings became highly erratic. After the reaction the reactor contained **no coke deposits** but the quartz tube had become a little cloudy.

TABLE 3 - 2: MASS RECOVERY IN OXYPYROLYSIS

Temp (°C)	Press. (mmHg)	Air (ml / g cardanols)	Mass recovery (mg liquid fraction/ g cardanol)	GC data		NMR data
				MVP (%)	EP (%)	MVP (%)
720	3	20	183	40	7.	34
650	5	40	56	----	----	5
726	7	20	180	41	7.5	31

All ^{1}HNMR spectra of the product oil at 720 °C showed the characteristic pair of doublets for MVP at 5.25 and 5.75 ppm. As shown in Figure 3-18 , the main difference between this spectrum, and the ones previously obtained in the pyrolysis was the increased ratio of aromatic to non-aromatic signals.

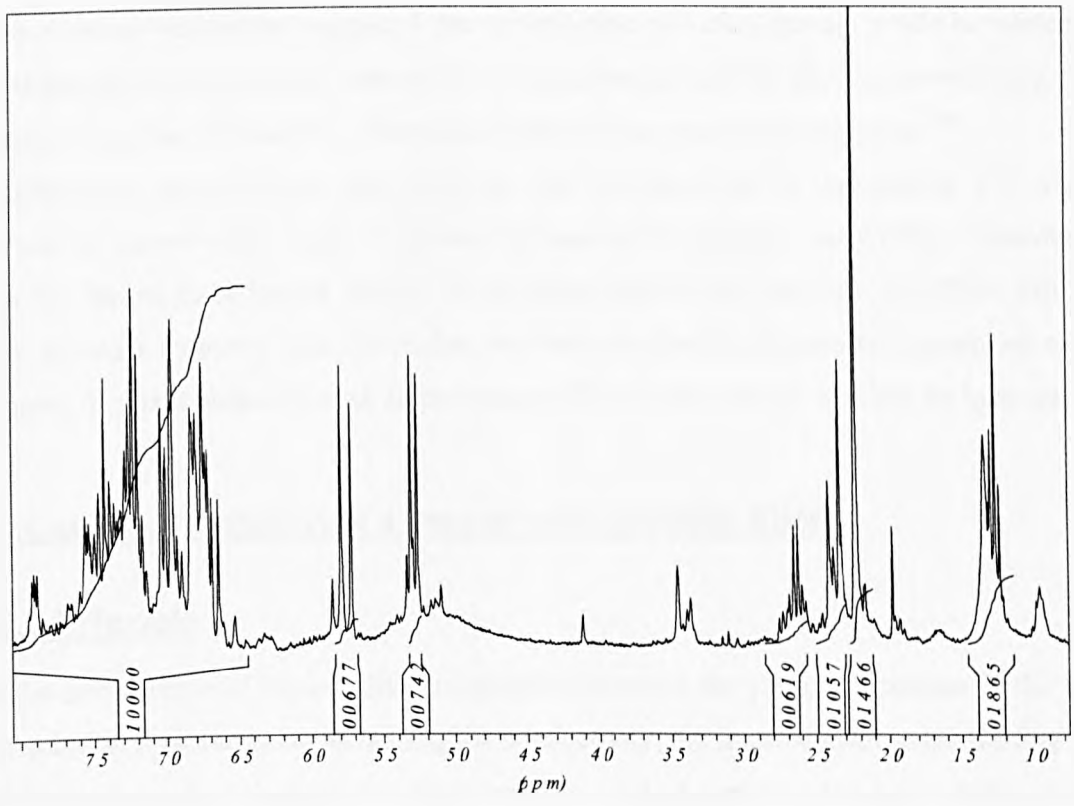
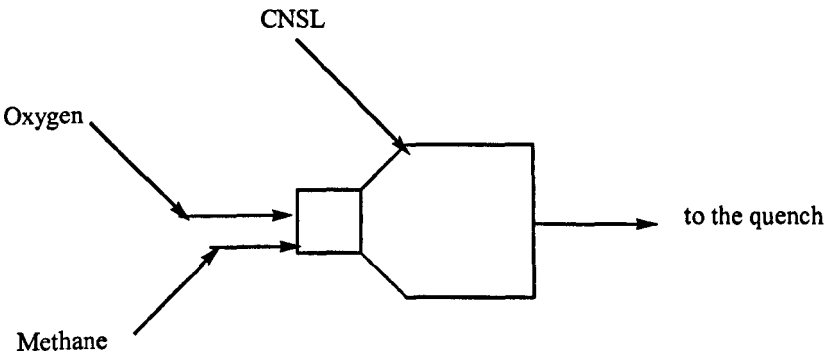


FIGURE 3 - 17: ^{1}H NMR SPECTRUM OF THE PRODUCT OF THE OXYPYROLYSIS OF CNSL

GC analysis showed the ratio of EP: MVP to be higher than at in previous FVP . This suggested either that MVP was less stable and underwent faster secondary reactions, or that the difference between the rates of the two reactions giving these compounds was smaller due to the presence of oxygen or due to localized high temperature. These observations could be related to that of Barbet which demonstrated that in the pyrolysis of propene

introducing sub-stoichiometric amounts of oxygen increased significantly the amount of high molecular weight olefins in the products.[261]

The mass ratio of the condensable fraction to the injected cardanols was only 18 % suggesting that the potential added value of the product was small.



SCHEME 3 - 7: PROPOSED INSTALLATION OF CNSL PYROLYSIS WITH AIR AND METHANE

Union Carbide researchers suggested that optimisation of such a process would be related to the shape of the mixing zone between hot combustion gas and the starting material in a way to ensure very fast (around 50 - 100 msec) heating to the reaction temperature.[262]

Modifications could increase the yield, like the one presented in the scheme 3-7, where methane is burned with oxygen to provide the heat of the reaction, and CNSL is introduced after the burner, to be heated quickly to the temperature of the reaction. As CNSL will not burn, the mass recovery could be higher, but these studies would involve equipments more complex than that presently used. Improvement of pyrolysis with air was left for later study.

3.4.Cardanol pyrolysis in a reactor with metallic fillers

3.4.1 Principle

As the introduction of oxygen only marginally improved the yield, an increase in the heat transmission was sought by increasing the conductivity. An improvement in the heating rate could be expected on changing the quartz rings to steel, chromium or nickel or better copper rings. Copper is 6 and 9 times more conductive than nickel and mild steel respectively. Metallic fillings and intra-heating devices have been used in laboratory scale pyrolytic equipments (most commonly using a Nichrome filament with nitrogen carrier,[263,264] iron/steel reactors,[265] and gold microreactors[266,267]).

The importance of a fast heating rate, to reduce the possibility of secondary reactions, was raised, when the Curie Point Pyrolyser[268] was developed and in recent studies of biomass

pyrolysis.[199] When fast heating rates have been obtained, results have been claimed to be cleaner, and more accurate from a kinetic point of view.

3.4.2. Pyrolysis on mild steel rings

Mild steel nuts were chosen in order that an external surface of 232 mm^2 was afforded allowing a comparison with other pyrolysis experiments on the basis of similar temperature, pressure, injection rate and metallic surface /volume of the reactor ratio. In two successive injections of cardanols (one time 1 g, other 5 g) in a quartz reactor tube, filled with mild steel rings, heated at 748 °C, mass recovery was reduced from run to run, varying from 28 to 12 % but the spectra showed that the distribution of olefinic/aromatic signals in the NMR spectra were similar, suggesting that the major products were the same. When the reactor was dismantled, a huge quantity of carbon was deposited on the steel nuts, and a very small amount in the remaining quartz tube. Later on, a similar effect was observed, as cardanols were pyrolysed in a stainless steel tube (similar to the quartz one), at 750 °C, giving MVP in 17 % yield. After the reaction, visual analysis of the interior of the reactor showed again large amount of coke.

3.4.3. Pyrolysis on copper rings

Copper rings were obtained by cutting a 1.5 mm diameter copper pipe into 15 mm length rings. Forty copper rings, with a global surface area of 235.5 mm^2 were put into the quartz tube in the first approach.

(i)Process description

Cardanols were then pyrolysed, at a rate of ca. 0.05 ml / 3 sec, at different temperatures (748 - 780 °C) and 0.05 mm Hg pressure. Over a series of 10 experiments using 1 ml of cardanol, mass recovery of the condensable fraction was twice that obtained in a clean quartz pipe reactor, and there were no significant variations from run to run.

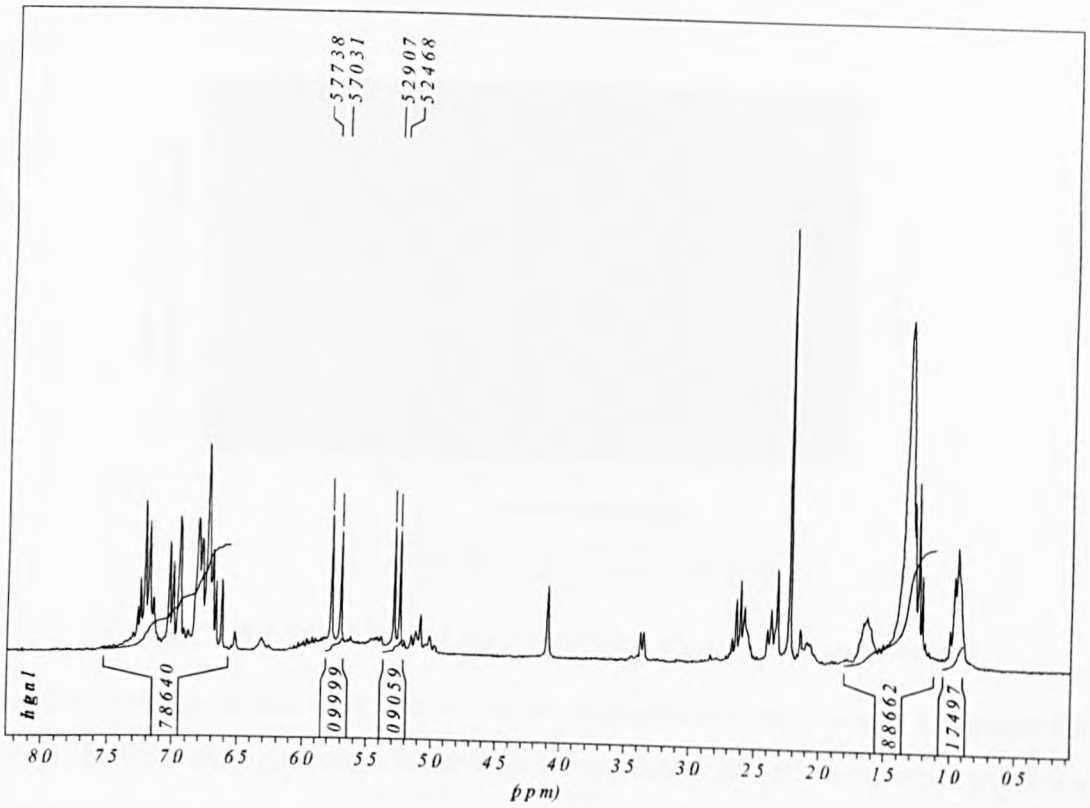


FIGURE 3 - 18: ^{1}H NMR SPECTRUM OF CARDANOL FVP ON COPPER RINGS AT 750°C, 0.1MM HG.

HNMR showed a high concentration of MVP, which was confirmed by GC. The copper rings recovered (after cooling under vacuum) still maintained their original shine, with a minor amount of black deposit in the first 5 - 15 rings from the injection point.

(ii) Influence of pressure

Now that an efficient method of heat transfer[i] had been developed, the influence of pressure was examined.

The variation of MVP yield (measured by HNMR) as a function of pressure (0.10 - 110 mmHg) is indicated in Figure 3-19 and shows 2 critical zones: at very low pressure (0.1 - 0.5 mm Hg) with a maximum of both mass recovery of the condensate and the highest content of MVP, and a zone between 1 - 100 mm Hg with a quasi-constant concentration of MVP and mass recovery.

[i] Other reasons, than the heat transfer, to explain better yields obtained in FVP on copper rings, are not precluded. The possible catalytic activity of different packings is analysed on page 112.

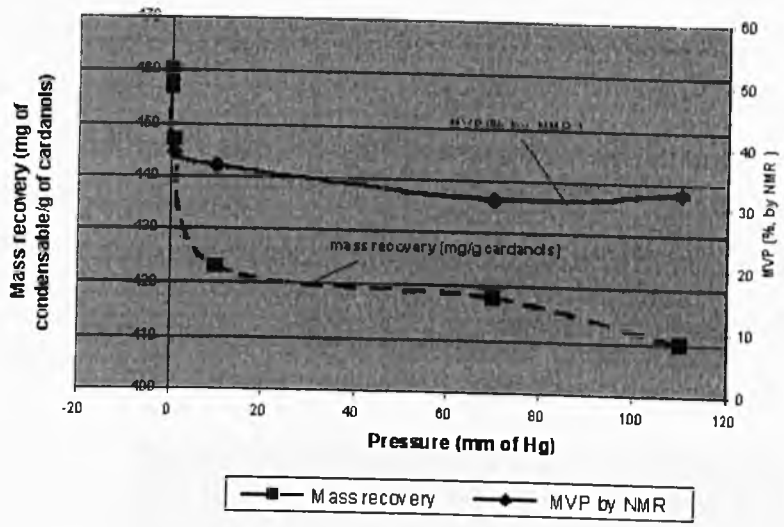


FIGURE 3 - 19: INFLUENCE OF PRESSURE ON CARDANOL FVP ON COPPER

Because the purpose of this work was to find the best possible conversion at a pressure that could be obtained under conditions suitable for an eventual scale up it was chosen to work at 1 mm Hg.

(iii) The influence of temperature

FVP of cardanols was performed at a range of temperatures.

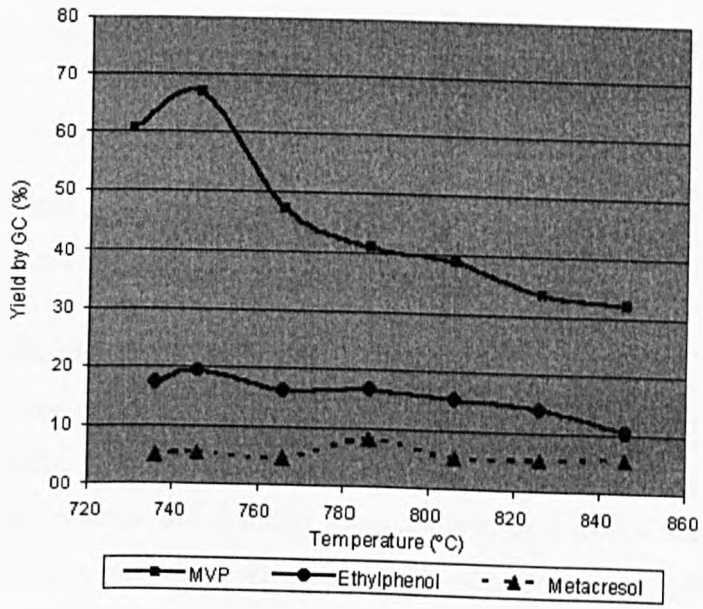


FIGURE 3 - 20: INFLUENCE OF TEMPERATURE ON CARDANOLS FVP ON COPPER

In the range investigated a maximum yield in MVP is obtained around 750 °C.

(iv) Influence of surface contact

An experiment was performed on 60 pieces of copper rather than 30 to additionally determine a relationship between area, temperature and conversion. Because of the dimension of the quartz tube, if more than 60 pieces were used, some of them would have been outside the heated part of the oven. Smaller pieces would not change the area but the packing mode and have not been tested, as it was anticipated that a copper tube would be used in a scaled up unit, and therefore usefulness of these additional data was doubtful. GC analysis was again used to quantify the main products of the reaction, i.e. MVP, ethylphenol, and cresol.

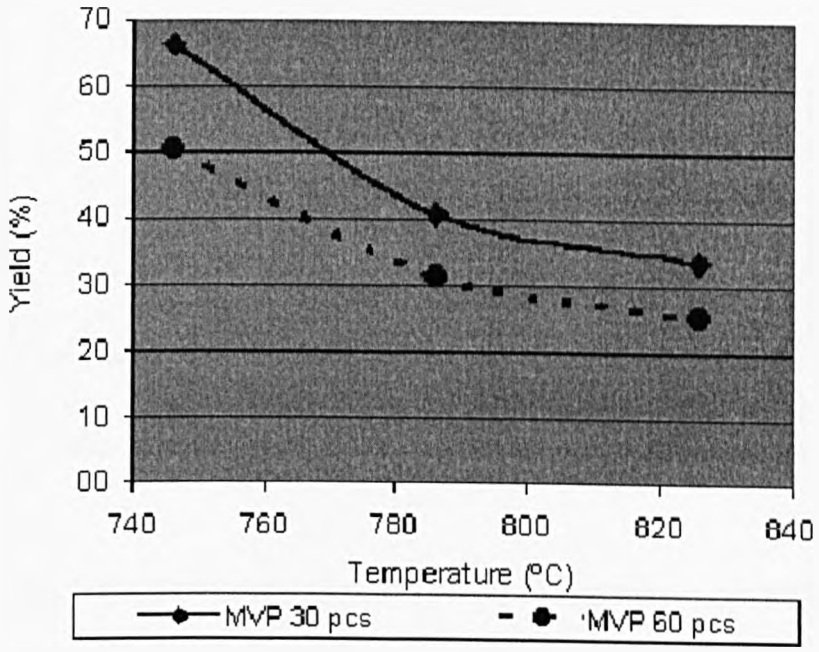


FIGURE 3 - 21: SURFACE CONTACT IN CARDANOLS FVP ON COPPER

Figure 3-21 shows that the increase from 30 to 60 pieces of copper, corresponding to an increased of surface contact time, led to a decrease in MVP yield.

(v) Separation of the condensable fraction.

As TLC analysis of the pyrolysed liquid fraction clearly indicated the presence of spots that could not be attributed to MVP, EP, 3-cresol, or phenol, and HNMR suggested that this would have aromatic protons, this fraction was separated by vacuum distillation. Standard vacuum distillation gave very poor distillate yields, therefore in a typical procedure, a recently pyrolysed sample was heated to 125 °C, during 5 minutes and the hot liquid was then (exposed to high vacuum distillation (5 mm Hg) to afford a pale yellow fraction (88 % yield). Subsequent analysis showed the oil to be a mixture comprising MVP (55 % by GC),

EP (12 %), cresol (4 %) and phenol (4 %) with some impurities and provided a residue (7 % wt) with an HNMR showing no vinylic signals.

A typical spectrum of a distillate obtained by batch distillation of a sample obtained by FVP (@ 730°C, 1 mm Hg) is shown in Figure 3-22.

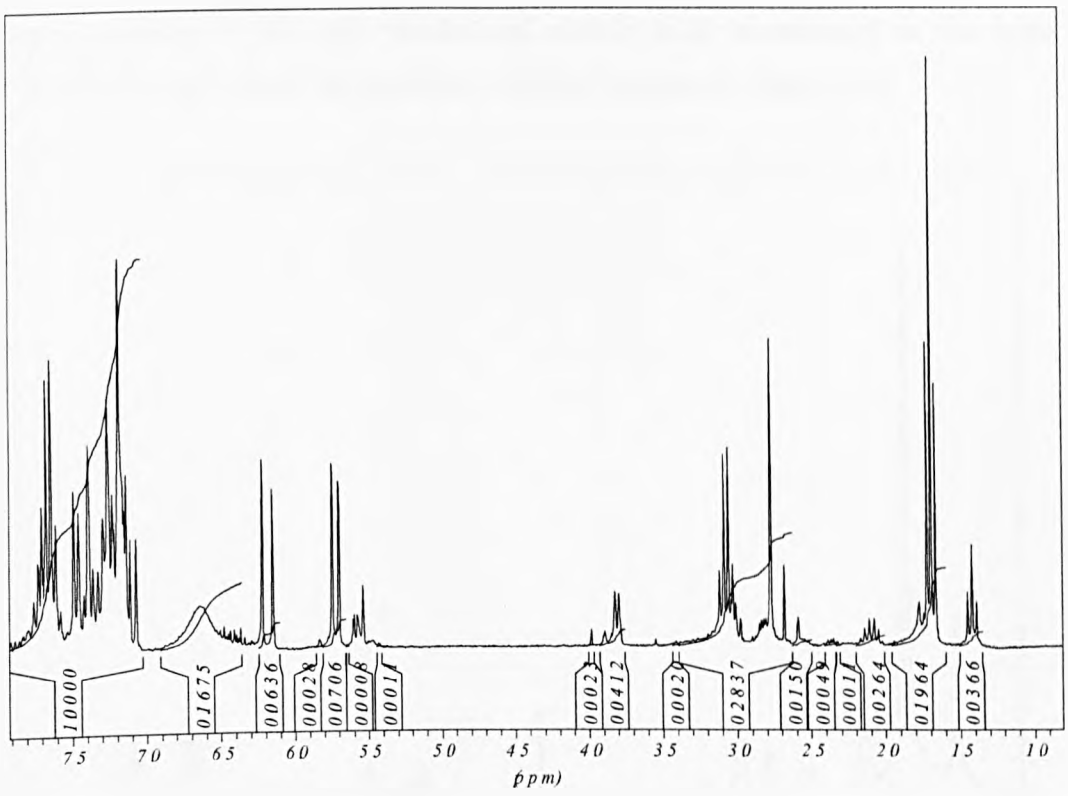


FIGURE 3 - 22: ^{1}H NMR SPECTRUM FROM THE DISTILLATE OF CARDANOLS FVP PRODUCTS

The difference between the normal boiling points of MVP (estimated by ChemDraw) and EP is just 0.6 °C, and 7 °C between EP and MC; boiling points at low pressure reported in the literature are similar[i], and batch distillation, even under high vacuum, did not provided separation A method of purification of an MVP solution containing also ethylphenol was reported in the literature, by solvent extraction, i.e contacting a n-butylether solution of the crude mixture in contercurrent with an alkali aqueous solution.[269] Because vinylphenols are notoriously labile toward polymerisation (high purity vinylphenol must be stored under refrigeration at a temperature preferably lower than - 20 °C), they are stored with methanol or phenolics in solutions[270,271]. The MVP solution resulting from the distillation did not show noticeable polymerisation after 6 months on the bench at room temperature, while pure

[i] Boiling points of MVP and EP at 20mm Hg is reported to be 120 °C.[272,273,274]

MVP (obtained by synthesis) become a sticky rubbery solid after just one week-end under the same conditions..

The purpose was to obtain vinylphenol as a starting material for synthesis, for example, of phenylefrine. Because neither ethylphenol nor cresol have double bonds, which is the reactive functionality of MVP to be modified in an eventual synthesis of phenylephrine, a further purification of the crude vinylphenol mixture looks unnecessary at this stage. A typical ^{1}HNMR spectrum of the distillation residue, is shown in Figure 3-23.

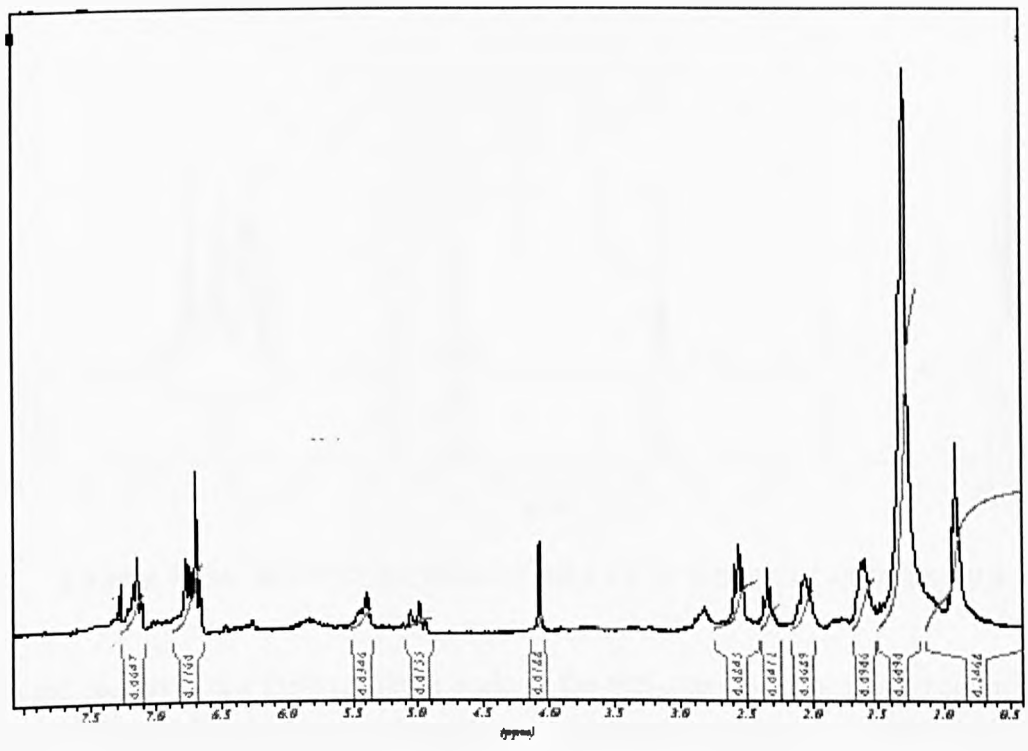


FIGURE 3 - 23: ^{1}H NMR SPECTRUM OF VACUUM DISTILLATION RESIDUE FROM CARDANOL FVP.

This spectrum is very similar to that of the tar collected on FVP with a clean quartz tube except that there are fewer protons in the olefinic part of the spectrum. A TLC of the sample using petrol-ethyl acetate (5-2) showed that it contained at least 7 compounds.

(vi) FVP of the distillation residue: a possibility of recycling.

Recycling unreacted starting materials is a common practice in many chemical processes. Analysis of the previous results, shows that neither an increase of temperature or contact time, could both eliminate the presence of the distillation residue and give the highest possible yield in the reaction. However further treatment of the residue by FVP could potentially transform these minor products into MVP. So the distillation residue was

pyrolysed using the same conditions used to pyrolyse cardanols. ^{1}HNMR of the products is shown in the Figure 3-24.

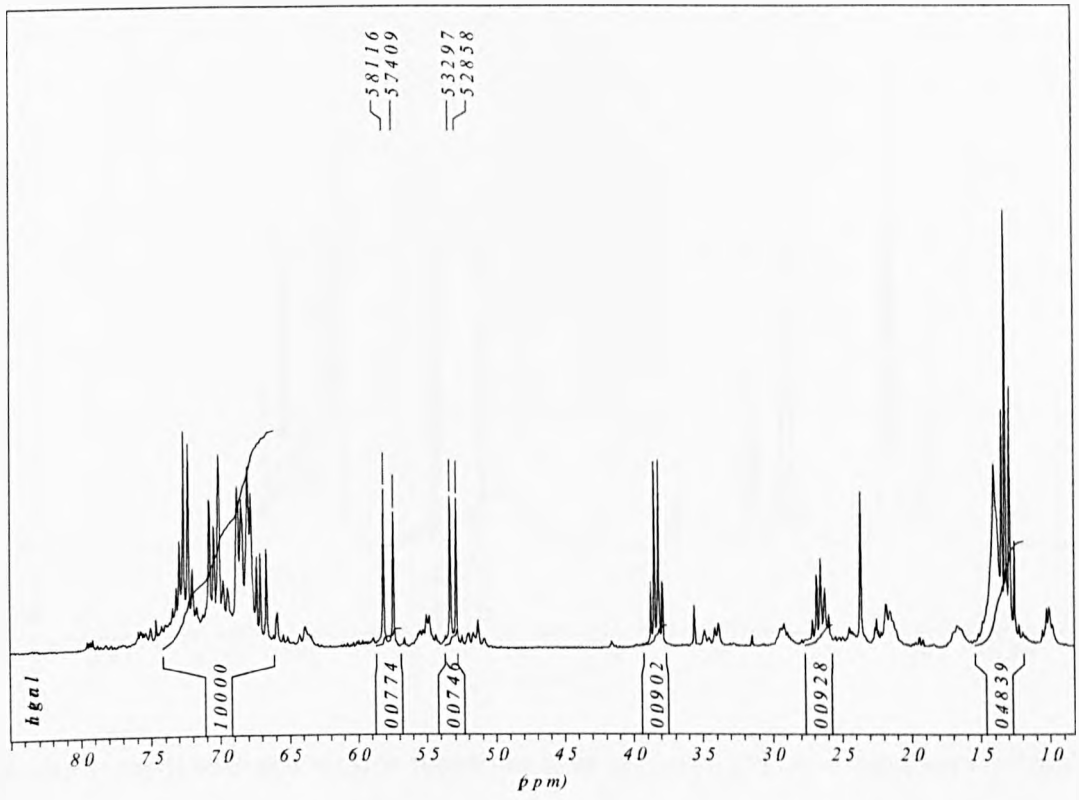


FIGURE 3 - 24: ^{1}H NMR SPECTRUM OF THE FVP OF THE DISTILLATION RESIDUE

With the exception that there are fewer peaks in the non-aromatic zone this spectrum is quite similar than the ones obtained in FVP cardanols. In FVP of cardanols at 746 °C, the **global yield** (the sum of the yields obtained in the first pyrolysis step and in the recycling) **is 68 % MVP and 20 % EP**.

3.4.4.FVP on aluminium cylinders

Aluminium cylinders where obtained by sawing aluminium rod into 15 mm lengths.[i] In a range of experiments, cardanols were flash vacuum pyrolysed (at 676-776 °C and 1 mm Hg) on 60 aluminium cylinders. As checked by ^{1}HNMR spectroscopy (see a characteristic spectrum in Figure 3-25) and confirmed by GC, the main product of the reaction was MVP. Samples were less coloured than the ones obtained on copper but the mass recovery was lower.

[i] The surface area was the same as that obtained with the copper cylinders, but the hydrodynamic of the gas-flow in the reactor was different as these cylinders did not have an hole in the middle as the copper ones did.

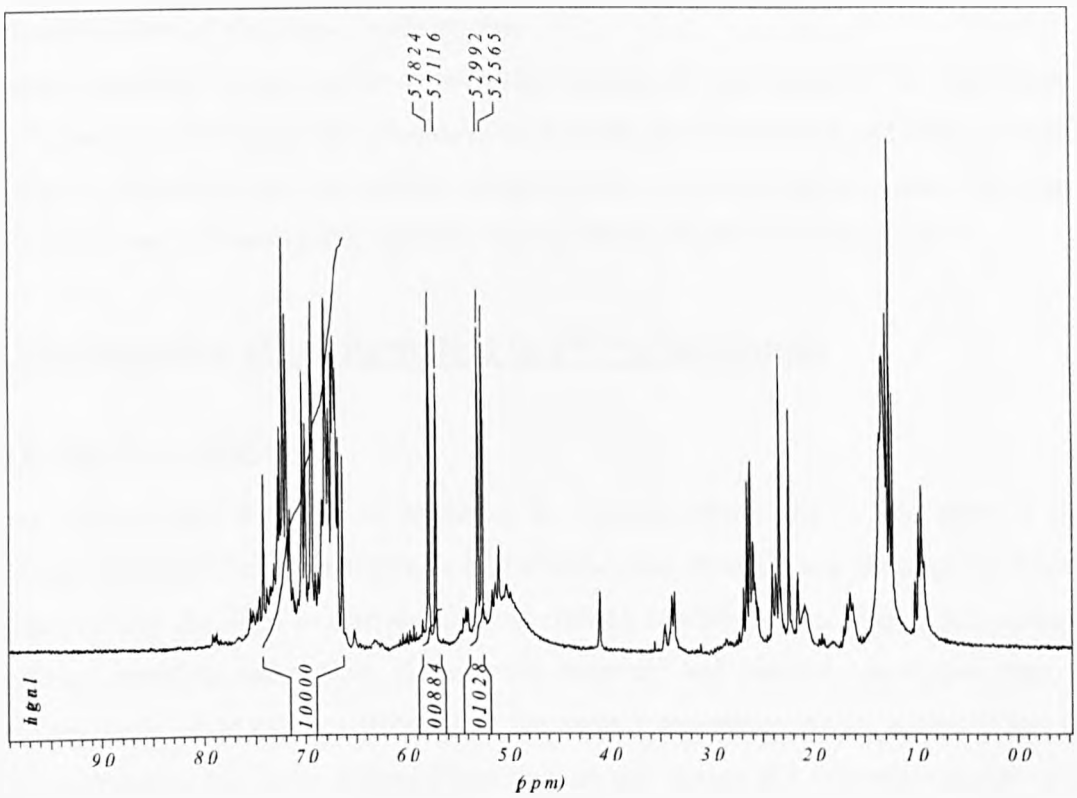


FIGURE 3 - 25: ^{1}H NMR SPECTRUM OF THE PRODUCTS OF CARDANOL FVP ON ALUMINIUM CYLINDERS

The variation in the yield of the main product (MVP) as a function of temperature (Figure 3-26) showed a maximum at 40 %, while it was 50.5 % in FVP on copper.[1]

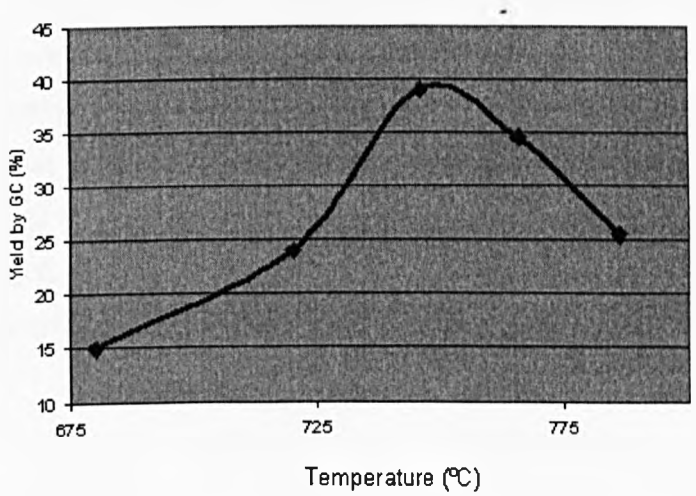


FIGURE 3 - 26: INFLUENCE OF TEMPERATURE IN CARDANOL FVP ON ALUMINIUM CYLINDERS

[1] FVP experiment on copper, with the same contact area, vacuum, and temperature range, reported in Figure 3-22

It is not known if this was due to the packing of the cylinders, and the change of the circulation pattern of the gases [i] in the system.

A visual inspection of the reactor showed that aluminium also inhibited the deposition of coke. However, as the purpose was to develop a viable process to pyrolyse CNSL/cardanols, and copper tubes are cheap and readily available, only a clear-cut improvement over copper would have been interesting; this question was therefore not further investigated.

3.5.Minimization of tar formation in FVP of cardanols

3.5.1. Surface effects

It was demonstrated that FVP of cardanols in a quartz reactor with a thin layer of coke generated additional (unwanted) products beside the ones obtained in a clean quartz reactor, showing clearly the need to operate in clean surface conditions. Because in two different processes – pyrolysis using quartz rings (small diameter), and pyrolysis on copper rings, the maximum yield of MVP was afforded in the same temperature range, a conclusion that could be drawn is that these different materials do not change the activation energy of the main reaction- i.e. do not have salient catalytic activity on the main reaction. However different materials did have marked effects on FVP in the conditions reported in this work. Copper and aluminium deposited little coke and tar, while steel accelerated the reactions that led to by-products.

The experimental results presented here and in the literature,[275, 276] clearly support the important role surface chemistry plays in promoting coke, tar and other secondary unwanted reactions involving primary decomposition products.

One of the suggested mechanisms (see page 75) of coke formation corresponds to gas phase reactions, which produce tar and coke precursors, followed by solid-surface catalysed reactions, one of them being dehydrogenation (leading to polyaromatics with higher ratio of carbon/hydrogen, and ultimately to coke) . According to the "Volcano principle",[277] a smooth relationship exists between heterogeneous catalyst activity and the strength of

[i] Heat transfer is not only a function of the conductivity of the material at the interface, but also of circulation patterns of the gases in the tube, i.e., it is higher when gases are circulating in a turbulent regime than in a laminar one. For more details see ref.126. A change in the heat transfer would change the conversion to MVP.

chemisorption. Therefore the global process of coke production by the mechanism previously described could be eliminated by **inhibition of the chemisorption of hydrogen.**[i]

TABLE 3 - 3: CLASSIFICATION OF METALS ACCORDING TO THEIR ABILITIES IN CHEMISORPTION.[214]

Group metals		Abilities in hydrogen chemisorption
A	Ti, Zr, Hf, V,Nb, Ta, Cr, Mo,W,Fe, Ru, Os	+
B_1	Ni, Co	+
B_2	Rh, Pd, Pt, Ir	+
B_3	Cu	-
C	Al, Au	-
D	Li, Na, K	-
E	Mg, Ag, Zn, Cd, In, Si, Ge, Sn, Pb, Sb	-

(+ means that strong chemisorption occurs, +/- means that it is weak, - mean unobservable)

The literature (see Table 3-3) indicates that nickel and iron (the main constituents of stainless steel), easily chemisorb hydrogen, while the chemisorbtion is unobservable in the case of some others metals (gold, copper,[ii] silver, zinc, aluminium, cadmium, indium, germanium, lead, bismuth).

Because understanding of the fundamental processes leading to coke formation on surfaces is in its infancy, it is inadequate to make definitive statements (about coke and tar control); however this rationalisation is consistent with surface treatments in the literature aiming to reduce coke/tar formation in laboratory and industrial scale pyrolysis. Alonizing™ (or aluminising), is a Shell-patented method to protect internal walls of pyrolysis tubes, which involves the diffusion of aluminium into the alloy surface by a chemical vapour deposition technique. The coating provides an alumina scale, which is reported to be effective in reducing *coke* formation and protecting from oxidation and other forms of corrosion.[278] It has been demonstrated that *silica* coated steels, have similar effects.[201,275] Cracking reactions in gold-coil reactor[223, 279, 280,281] led to cleaner reaction mixtures than the Vycor (a quartz type) reactor.[267]

FVP on technical copper would be an extension of other methods used in pyrolysis reactions, based on the same physical principles.[iii]

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[i] A critical step in dehydrogenation in heterogeneous catalytic processes is the formation of a chemical bond between hydrogen atoms of the molecule to be dehydrogenated and the catalyst. The ability to form this bond is measured by the hydrogen chemisorption.

[ii] Copper indicated here is copper metallic, valence 0. Technical copper catalysts can chemisorb hydrogen weakly and have been used selectively reduce polyunsaturates to monoalkene.

[iii] It is noteworthy that even in using materials with no chemisorbtion like gold, surface treatment can change the conversion of the reaction. In a study on butane pyrolysis in a gold-coil reactor, etching the surface with nitric acid and heating it to 500 °C, decreased the conversion to 50 %.

It is possible to conclude that: Pyrolysis of cardanol is mainly a non-catalytic reaction. Secondary reactions on the surface that lead to production of tar could be minimized by the choice of materials with low hydrogen chemisorbtion. Choice of suitable material as a possibility to minimize tar and coke, in laboratory experiments, was clearly observed in previous pyrolysis work without such rationalisation, and gold (also a material with low hydrogen chemisorbtion) was selected as an inert material for the reactor wall, our present work show that copper or aluminium, far cheaper materials, could easily be used instead.

3.5.2.Heating rate

Experiments using the quartz tube show coke and mainly tar in higher amounts than in the copper ring filled reactor. However as both have minimal hydrogen chemisorbtion, this looks contradictory with the previous statement of surface related production of coke. However it is likely that this is related with different heating rates in quartz/copper rings reactors (the heat transfer is proportional to the thermal conductivity of the material). A high heating rate is likely to provide faster the more stable thermodynamically products, (i.e. MVP in the case of cardanol FVP) while a low heating rate would afford, in the same time interval, more incompletely cracked intermediates (with high molecular weight). To further crack these intermediates, the reaction time should be increased, but as has been seen (in Figure 3-22) increasing the reaction time is likely to induce further cracking of MVP produced. Alternatively, the intermediates should be recycled.

3.5.3.Vacuum

Vacuum conditions are essential to ensure a smooth vaporisation of cardanols. Despite the fact that the need to use vacuum to vaporize cardanols without major decomposition is well documented, experiments reported in the literature (see details on page 73 and pages 79-80) are all performed at atmospheric pressure. This may be one of the causes of their low yield.

3.5.4.Conclusions

The tar-like fraction in cardanol FVP has been minimized through optimisation of reaction parameters (vaporisation under vacuum, high heating rate, and a reactor with a clean surface material with low hydrogen chemisorbtion). [i, i, ii]

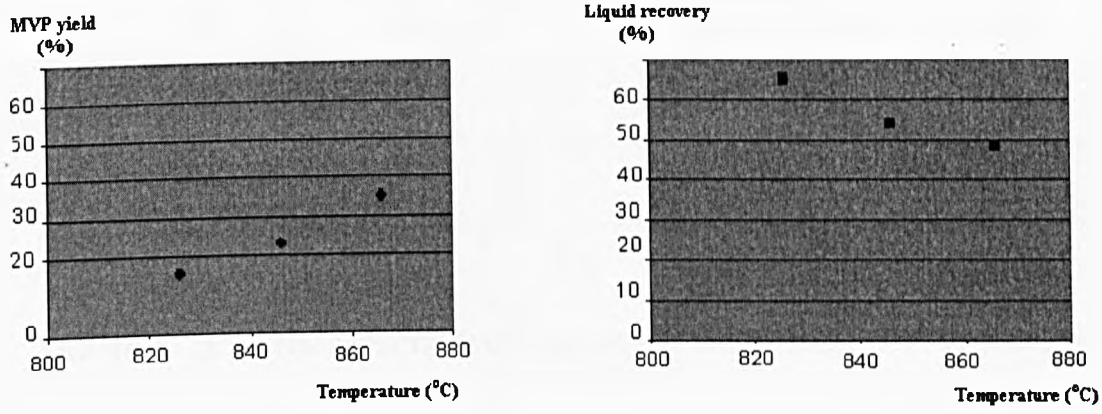
[i] After discussing with Dr. Chris Wallsgrove from Selas (a world leading company involved in the design of pyrolysis reactors), the author believes that the use of FVP technology would provide better yields than equipment with nickel-chrome filaments and others devices with high hydrogen chemisorption, not only in CNSL pyrolysis but also in industrial scale pyrolysis of compounds that are difficult to volatilise, or which reaction provide compounds with high commercial value, as most of the present designs (pyrolysis in tubular reactors, at normal pressure, and using steam as diluent) based on a variation of the methods used to produce ethylene, led to coke production in the vaporisation and the reaction sections.

3.6.FVP of cardanol derivatives

The next step, to improve the knowledge on the FVP behaviour of cardanol, was to perform a study on selected cardanol derivatives. Two derivatives to be pyrolysed selected were cardanol (15:0) and anacardic acid. The pyrolysis of the former would demonstrate the importance of the allylic bonds in FVP reactions, while the latter would provide information on the influence of the substituents on the aromatic of the ring.

3.6.1.FVP of cardanol (15:0)

Injection of cardanol (15:0), (previously melted on a water bath), into a quartz tube filled with copper rings at 740 to 826 °C gave very high mass recovery.



Liquid recovery (%) is the mass of the liquid fraction recovered after the reaction, per unit of mass of cardanol (15:0) injected in the reactor, as a %.

FIGURE 3 - 27: YIELD AND MASS RECOVERY IN CARDANOL (15:0) FVP

However little material was in fact pyrolysed, and predominantly starting material was recovered, as could be seen in the Figure 3-27, which shows the variation of the yield of MVP, respectively the amount of the liquid fraction recovered after the reactor, as a function of the temperature of the reaction, and the Figure 3-28 which shows the ^{1}HNMR of the liquid fraction obtained by FVP of cardanol (15 : 0) at 826 °C.

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[i] Dr Wallsgrove only agrees partially with this statement, as it is more difficult to operate at vacuum than at normal pressure, therefore FVP installations are less reliable. He also pointed out that because FVP, as described, does not exist on industrial scale, the need to develop large-scale technology is likely to increase the capital costs of the first of such plants, in comparison with established technology. To cover costs to develop a large scale unit, and considering additional utilities and safety items, Selas (Dr. Wallsgrove, personal communication)estimated that for a 1000 tons unit/year the cost of the FVP furnace would be 5 times the cost of the same furnace operating at normal pressure with steam as diluent. Assuming that conversion would be the one provided in Figure 2-21, standard cost of the latter pyrolysis oven could be estimated using relations provided by Walas

[ii] For example in the commercial pyrolysis (at normal pressure with steam as inert) of pinene (in the synthesis of menthol), a large part of the starting material is reported to be lost as tar-coke in the vaporisation section of the reactor, coke production in the remaining part of the reactor is minimised due to surface treatment of the reactor tubes. (Dr. Wallsgrove, personal communication).

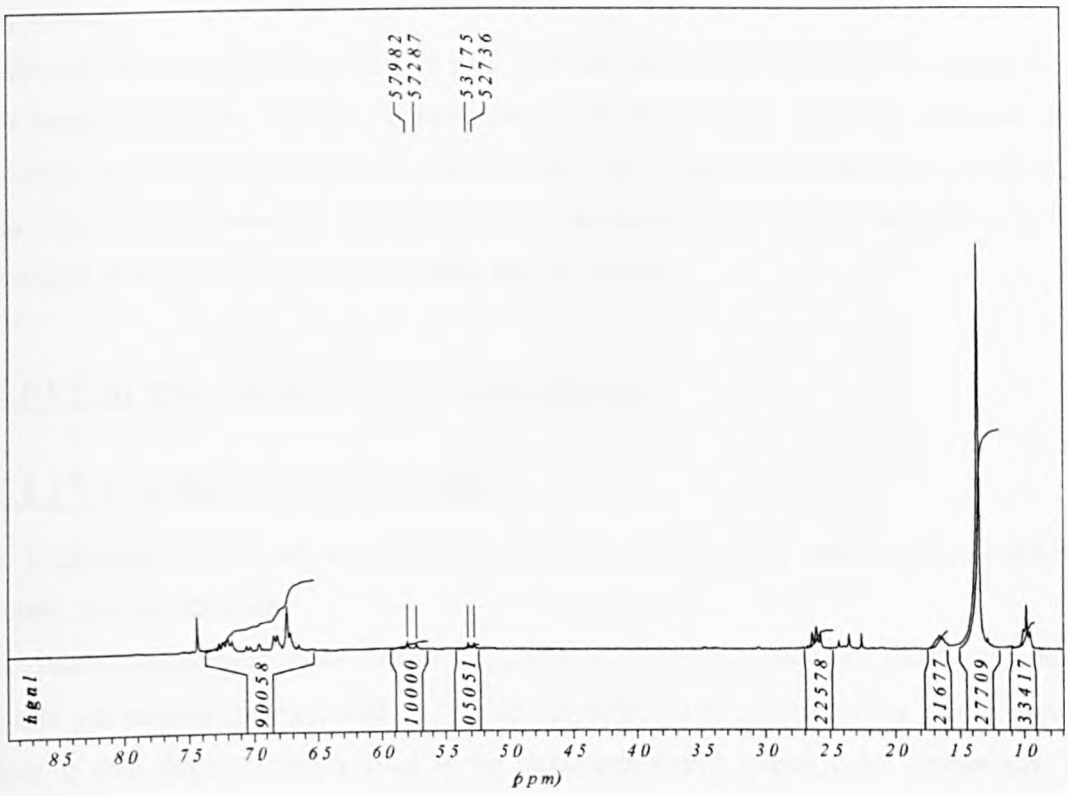


FIGURE 3 - 28: ^{1}H NMR SPECTRUM OF PRODUCT OF CARDANOL(15:0) FVP AT 826° C

The ^{1}HNMR clearly shows besides the characteristic signs of cardanol (15 : 0) (same aromatic signals as cardanol, and the characteristic benzyl group triplet, α-to benzyl, and the long chain broad signs, and the terminal-chain multiplet), the characteristic doublets of the vinyl group of MVP. Theory indicates that radical initiation of reactions of unsaturated cardanols occurs between the two alkenes. It is not surprising therefore that no reaction occurs at 740 °C using 15 : 0 cardanol, and that a temperature in excess of 820 °C was required to initiate any reaction.

3.6.2.FVP of anacardic acids

On the basis that anacardic acids should, at temperatures lower than 400 °C decarboxylate easily, giving cardanols, it was expected that FVP could also give MVP.

If, in the FVP reactions of CNSL, a dehydrogenation reaction could be induced, it would likely to be at the expense of EP.

As it has been established that carbon dioxide has a positive effect in dehydrogenations in the gas phase,[282,283] it was speculated that FVP of anacardic acids could, due to the argument above, give a higher yield of MVP. Preliminary experimental results could not confirm this hypothesis, as the yield of MVP obtained by FVP of anacardic acids (48 %, @ 760 °C) was

lower than the one obtained from FVP of cardanols (64 %, @ 760 °C) at the same temperature.

As the role of the allylic bonds in the FVP reaction and the methodology to reduce the tar have been established, and no improvement in the MVP yield could be obtained using anacardic acid instead of cardanols, the next step was to perform a sequential study of the other constituents present in technical CNSL obtained in the solvent extraction process developed in Chapter 2, e.g. the flocculate and the cardols.

3.7.FVP of non-cardanol CNSL constituents

3.7.1.FVP of the flocculated solid

The flocculated solid is an aggregate of cardanols, salts (mainly potassium) and other ill defined organic materials.

Coke inhibitors reported in the literature include salts of alkali metals or alkali-earth metals at parts per million (ppm) quantities, which are believed to promote coke gasification by steam. It was therefore not known if the flocculate could inhibit coke production. The flocculated solid obtained from acetonitrile-petrol separations (50 % solution in THF), was injected, three successive times, in the copper ring filled reactor at 740 °C. NMR elucidation of the recovered products (around 52 %) showed that it was mainly THF with around 4-5 % product, suggesting either that this fraction does not crack, or that is much less volatile than cardanols, and that most of it does not even reach the hot part of the reactor.

3.7.2. FVP of cardols

The approach to the FVP of cardols followed the same methodology as the one used for cardanols. The first step was to analyse whether it was possible to vaporize cardols. Introducing cardols (1.00 g) directly in the hot zone (at 450 °C) of a quartz tube filled with copper rings, led to the recovery of around 8 % of a liquid fraction. ^{1}HNMR analysis showed no trace of a vinyl signal, while TLC using ethyl acetate suggested that the reaction mixture had a high polarity (Rf = 0). Attempts to change the copper rings for quartz rings or aluminium cylinders did not modify the results.

It is therefore highly likely that cardols were generating tar in the preliminary CNSL FVP experiments. However it is not possible to rule out the possible generation of a dihydroxybenzylic radical which may decompose into a meta vinyl resorcinol, once the problem of vaporisation of cardols is solved. A possible solution to this problem could arise from the approach used in the MS-EI assay, i.e to introduce cardols in a stream of nitrogen,

and vaporize them in an additional oven and then pyrolyse-them. This would involve the use of additional equipment, not available for this research.

3.7.3.FVP of Bhilawanol Shell Liquid

Bhilawanol Shell Liquid (Semecarpus oil) was submitted to FVP in the temperature range of 400 - 800 °C, using the procedure previously described for cardanols. The liquid fraction collected varied between 57 - 18 % (by weight) of the starting material. None of the HNMR spectra of these samples showed any signal characteristic of a vinyl phenol. Work on these sample was suspended because of the author's violent allergy to the compounds present in the oil.

Conclusions

The results presented could not indicate that there is a contribution of non-isoprenoic dihydroxyaromatic compounds (cardol or alkenylcatechols from Bhilawanol Shell Liquid) in the production of vinylaromatic structure. However the possibility to obtain vinyl derivatives by changing the procedure of vaporisation could not be excluded.

3.8.Pyrolysis of CNSL

Technical CNSL contains cardanols, cardols, and an agglomerate (of cardanols, metallic salts and others unidentified compounds). Cardanols, the major constituents, give mainly MVP under pyrolytic conditions, while cardols apparently afford a decomposition mixture. Because the amount of cardol is relatively small, a simplified procedure to purify the oil prior to pyrolysis was therefore devised, focussing in the elimination of metallic salts.
CNSL was therefore dissolved in dichloromethane, washed with HCl, vacuum dried and flash pyrolysed on copper at 760 °C giving a condensable fraction (42 % by weight based on CNSL, with 47.5 % MVP by GC).
As a control Cardolite NC 500 (a distilled CNSL grade) supplied by Cardolite (estimated price, given by the supplier 4 USD/kg) gave 44 % mass as the condensable fraction of the products, with 48.5 % MVP by GC).

3.9.Could this be a useful route to meta-vinylphenol ?

Could one of the new methods presented here be useable to transform CNSL into MVP/EP on a larger scale ? Obviously an answer to this question lies in the economics of CNSL FVP. A rough idea of the feasibility is obtained comparing the value of the products of the

reaction with the main costs (the price of cardanols, of energy for the all process, the cost of the equipments, and others costs). Such a study, using as input the experimental data collected here, is presented in Annex and indicates that FVP in copper tubes is feasible. Sensitivity analysis shows that even considering the potential value of 3-vinylphenol at the present market value of ethylphenol, or if the yield of vinylphenol in the industrial unit was 2/3 of the one obtained in the laboratory scale, this unit would still make a profit. Similar calculations, but using published data of the previous CNSL pyrolysis in tubular reactors, and our data on oxypyrolysis show that in all other CNSL pyrolysis cases the cost of starting material is higher than the value of the products.

4. CONCLUSIONS & RECOMMENDATIONS

4.1.General

Previous research (see Table 3-1) has shown that it was possible to obtain meta-vinylphenol by pyrolysis of cardanols in a tubular reactor, but with less than 30 % yield. Present work shows that it is possible to increase this yield up to 64 % (see Figure 3-21), using vacuum and copper tubes. As vaporisation is a crucial question in the pyrolysis process, and because vacuum could insure smooth vaporisation of the cardanols, this was a justified premise of the study. Copper has been shown to inhibit secondary, coke producing reactions. As coke itself catalyses secondary reactions (compare Figure 3-14 with 3-17) either the use of copper or others materials with low hydrogen chemisorbtion have an expected beneficial effect on the reaction yield. A preliminary economical analysis, based on the experimental results, using the cost of the equipment estimated by Selas, and others costs (cost of CNSL, manpower, energy,[i] taxes and others) estimated on basis of current values in Wales, indicated that with the new approach presented in this thesis, the value of the products[ii] is higher than the commercial value of the starting material, and this was not the case in previous studies.

4.2.FVP on copper

Because for three different FVP processes – pyrolysis on quartz, on copper and on aluminium the maximum yield occurs at the same temperature, a clear conclusion that could

[i] Energy consumption is mainly for the pumps, (vacuum pumps, feed pump and others), as the energy for the reaction is to be provided by burning the non-condensable gases resulting from the cracking. Heat balance shows that in addition to providing thermal energy for the pyrolysis process, these gases could also provide energy for other thermal processes of an eventual industrial plant.

[ii] In this study the price ex-factory of MVP have been assumed to be 75 % of 3-ethylphenol, its more likely precursor in an alternative chemical synthesis.

be drawn is that these different materials do not change the outcome of the main reactions- i.e do not have an appreciable catalytic effect. In the FVP conditions reported in this work, copper and aluminium deposit little coke while steel leads to its production. Extension of this work on FVP to materials with low hydrogen chemisorbtion (aluminium and copper), in the pyrolysis of other materials susceptible to be coke precursors (highly unsaturated, aromatic compounds, *etc...*) still needs to be performed.

4.3.Cardanol FVP

Pyrolysis of cardanols follows the same characteristic pattern as the pyrolysis of alkylaromatics, i.e. giving as the main products MVP in place of styrene. Yields of minor compounds are a function of operational conditions. FVP of cardanol (15:0) in the same apparatus and conditions as the one used for mixed cardanols, gave a smaller conversion. This is consistent with the possibility that reaction is initiated by homolytic scission of a carbon-carbon bond which is simultaneously α to a double bond and β to another one in the alkyl chain.

In FVP on copper rings, cardanols, in liquid phase, are introduced into a tube filled with copper rings (alternatively a copper tube), under vacuum (or with gas carrier) and externally heated at 740 - 760 °C. The volatile products contain MVP, EP in high yield. Additionally, as well as a non-condensable gaseous fraction, 3-cresol, phenol and a non-identified aromatic fraction are obtained as minor compounds. The distribution of the reaction products is a function of temperature and a maximum of MVP is obtained at 750 °C. The non-identified aromatic fraction can be separated by simple batch vacuum distillation and be recycled. Eventually a 2 stage condenser could selectively condense the non-identified aromatic fraction; this needs to be checked on a larger scale. As the other components of the liquid fraction do not have double bonds, MVP can undergo selective reactions, without being separated from EP, 3-cresol and phenol and the products be separated at a later stage. This technique presents the advantage over previous procedures for CNSL pyrolysis, in providing high yields of MVP, using simple and cheap equipment.

In the conditions of this study, FVP of cardols, and bhilawanol did not give vinyl compounds.

4.4.Recommendations for further study

1. As shown by this work, Flash Vacuum Pyrolysis on materials with low hydrogen chemisorbtion (copper and aluminium), of chemicals susceptible to be coke precursors (highly unsaturated, aromatic compounds with low volatility) confirms the possibility of

having cleaner reactions, significantly increasing yields, in comparison with others modes of pyrolysis.

2. Profitability, indicated by a rough preliminary feasibility analysis, suggested that FVP of cardanols could be economically feasible and that the cost to produce MVP, by CNSL pyrolysis, is smaller that the present market cost of ethylphenol, its most likely precursor. To scale-up the present methodology to an industrial scale there is a need to a) clarify the relationship between the dimension of the copper tube the remaining parameters of the reaction (temperature, pressure) and the yield of MVP, b) investigate the concepts of two stage condensation of the products of reaction and recycling and c) assess the environmental impact of proposed process. This could be done in a demonstration plant (capacity cardanols 2 kg/h) that could also provide samples to study chemical routes to drugs (phenylephrine, termoporfin, tramadol, anipamil, picenadol and exelon) and others fine chemicals (pyrethroids...) with MVP substructure.

CHAPTER 4- SOME NEW CHEMISTRY OF CNSL CONSTITUENTS

1. INTRODUCTION

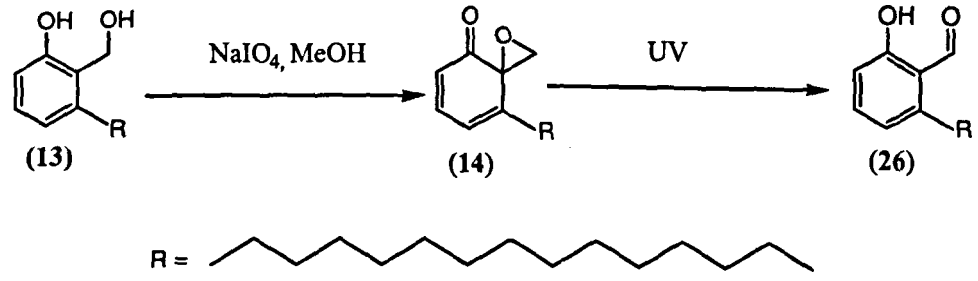
Anacardic acids and cardols, both constituents of CNSL are also expected to provide routes to new chemicals. From the array of possible questions that could to be investigated two were analysed in the present work:

1) What kind of chemistry would be obtained from 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (**14**) ?

2) Could CNSL derivatives provide synthons for the design of new anti-HIV drugs ?

1.1. 8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

The oxaspirodienone (**14**) was obtained by Tyman and collaborators by reduction of anacardic acid (15:0) to the pentadecylsalicylic alcohol (**13**), followed by oxidation with sodium metaperiodate. It was then converted into the corresponding salicylic aldehyde (**26**) by treatment with UV light.



SCHEME 4 - 1: OXIDATION OF PENTADECYLSALICYLIC ALCOHOL

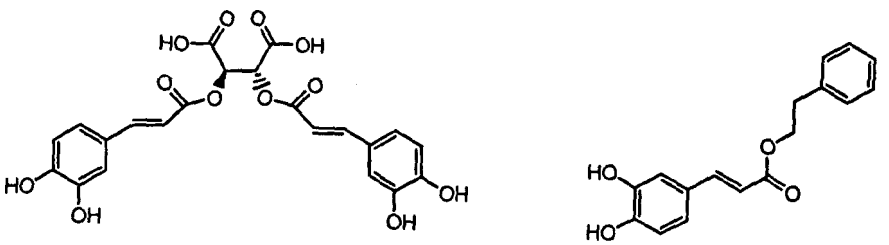
However the spirodienone (**14**) has 3 different functional groups, and so is a perfect candidate to provide a range of selective reactions, and therefore a multiplicity of different new chemical structures. Other oxaspirodienones have been reported to undergo an array of reactions with nucleophiles, and to give a range of Diels Alder adducts.[285-290]

The development of a matrix of new products, that could be generated by either nucleophilic additions or Diels Alder cycloadditions, involving the oxaspirone (**14**), looked therefore to be worthwhile.

1.2.CNSL constituents derivatives with potential anti HIV properties

A variety of anti-HIV agents rely on inhibition of key enzymes involved with the virus life cycle. Among these enzymes, three have been identified as important targets for therapeutic developments: *reverse transcriptase*, *protease* and *integrase*. The first two have been extensively studied with inhibitors already on the market like AZT and

indivinar. The third and less studied enzyme (integrase) is known to be essential for effective viral replication. Additionally, the fact that it is not indigenous to mammals, makes it a very attractive target for selective attack. Two natural integrase inhibitors are represented in Figure 4 –1 Cape (**28**) is the reference anti-integrase compound used in most published research.



(27)
Chicoric acid

(28)
Cape

FIGURE 4 - 1: NATURAL INTEGRASE INHIBITORS

A consistent feature of many integrase inhibitors is the presence of two aromatic rings (with one at least with a dihydroxyl pattern) separated by an appropriate linker.

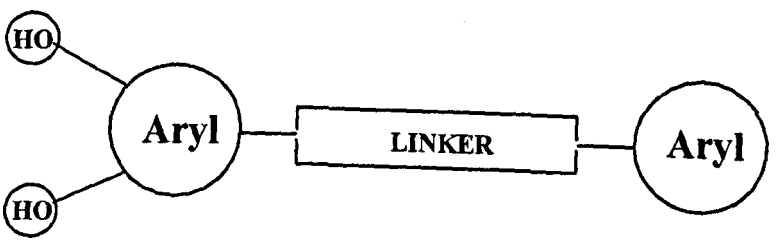
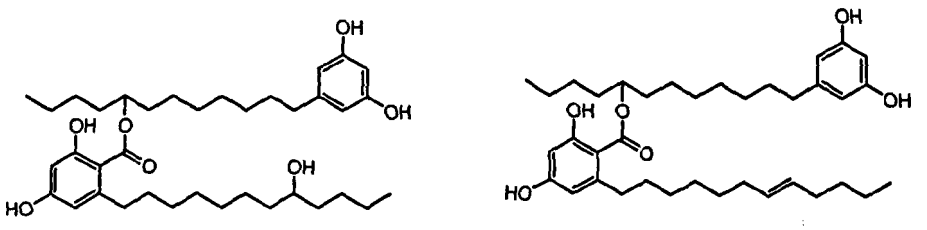


FIGURE 4 - 2: COMMON STRUCTURAL FEATURE TO INTEGRASE INHIBITORS

This may indicate that these inhibitors interact with the enzyme at a characteristic binding site related with the existence of a dihydroxylaryl substructure connected to an aryl structure. One limitation of the presently investigated inhibitors, is the collateral toxicity supposed to arise by oxidation of the catechol-like dihydroaromatic to reactive quinone species. Once formed these have been reported to undergo nucleophilic reactions with cell elements with a variety of adverse effects, limiting their possible use as drugs candidates. In order to address this problem, a resorcinol like structure is an ideal candidate for integrase inhibitor design, as the dihydroxy pattern is not properly situated for the unwanted quinone reaction. Additional evidence that dihydroxy resorcinols could be an interesting target for anti-integrase activity is the isolation of two of such compounds (**15**) & (**29**) which have been found to show very high activity.[121]



(15) (29)

FIGURE 4 - 3: BIS-RESORCINOLS WITH HIV-INTEGRASE INHIBITION PROPERTIES

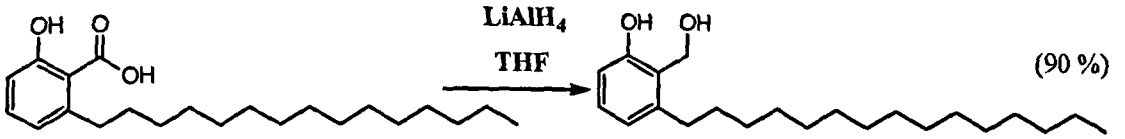
These are clearly related to cardols and anacardic acids which therefore provide potential synthetic starting points.

2. RESULTS AND DISCUSSION

2.1.Oxaspirodienone chemistry

2.1.1.Synthesis of the oxaspirodienone

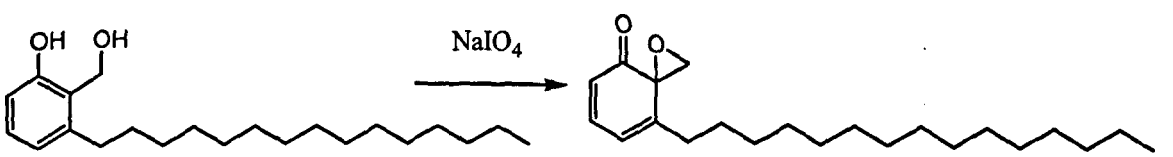
Anacardic acids separated as described earlier, were hydrogenated over palladium on charcoal to afford the saturated congener, anacardic acid (15:0) (**1a**). Using lithium aluminium hydride in THF, this compound was reduced to pentadecyl salicylic alcohol (**13**), identified by HNMR, in 90 % yield.



(1a) (13)

SCHEME 4 - 2: REDUCTION OF ANACARDIC ACID (15:0)

It was found that critical to the yield of the reaction was to control the temperature during the quench to 8 - 10 °C. The crude product was easily re-crystallised from hot acetonitrile to afford a white powder.



(13) (14)

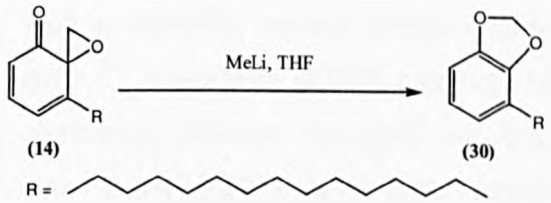
SCHEME 4 - 3: OXIDATION OF PENTADECYL SALICYLIC ALCOHOL (13)

Previously [118] the spirodienone (**14**) had been obtained in 12% yield by oxidation of pentadecyl salicylic alcohol (**13**) with sodium metaperiodate in hot methanol. The yield was

improved to 47 % by using a two-phase reaction using dichloromethane-water and a phase transfer catalyst at room temperature. By recrystalisation from petrol, the spirodienone was obtained as an unstable white solid that could be kept for 24 h in the fridge. Attempted activation of sodium periodate with acid or base [hydrochloric acid (1%), acetic (1%), sodium hydroxide (1%)] decreased the yield of the reaction.[i] Analysis of the crude reaction mixture by ^{1}HNMR shown that attempted uses of an alternative oxidant (sodium-di-chromate) led to ring cleavage.

2.1.2.Rearrangement to benzodioxole.

Treatment of the oxaspirodienone (**14**) with methyl-lithium was expected to lead to the attack on the dienone or ring opening of the epoxide allowing a range of substituents to be introduced. However, in fact it afforded the pentadecylbenzodioxole (**30**) in 54.5 % yield, by an apparent rearrangement (Scheme 4-4).



SCHEME 4 - 4: REARRANGEMENT OF OXASPIRODIENONE (**14**) TO PENTADECYLBENZODIOXOLE (**30**)

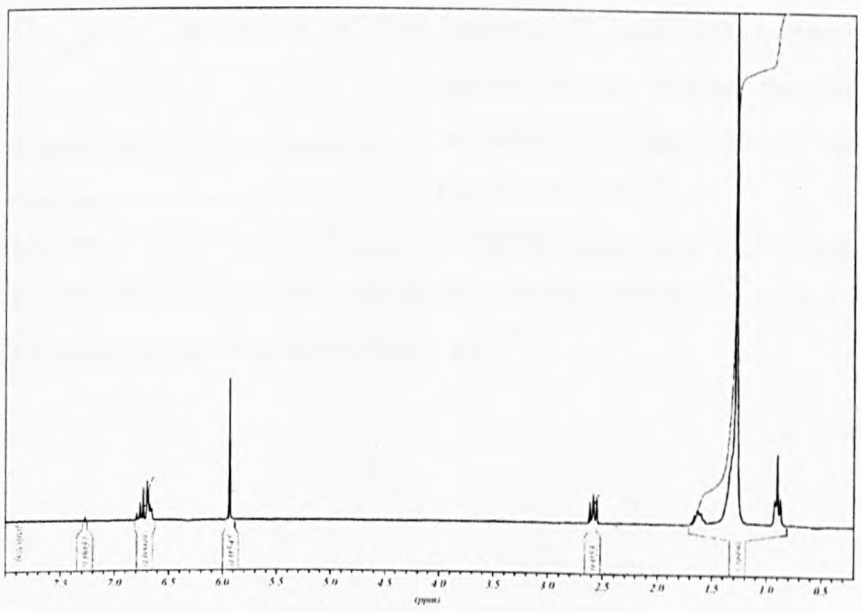
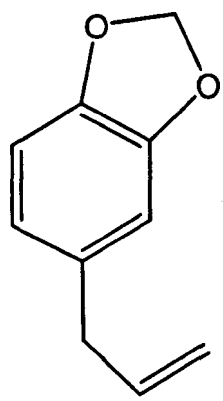


FIGURE 4 - 4: ^{1}HNMR SPECTRUM OF 4-PENTADECYL-BENZO[1,3]DIOXOLE

[i] Another salicylic alcohol, 2,4- dibromo-6-hydroxymethyl-3-methoxy-phenol, is reported to have been oxidized to the corresponding spiro compound, with aqueous sodium metaperiodate with HCl.[293]

Compound (**30**) had the same mass, and provided the same elemental analysis as (**14**), and exhibited the expected ^{1}H and $^{13}CNMR$ spectra. The dioxole characteristic group, the methylene protons between two oxygen, appeared as a singlet at δ 5.9 (similar to the chemical shifts of others dioxoles reported in the literature).[290, 301, 302] The aromatic protons appeared as a multiplet at δ 6.65 - 6.8, while the chemical shifts corresponding to the benzylic protons and the linear carbon chain were similar to those of (**14**) demonstrating that the alkyl chain was unchanged. The IR spectrum, showed no broad peak at 3600 cm^{-1}, indicating the lack of a free OH group, peaks at 1250 cm^{-1} and 1054 corresponded to the aryl-O-CH_2 structure, while a peak at 906 cm^{-1} indicated an aromatic structure.

This simple approach to a benzodioxole (BDXO) in three steps from a natural acid was interesting, as it could eventually lead to a better understanding of the biological pathways that lead to naturally occurring BDXO.



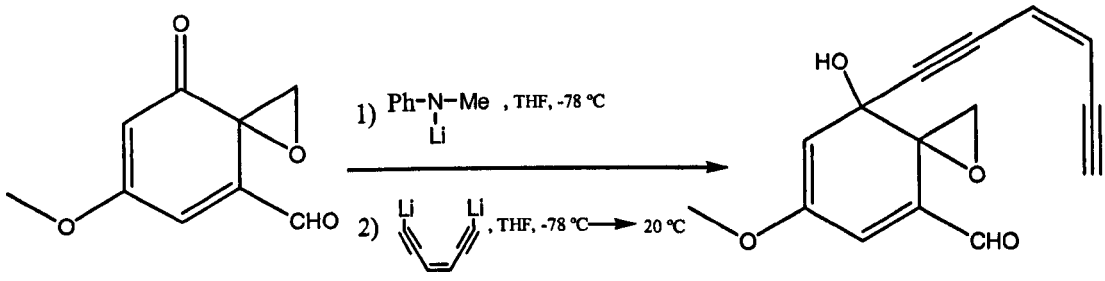
(31)

FIGURE 4 - 5: SAFROLE, BDXO OF SASSAFRAS

These are found in a variety of food, essential oils, and flavours, such as sassafras, nutmeg, parsnips, carrots, parsley, and sesame seeds.[291] A synthetic BDXO, piperonyl butoxide is a well known commercial pesticide synergist with pyrethroid and carbamates insecticides. BDXO have been reported to be a common substruture of compounds with strong nematocides and arthropodicidal properties,[313, 314] to have been associated with prevention of liver necrosis[i],[292] and shown cytotoxic activity against several human tumour cell lines, including multidrug resistant nasopharyngeal carcinoma cells.[293]

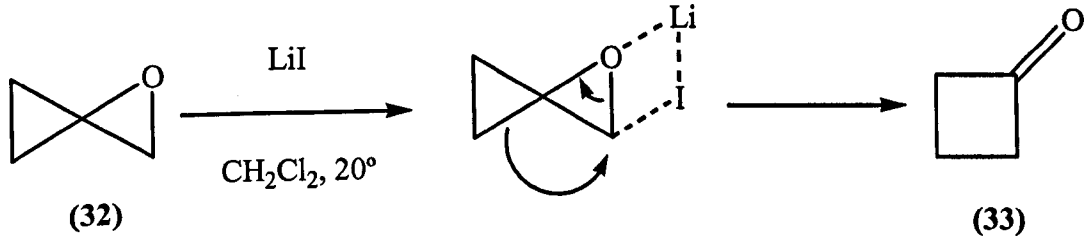
The rearrangement of the oxaspirodienone to BDXO (presented in Scheme 4-2) was a surprise as the literature reports that addition of a lithium acetylide to related spirodienone occurs at the keto group (see Reaction Scheme 4-5).[296]

[i] Safrole, a BDXO and a major (90 %) component of the sassafras oil (flavouring agent used in the beverage industry) is an hepatocarcinogen, and its use was banned by the FDA in 1976.[294] Up to 85 % of parsley oil, and 75 % of the nutmeg is a BDXO ,myristicin, which has been reported to stimulate hepatic regeneration, and exhibit a monoamine oxidase inhibitor action, acting as an hallucinogenic.[295]



SCHEME 4 - 5: ORGANOLITHIUM ADDITION TO A SPIRO COMPOUND

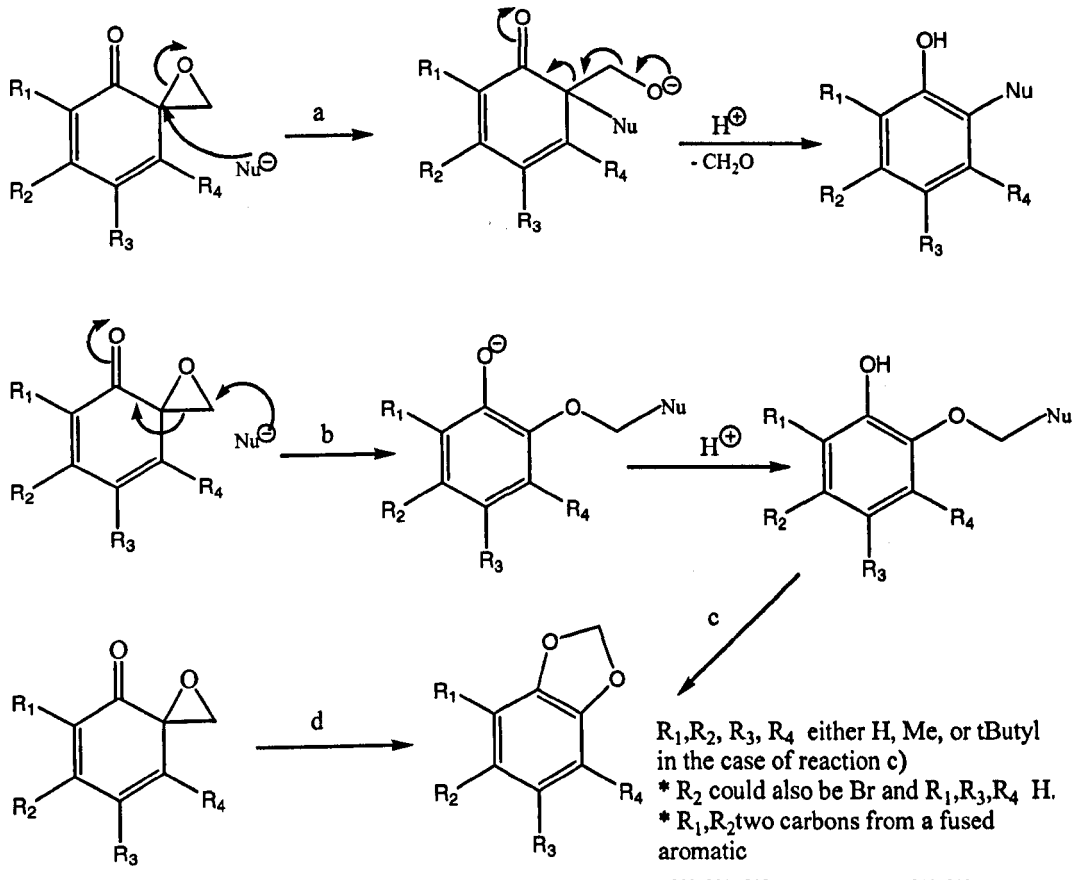
However the dioxole (**30**) was also obtained by treating the dienone (**14**) with butyl lithium, lithium bromide, or lithium di-isopropyl amide, suggesting that the reaction was due to either a "base" effect or to a "lithium" effect. Lithium induced rearrangements have been reported previously, in the transformation of oxaspiropentane (**32**) to the cyclobutanone (**33**).[297]



SCHEME 4 - 6: LITHIUM INDUCED REARRANGEMENT OF A SPIRO COMPOUND

To check this hypothesis, (**14**) was reacted with non-lithium nucleophiles (piperidine and morpholine), but both these reactions also afforded (**30**) in 85 % and 74 % yield, as the major detectable compound. As this suggested that the rearrangement was base induced, it was then decided to analyse what kind of pH could optimise the yield of the reaction and, in parallel experiments, the spirodienone was reacted with a range of bases in dichloromethane. Potassium t-butoxide let to a tarry mixture, but amines (IPA, DEA, and TEA) gave quantitative yields of the rearrangement product, the reaction with TEA giving the fastest reaction. As the rearrangement was proved to be base catalysed, it was decided to test the behaviour of (**14**) with acid. When compound (**14**) was dissolved in acetic acid, no reaction could be observed, while in a dichloromethane suspension of zinc dibromide it also afforded the rearrangement product (44 %).

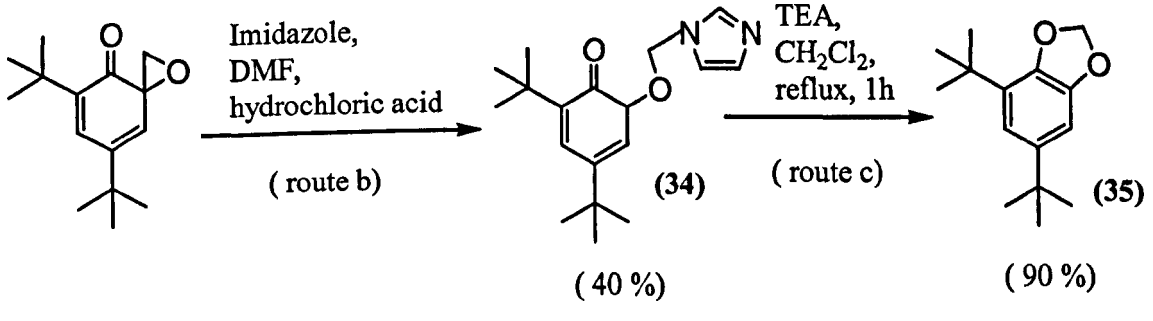
In addition to the addition to the keto group (see Scheme 4-5), the literature reported three others basic cases of nucleophile reactions with substituted oxaspirodienones .[290, 298, 299]



References: reactions (a), [298, 299, 301, 300] reaction (b), [290, 301, 302] reaction (c).[290, 302]

SCHEME 4 - 7: NUCLEOPHILES REACTION INVOLVING OXASPIRODIENONES

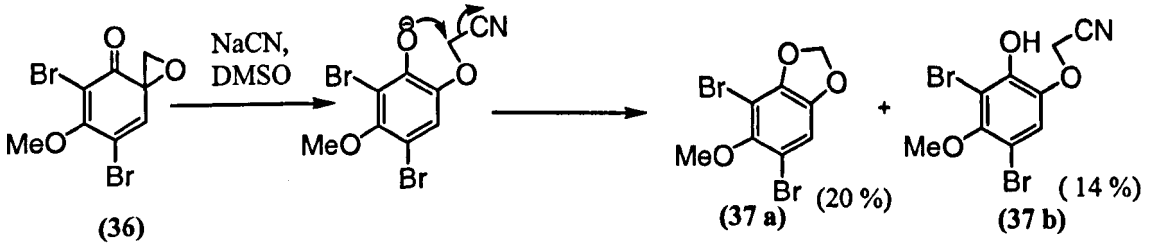
When the nucleophile was malononitrile, (or either chlorotrimethylsilane, or p-toluene sulfonic acid), reaction led to a displacement of the quarternary spirocyclic carbon (see reaction (a) in the Scheme 4-7 to form a substituted ortho phenol. Stereoelectronic requirements for the S_N2 process dictate that the nucleophilic approaches close to the R_4 substituent. Thus steric effects should dominate when the attack follows route a). Consequently when obstructed by an ortho substitution (position R_4), this reaction does not take place. In support of this mechanistic proposal, the literature indicates that nucleophilic attack of the more hindered carbon epoxide has only been documented when hydrogen is in position R_4.



SCHEME 4 - 8: NUCLEOPHILE ATTACK BY ROUTES B) AND C)

Hindrance due to the long carbon chain in (**14**) could therefore explain why this reaction could not be observed in the present work.

When the nucleophile was imidazole (or sodium cyanide) reaction led to epoxy ring opening reactions at the secondary carbon (see route (b), scheme 4-8 and 4-9). Caccioli was the first to observe that by treating (**34**) with an amine, it was transformed into the corresponding benzodioxole (**35**).



(**36**) (**37 a**) (**37 b**)

SCHEME 4 - 9: NUCLEOPHILE ATTACK BY SIMULTANEOUS ROUTES B) AND C

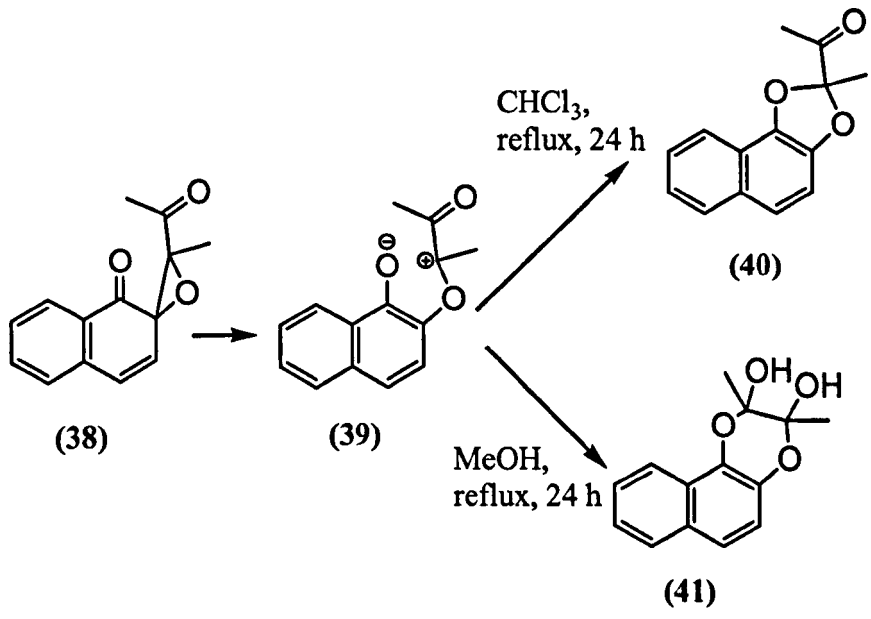
Waldmann postulated a similar pathway, by treating (**36**) with NaCN in DMSO The cyanide nucleophile is reported to attack the epoxide, yielding the benzodioxole (**37 a**), and the cyanohydrin (**37 b**).[303] However the yields in this cases are low. Similar results were reported by Gesson.

In the present study, despite having used the same laboratory procedure as those reported (using imidazole/ sodium cyanate with pentadecyl-oxa-spirodioxole) no evidence of epoxy ring opening by attack on the less hindered carbon was found.

Literature indicated that rearrangement products (reaction c)have been obtained by treating the oxaspirodienone with t-butylchlorodimethylsilane[i]/ triethylamine or in same case by simple heating (in function of the kind of oxaspirodienone, this reaction was reported to be performed at temperature ranging from 60 to 20 °C).

Waldmann reported that heating the oxaspiro (**35**) in toluene afforded the correspondent benzodioxolane (**36**) in 78 % yield.[303] Adam found that the spiroepoxide (**38**) rearranged at room temperature into the dioxole (**40**) as shown in scheme, but in methanol afforded the naphto-1,4-dioxine(**41**).[304] This could be accounted for in terms of opening the spiroepoxide ring, and the resulting zwitterionic intermediate (**39**) (or corresponding biradical species) recyclizing to the 1,3-dioxole or being trapped by methanol.

[i] The fact that the two chlorosilane nucleophiles gave different products does not allow any conclusion because in this second case others reagents, shown to induce rearrangement (the amines) were present in the reaction mixture.



SCHEME 4 - 10: REARRANGEMENT OF AN ACTIVATED OXASPIRODIENONE

In the present study, the existence of such dipolar/diradicalic intermediate would be possible as it would have, at one end, a primary carbocation/radical stabilised by resonance due a vicinal oxygen (Figure 4-4).

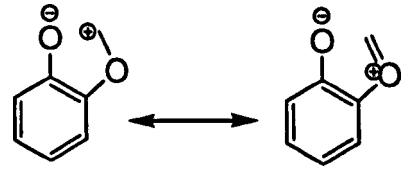
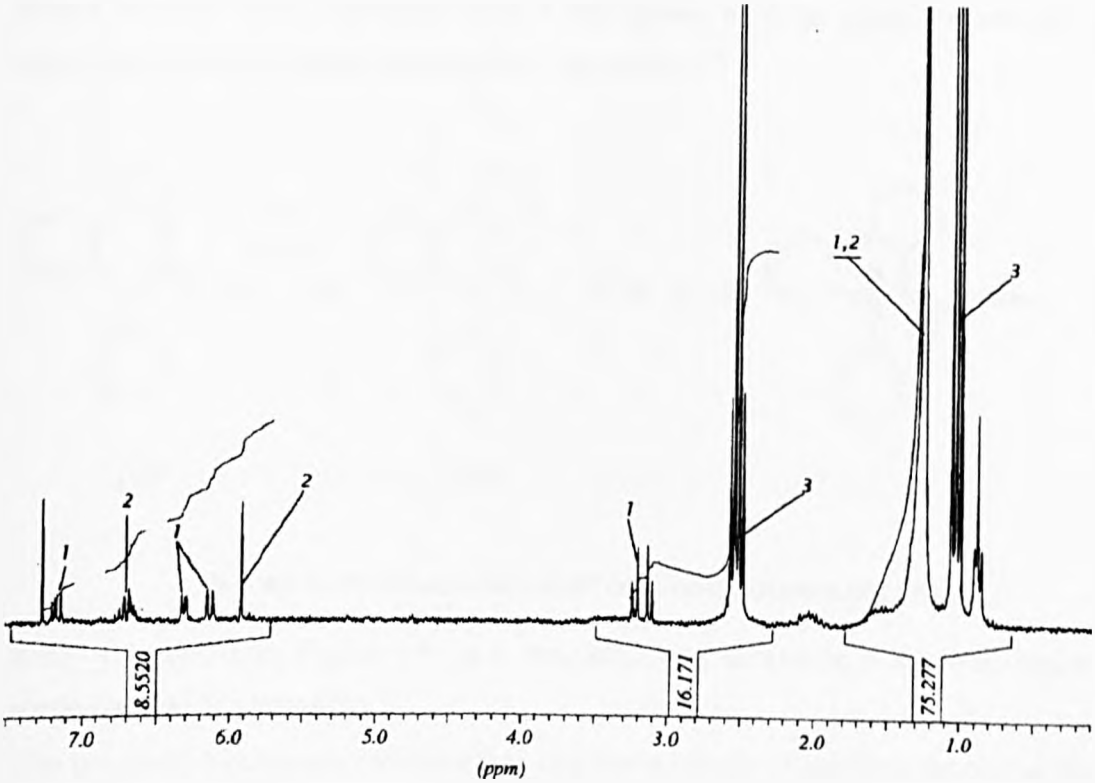


FIGURE 4 - 6: RESONANCE STABILISED ZWITTERIONIC INTERMEDIATE

Therefore to check the possible existence of an intermediate, the formation of pentadecylbenzodioxole was followed by ^{1}HNMR. Because previous data indicated that the amines provided cleaner products, and because an amine would trap an eventual carbocation intermediate, two amines (triethylamine (TEA), isopropylamine (IPA)) were added in two separate experiments to the oxaspirodienone dissolved in $CDCl_3$ and the reaction followed until completion by NMR. In none of these experiments could products beside pentadecylbenzodioxole be detected, TEA providing the fastest reaction complete in less than 24 h.



Signals labelled with 1-correspond to the oxaspirodienone (**14**), 2 to the pentadecylbenzodioxolane (**30**) and 3 to triethylamine

FIGURE 4 - 7: ^{1}H NMR SPECTRUM **OF THE REACTION BETWEEN OXASPIRODIENONE AND TEA**

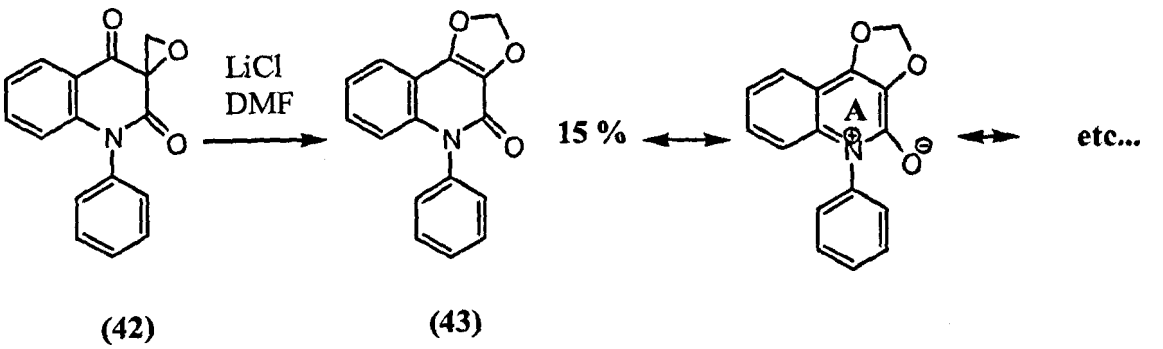
Figure 4-7 corresponds to the ^{1}HNMR obtained after 6 h of reaction, which shows clearly only the signals matching the chemicals shifts of the oxaspirodienone (1), the pentadecylbenzodioxolane (2) and triethylamine (3)

The evidence presented in this work and the known fact, that transformation of an oxaspirodienone into a benzodioxolane is possible by simple heating, suggests that possible mechanisms could be an intramolecular [$_\pi$2 + $_\sigma$2] cycloaddition reaction, or a 1,3 sigmatropic migration of carbon analogous to the rearrangement of a vinylphosphirane to phospholene.[305]

In the rearrangement of an oxaspirodienone to a benzodioxole, there are two conflicting energetic effects. Firstly the transformation of a carbonyl group into an ether unit is energetically unfavorable, it is the opposite of the driving force behind the Claisen rearrangement of allyl vinyl ethers to the corresponding carbonyl compounds. On the other side, there is the relief of the epoxy ring strain, which favors the concomitant formation of a five –membered dioxole ring, and of a resonance stabilized aromatic ring. The second factor obviously dominates and constitutes the driving force for this process. It is interesting to note that the Beildstein-Crossfire 2000[1] database indicated only one rearrangement (given in

[1] Consulted last time in August 21 2003.

Figure 4-5) in which a structure with a keto group α to an epoxy, which was not a substituted oxaspirodienone, rearranges to a dioxolane.[306]



(42) (43)

FIGURE 4 - 8: REARRANGEMENT OF A SPIRO QUINOLINE DIONE

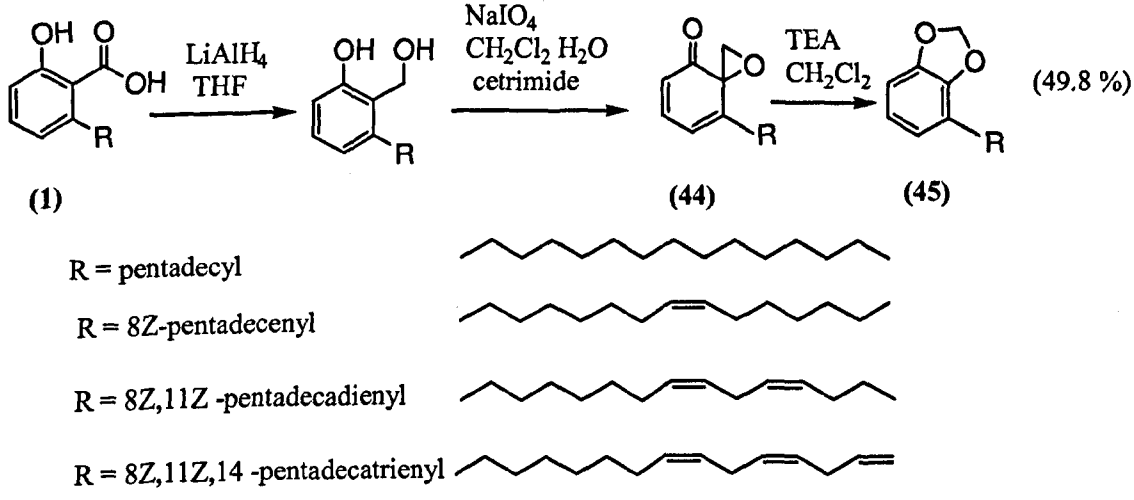
Ring A in (42) (see Figure 4-8) is a mesoionic ring similar to a syndone, which is a particular case of aromaticity.[307]

The proposed mechanism indicates that electronic effects of substituents on the dienone ring play a significant role in controlling the ratio of rearrangement to other reactions. the more electron rich the dienone moity the higher the amount of benzodioxole and this could explain why the addition of methyl lithium to the alkyl substituted oxaspirodienone (14) yields a benzodioxole (29) (see scheme 4-2), while the same nucleophile added to the methoxy-formyl substituted oxaspirodienone (30) afforded the alcohol (31) (see scheme 4-3). A brief survey on the literature available on [1,3]carbon sigmatropic shifts reveals that these involved both stepwise and concerted processes,[308] and have been induced and accelerated by a number of complexing agents and electron donors reagents.[309,310] These characteristics are common with the rearrangement to benzodioxole observed under moderate reaction conditions used in this work and reported from the literature.

Because it was suggested that the latent aromaticity of the spirodienone was driving the re-arrangement, a new approach was to try to hydrogenate selectively either one of the double bonds or the carbonyl group. First two procedures reported to allow the selective reduction of an unsaturated ketone group to the corresponding alcohol were used (reactions in presence of dimethylcuprate, or in a presence of a catalytic amount of aluminium isopropoxide (the Meerwein-Ponndorf-Verley reaction). Both afforded the rearrangement product (29). Because dimethylcuprate was produced "in situ " by a reaction between methyl lithium and copper iodide, the influence of methyl lithium previously reported could not be excluded; and aluminium isopopoxide is reported to form complexes with carbonyl group

suggesting a Lewis acid induction of the sigmatropic rearrangement, a totally different attempt was to try the selective reduction of the non-polar bonds by a di-imide method, as this procedure involves a cyclic mechanism not connected with eventual complexation of the carbonyl group/ or an eventual lithium salt. However, this method also afforded the rearrangement product (**29**).[311,312] Hydrogenation on palladium, expected to led to a complex of the spirodienone on the palladium catalyst and to hydrogenation of the carbonyl group faster, afforded the pentadecyl salicylic alcohol (**13**) and these attempts to hydrogenate selectively one of the functional groups of the spirodienone were abandoned.

2.1.3.-The rearrangement to benzodioxole of unsaturated anacardic congeners



SCHEME 4 - 11: SYNTHESIS OF DIOXOLOLE (MIXTURE)

Having shown that the main compound that could be obtained in quantitative yield from the oxaspirodienone was its rearrangement product, the mixture of unsaturated congeners of anacardic acids (**1**), was reduced to the corresponding anacardic alcohols using the same procedure as for the saturated congener. The crude mixture was oxidized to the epoxide (**44**) which was rearranged to the corresponding mixture of dioxole (**45**) (overall yield 49.8 %). (**45**) was identified by the HNMR spectra shown in the Figure 4-9.

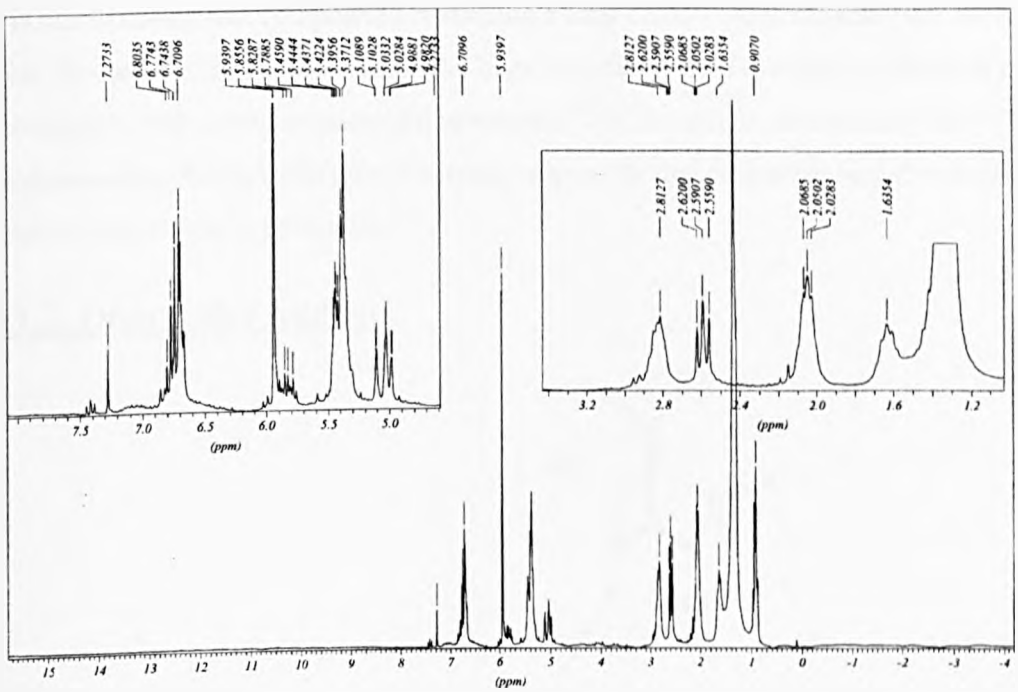
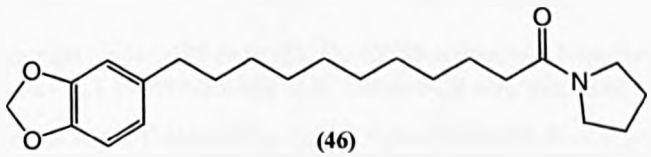


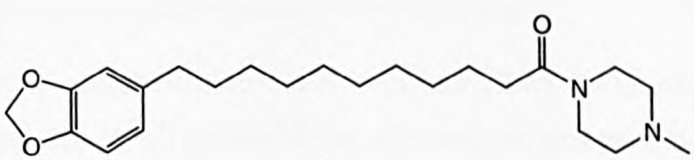
FIGURE 4 - 9: ^{1}H NMR SPECTRUM **OF BENZODIOXOLE (MIXTURE OF HOMOLOGUES)**

The dioxole characteristic group, the methylene protons between two oxygen, appeared as a singlet at δ 5.9, while aromatic protons appeared as a multiplet at δ 6.65 - 6.8, (similar to the chemical shifts of (**14**)), while the others chemical shifts, common with anacardic acids corresponded to terminal vinyl groups, internal alkenes, the benzylic protons, protons α to two double bonds, α to one double bond, α to the benzylic protons, to the remaining hydrogen in the carbon chain, and to the terminal methyl groups.

The double bonds in the 8- position of the chain afford an easy position for cleavage by oxidation, that could allow the mixture to be transformed into a compound with one derivatizable functional group.



(46)

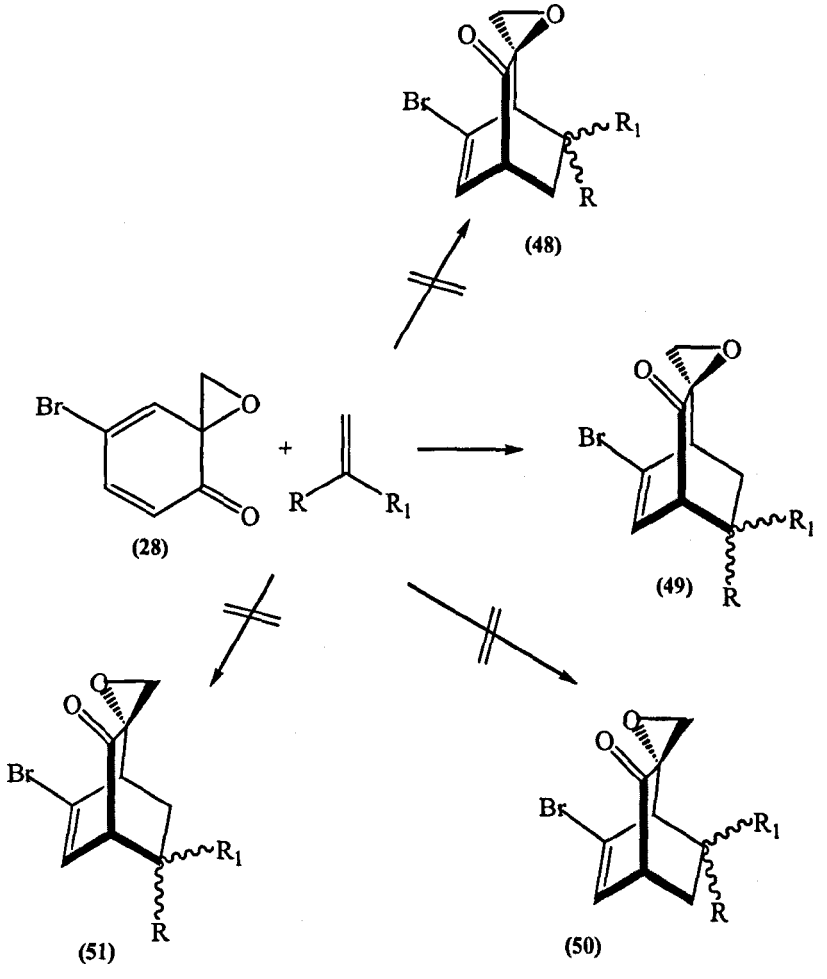


(47)

FIGURE 4 - 10: PYRROLIDINE AND N-METHYLPIPERAZINE AMIDES WITH NEMATOCIDAL ACTIVITY

It is worth noting that compounds containing a long carbon chain dioxole (see **36, 37**) but with the chain in the para-position have been reported to be a common substruture of compounds with strong nematocidal properties.[313] It has also been reported that 5-(3,4-methylenedioxybenzyl)-dioxolane possess arthropodicidal properties and shows synergetic properties with others pesticides.[314]

2.1.2. Diels Alder adducts

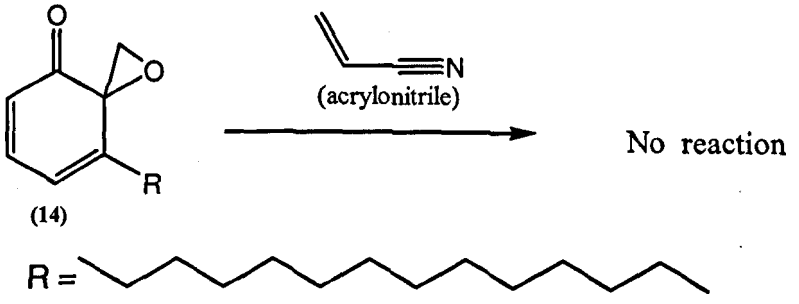


SCHEME 4 - 12: POSSIBLE ADDUCTS IN DIELS ALDER REACTION OF 4-BROMO-6-SPIROEPOXYCYCLOHEXA-2,4-DIENONE WITH ELECTRON-RICH AND NEUTRAL DIENOPHILES.

Compounds were referred as*α* or β (depending on the regiochemistry), *N* or *X* (*endo* or *exo*) and S or A (*syn* or *anti*), **(48)** *α(N or X)S* , **(49)** *α(N or X)A*,**(50)** β *(N or X)S*, **(51)** β *(N or X)A*. (R , R_1) was (O Et, H), (OMe, Me), (OTMS,H), (Ph,H), (OAc, H), (OBz,H) or (H, NMeAc). Yields varied, depending on the dienophile, between 52 % for 2-methoxy-1butene to 88 % for styrene.

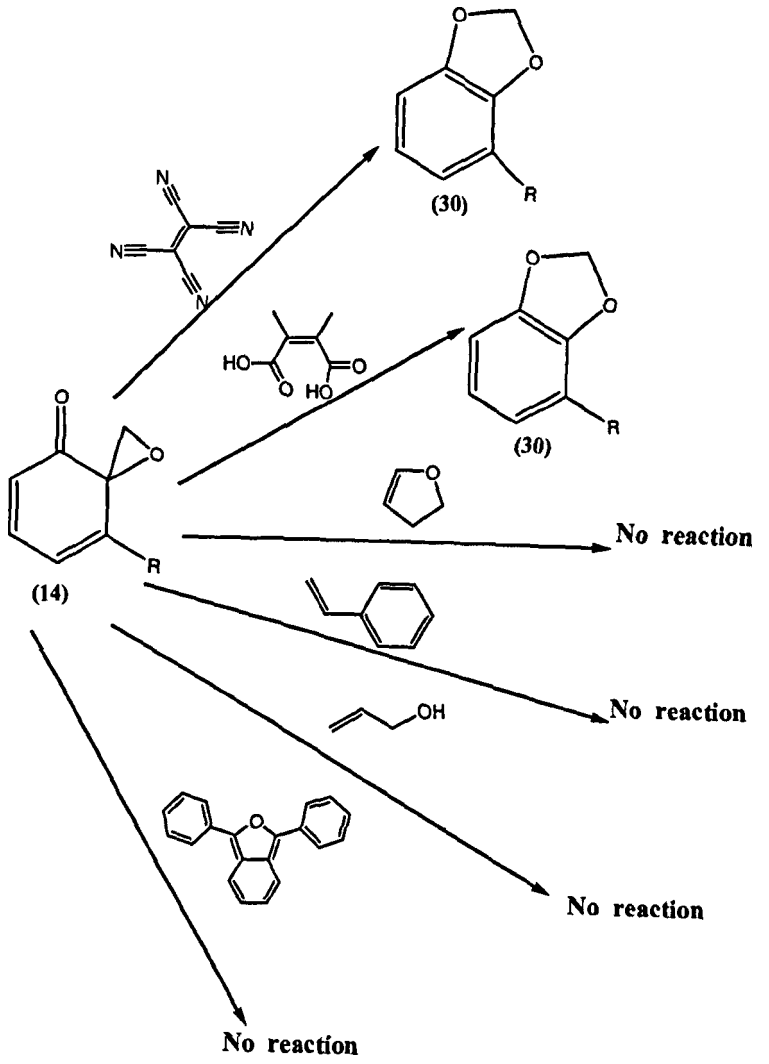
Gesson published a comprehensive study on Diels Alder (DA) adducts obtained by spiroepoxydienone (**28**) [4 +2] cycloaddition with various dienophiles (enol ethers, enol esters, styrenes, N-methylvinylacetamide). Identifying products by X-ray crystallography, he reported complete regio and syn-diastereofacial selectivity, but a switch in endo/exo selectivity between enol ethers and styrene (endo addition), enol

ester (low selectivity) and enamide (exo addition).Syn/endo adducts were also observed with Diels Alder (DA) reaction between other cyclohexadienone and maleic anhydride, methyl acetylenedicarboxylate and cyclopentadiene. Subsequent molecular orbital analysis confirmed that these reactions were under diene LUMO control, and that the observed regioselectivity was in agreement with orbital coefficients. The Gesson results suggested that yields increased with a decrease in the electrophilic character of the conjugating group on the dienophile, i.e. lowering the LUMO energy of the dienophile. Therefore, a dienophile electron withdrawing group adjacent to the double bond, like acrylonitrile was chosen as a reagent to have a high yield reaction. Because **(14)** has an alkyl substituent instead of halogen as **(28)**, it was expected to provide a higher energy HOMO and have a positive effect on the reaction.



SCHEME 4 - 13: ATTEMPTED DA REACTION BETWEEN THE OXASPIRODIENONE (14) AND ACRYLONITRILE

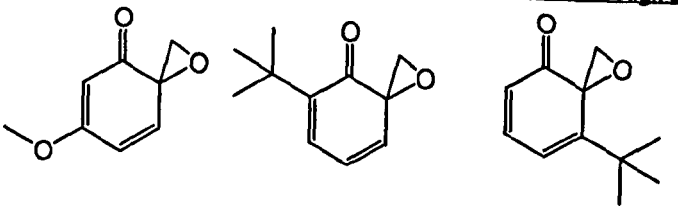
Therefore solution of the oxaspirodienone **(14)** and acrylonitrile (5 equivalents) in ethyl acetate was stirred at room temperature (3 days) and under reflux (3 h). Removal of the solvent and acrylonitrile in vacuo, afforded the starting spiro-compound. The procedure was repeated using the dienone-dienophile neat. As this also did not give any reaction, the procedure was performed in $CDCl_3$ and followed by NMR, but again no trace of product could be detected.



SCHEME 4 - 14: ATTEMPTED DA REACTIONS OF THE OXASPIRODIENONE (14) WITH A RANGE OF DIENOPHILES

The procedure was then repeated using, instead of acrylonitrile, dimethyl maleate and tetracyanoethylene which provided other electron poor dienophiles. Both these reactions afforded the rearrangement product as sole product. Since the Gesson FMO calculations indicated that DA reactions with spirocyclohexadienone were under LUMO diene control, electron rich/ neutral dienophiles were tested. 2,3- Dihydrofuran, styrene and allyl alcohol were used instead of acrylonitrile, but no products could be detected. To try to trap one of the double bonds of (14), 2,5-diphenyl-3,4-isobenzofuran was used instead of acrylonitrile but no reaction could be observed. Attempts to form Diels Alder adducts with (14) were *therefore discarded.*

a-Oxaspirodienone with substituents that suppressed dimerization through Diels Alder



b-Oxaspirodienone with substituents that dimerize through Diels Alder

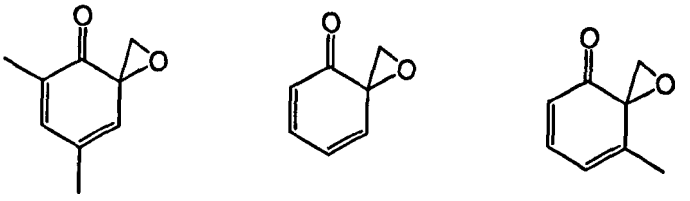


FIGURE 4 - 11: OXASPIRODIENONE SUBSTITUENTS INFLUENCE IN DIMERIZATION THROUGH DIELS ALDER REACTION-

In the light of previous studies, these results were disappointing, but literature also indicates that dimerization, that usually occurs at room temperature through an *endo* DA, may be suppressed by bulky substituent on the spirodienone (see Figure 4-11), suggesting that a steric hindrance due to the long carbon chain may be the cause for the non-reactivity of (**14**) in Diels Alder reactions.[285, 315,290]

2.1.3.Oxaspirodienone chemistry conclusions

1.Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one was obtained in a two step reaction; by reducing anacardic acid (mixture of congeners) to 2-hydroxymethyl-3-pentadecyl-phenol, followed by the oxidation of the latter with sodium metaperiodate.

2.This dienone has been shown to be unreactive in a range of Diels Alder reactions.

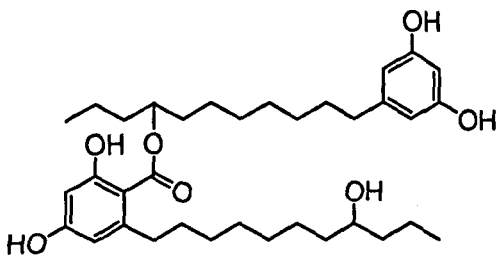
3.The oxaspirodienone undergoes a [1:3] sigmatropic rearrangement to a benzodioxolane (analogous to vinylcyclopropane to cyclopentene) under a variety of conditions investigated. A quantitative yield could be obtained by treating the oxaspirodienone with a mild base, TEA.

4.The same procedure has been shown to be applicable to the mixture of unsaturated congeners of anacardic acid allowing a mixture of benzodioxolane with an unsaturated carbon chain to be obtained.

5.The rearrangement provides a possible rationale for the existence of benzodioxolanes in nature (where it is a quite common substructure) and may eventually provide an insight on a new biochemical pathway that should be investigated.

2.2.Reactions towards synthesis of HIV integrase inhibitors

It was of interest not only to develop a route that could lead to natural products with HIV integrase inhibitor properties (**15**, and **29**) but also that could be flexible enough to allow the synthesis of analogues (**52-55**) for screening purposes. As most integrase inhibitors have aromatic rings substituted with polar, or hydrogen bonding substituents,[316] cardanol and anacardic acid, could be derivatized with such substituents' and therefore the proposed synthesis would afford a general template.



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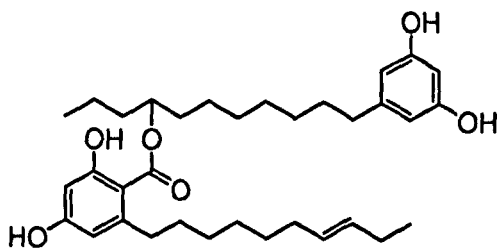

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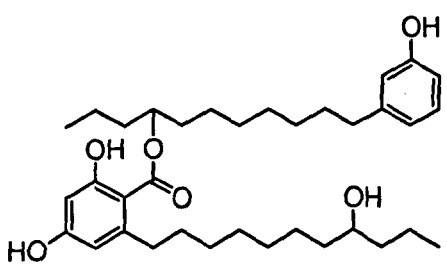

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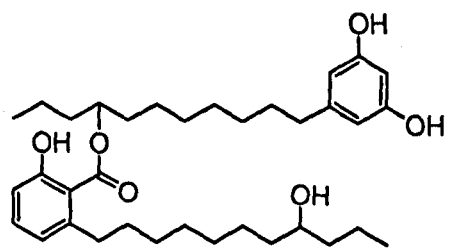

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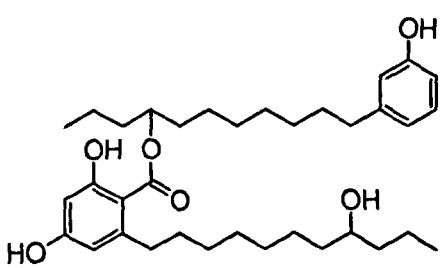

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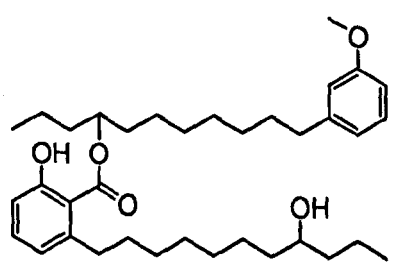


(55)

An additional advantage of the proposed methodology is the use not only of cardol but also of anacardic acid.

2.2.1.Retrosynthetic analysis

Analysis was performed on compound (**15**).

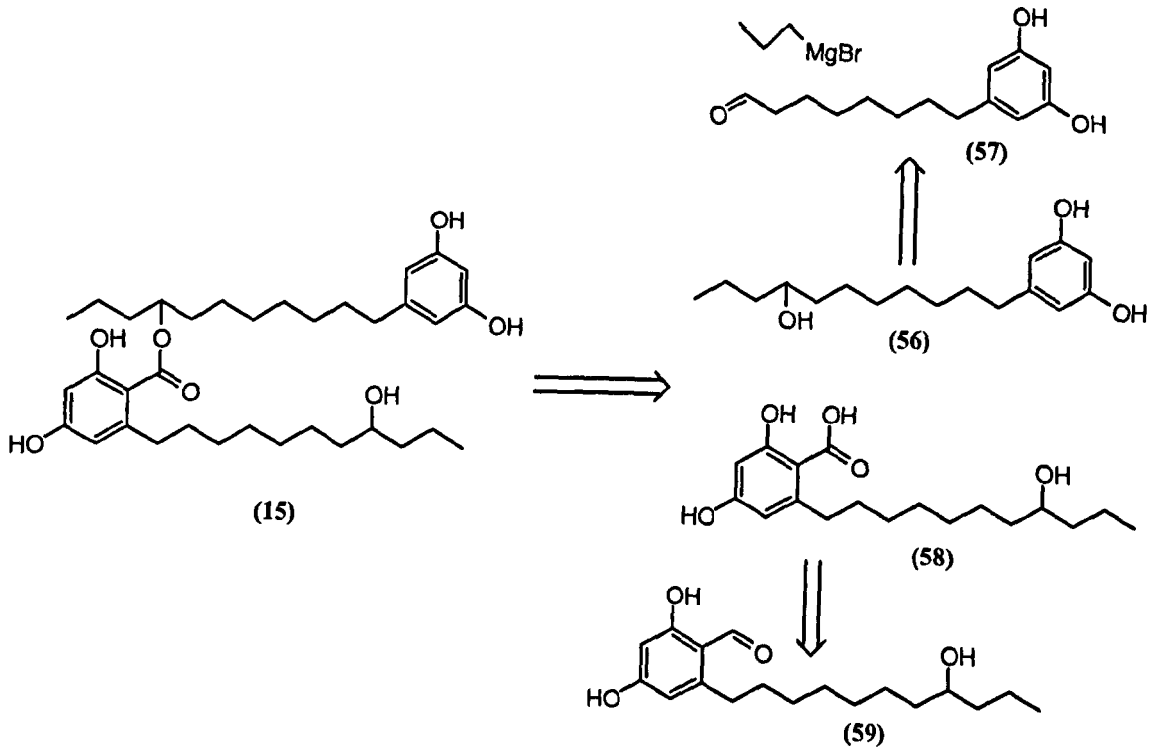


FIGURE 4 - 12: RETROSYNTHETIC ANALYSIS FOR DIHYDROXYAROMATIC (15)

The disconnection of (**15**) through the ester bond provided the alcohol (**56**) and the substituted salicylic acid (**58**). Alcohol (**56**) could be easily obtained from a Grignard reaction between n-propylmagnesium bromide and the aldehyde (**57**). The aldehyde has been reported to have been obtained by Tyman and collaborators by ozonolysis of cardol.[i] The acid (**58**) could theoretically be obtained by Kolbe Schmitt reaction and related methods, from the corresponding 5-substituted alkylresorcinol, but literature shown that the yields obtained using this reaction with other resorcinols are low.[317,318] Therefore formylation looks a better approach for indirect carbonylation. A range of oxidants are reported to convert an hindered aldehyde group into the corresponding acid group.[319,320] A variation of this protocol could be devised to synthesize (**28**), using instead of (**58**) the alkylsalicylic acid (**60**) that may be obtained via a Wittig reaction of (**57**), followed by the regioselective carboxylation of the aromatic ring (via formylation/oxidation). The key reactions in this proposal are therefore a) the cleavage of the double bonds in the alkyl chain of the natural phenols (anacardic acid, methoxycardanol and cardol); b) coupling of the resulting aldehydes, and c) the conversion of the alkylresorcinols into the corresponding substituted alkylsalicylic acids.

[i] Ozonolysis of cardol is reported to have provided 8-(3,5-dihydroxy-phenyl)-octanal, but this product was just characterised by TLC, and GC-MS, as it was decomposed before the ^{1}HNMR characterisation.[324] Santos and collaborators reported ozonolysis of acetylated cardol in high yield.[325]

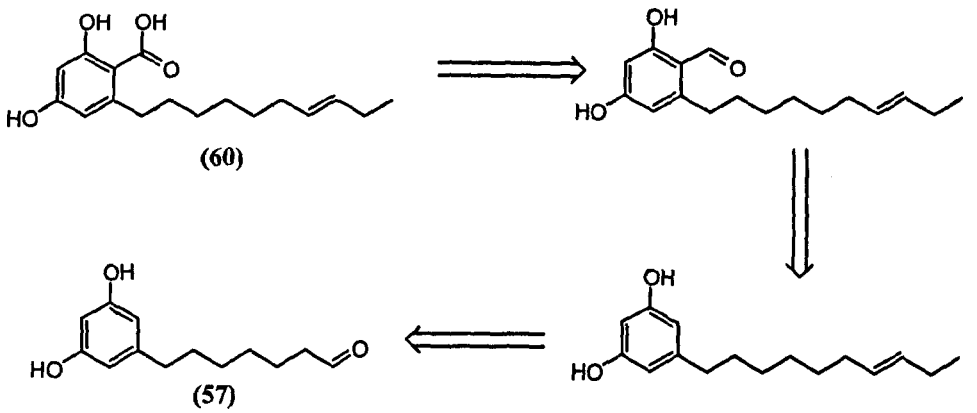
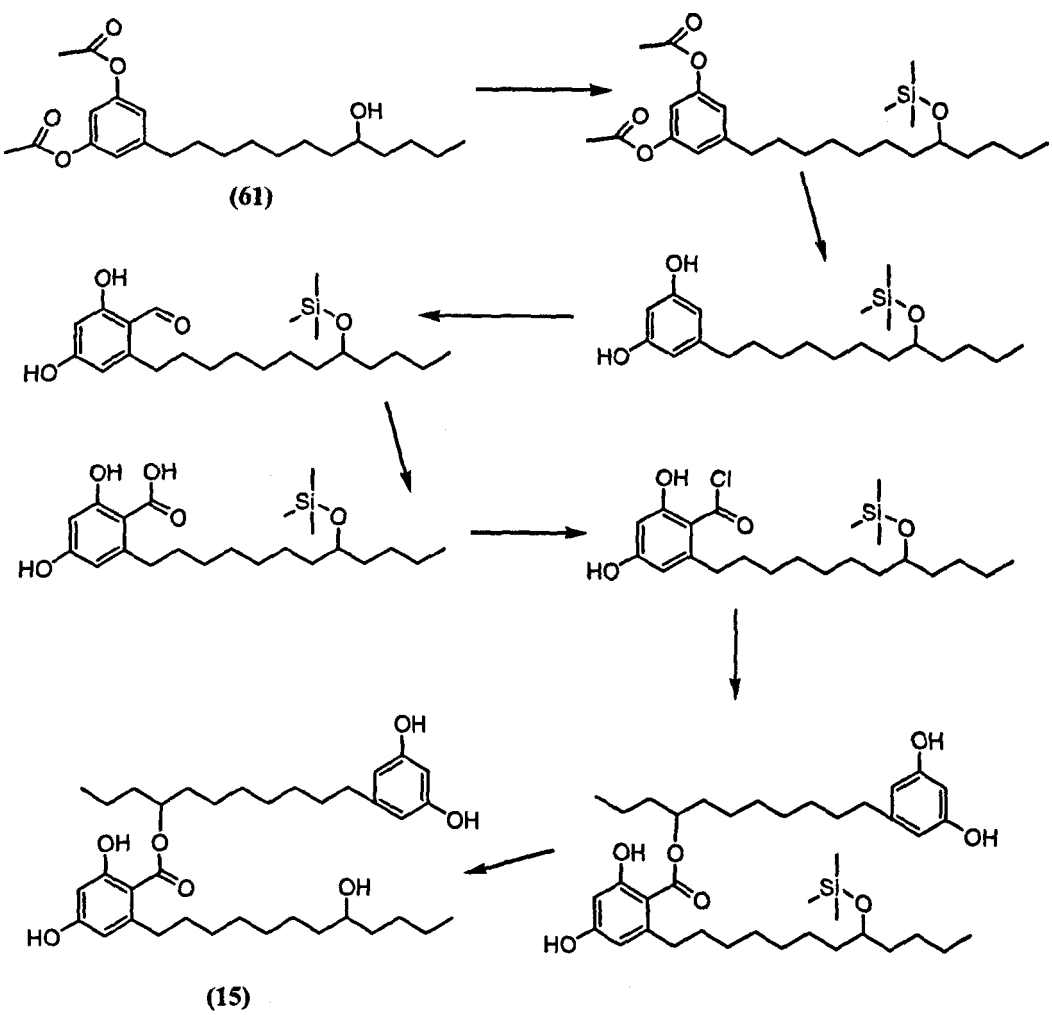


FIGURE 4 - 13: RETROSYNTHETIC ANALYSIS TO OBTAIN DIHYDROXYAROMATIC (44)

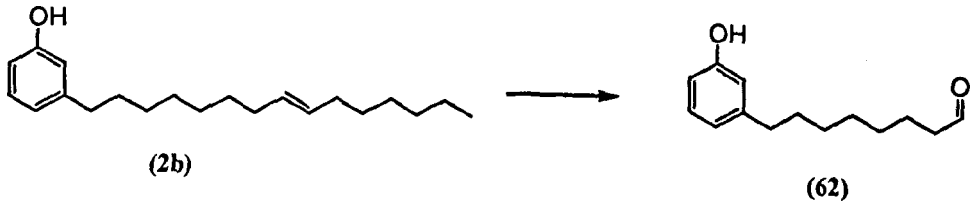
The same logic could be used to produce the analogues (**52-55**) using cardanol, anacardic acid and methoxycardanol instead of cardol. If such chemistry could be developed and accounting for a number of functional groups that need to be protected, a potential route to obtain (**15**) in 8 steps from the alcohol (**61**) is given in Scheme 4-15.



SCHEME 4 - 15: PROPOSED REACTION SCHEME TO OBTAIN DIHYDROXYRESORCINOL (15)

Compound (**15**) has two stereochemical centers, but the correct configuration could be obtained by the choice of the correct isomer (**61**) that may be obtained by enzymatic resolution of the correspondent alcoholic mixture.

2.2.2.Ozonolytic cleavage of cardanol



(2b) (62)

SCHEME 4 - 16: CARDANOL (15:1) OZONOLYSIS

8-(3-Hydroxy-phenyl)-octanal (**62**) has been obtained by ozonolysis of cardanol, (exemplified with cardanol(15:1) in the Scheme 4-16), in structural work to establish the double bond position in the unsaturated constituents.[40] and recently in the development of resins (non-formaldehyde phenolic resins and as intermediates for non-oestrogenic polycarbonates). [62, 321]

In the present work cardanol (separated by the petrol-acetonitrile partition method) was cleaved by ozonolysis in a range of solvents and the ozonide cleaved to aldehyde using different reagents to establish appropriate conditions. This could lead to a procedure applicable also to other CNSL constituents.

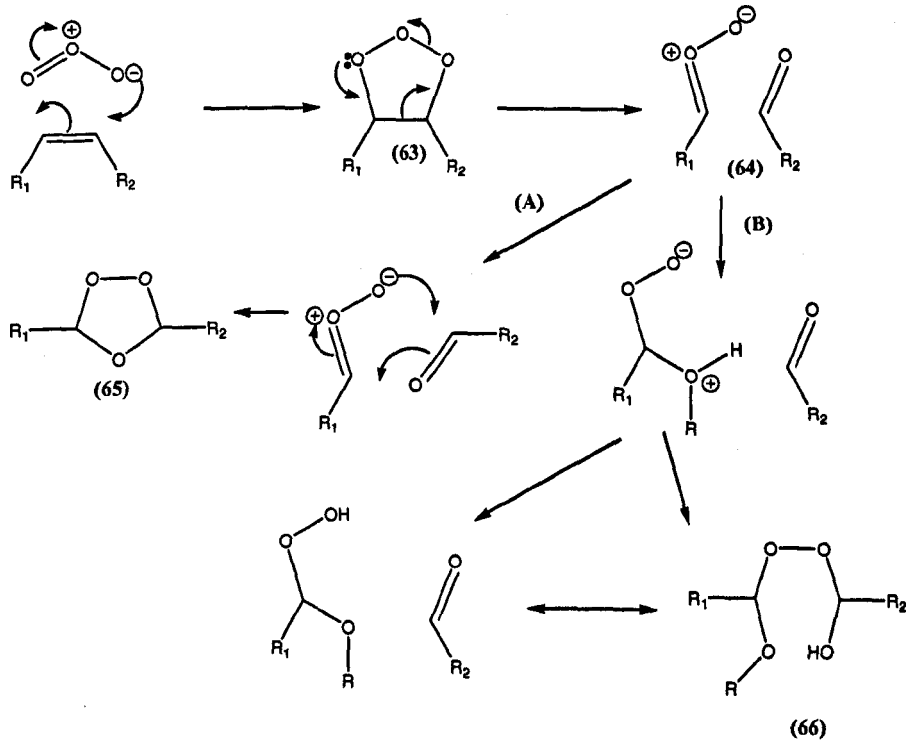
TABLE 4 - 1: YIELDS IN CARDANOL OZONOLYSIS

Cardanol		solvent	temperature (°C)	Reducing agents	Yields of (**62**) (%)
Mass (g)	Conc (M)				
20	0.66	methanol	-4	DMS a)	12
20	0.66	methanol	- 4	Zn/Acetic acid	31
2	0.07	THF	- 78	Zn/Acetic acid	97
2	0.07	dichloromethane	- 78	Zn/Acetic acid	97
20	0.66	dichloromethane/ methanol (3/1)	- 5	Zn/Acetic acid	45
20	0.66	dichloromethane/ methanol (1/4)	- 5	Zn/Acetic acid	34

a) dimethylsulfide

All these reactions were performed using two "ozone equivalents". The ozone equivalent is the number of molecules of ozone needed to cleave all the double bonds of cardanol. The

degree of unsaturation of cardanol was estimated by ^{1}HNMR. The flow rate of ozone to the reactor was set by a calibrated flow meter.[i] In comparison with zinc/acetic acid, the use of dimethylsulfide as a reducing agent decreased the yield of the reaction. Reactions performed at low temperature in dichloromethane or THF provided the highest yield, but these were performed also at very low concentration because the polar ozonide (**65**) (generated during the reaction) is not very soluble in these solvents, and could reach concentrations that may lead to an explosion. Methanol could solubilize any concentration of ozonide and therefore the reaction was performed in this solvent with a higher concentration of starting material, and even at –5 °C; however the yield was much lower that the one obtained with the previous two solvents. Similar observations were reported by Tyman.[324, ii,iii] The possibility of using a mixture of solvents to increase the selectivity of ozonolysis reactions in reactions with high concentration, suggested by the literature,[333] was confirmed in our experiments with dichloromethane-methanol.



SCHEME 4 - 17: CRIEGEE MECHANISM FOR THE FORMATION OF PEROXY COMPOUNDS

[i] The most common procedure to control the completion of ozonolysis is to check the moment when the exit gases from the reaction flask liberated iodine from a final trap flask containing aqueous potassium iodine. This procedure have not been used in the present work, as previous work done in the BioComposites had shown that with 2 eq ozone the reaction is usually complete. (Dr. Slava Tveresovsky, Personal. communication.)

[ii] in a paper published after the present work was done.(ref.324)

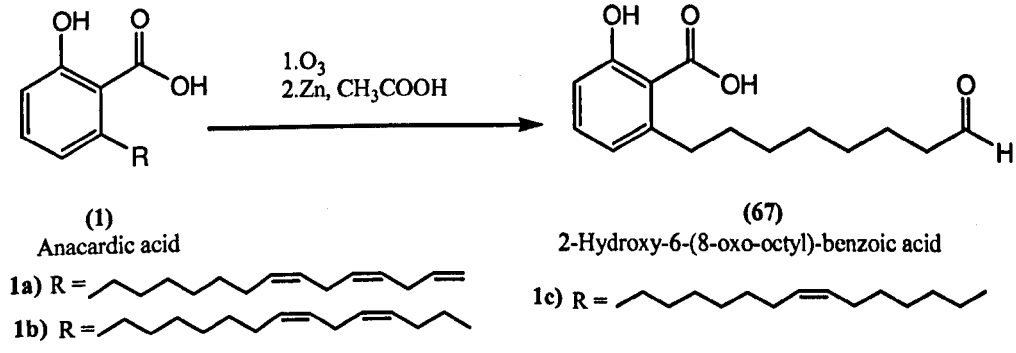
[iii] Tyman however compared ethyl acetate, methanol, petrol and carbon tetrachloride. Ethyl acetate (a non-participative solvent, as dichloromethane indicated in Table 4-1) provided highest yield and could be operated safely. Petrol let to the separation of the ozonide and show to be dangerous.

Criegee explained this phenomenon indicating that in the case of ozonolysis in proton-active solvents (alcohols, ammonia, hydrocyanic acid, etc..), beside the normal pathway (**A** in Scheme 4-8), the solvent reacts with the zwitterion intermediate (**64**) leading, in the case of methanol, to the formation of reactives methoxyhydroperoxides (**66**).[322].

Our first attempted solution for this problem was to use mixtures of methanol-dichloromethane, which provided mixed results. Facing a similar problem, Varma, who used cardanol ozonolysis to produce non-oestrogenic polycarbonates, performed the ozonolysis in methanol and reduced the resulting ozonide with sodium borohydride affording a quantitative reaction.[321]

In the next part of this work, a procedure using a mixed solvent was used for ozonolysis of anacardic acid. Despite an expected lower yield, this solvent system was considered to provide the "best technique" because it could work at high concentration and with an ice bath and could be scaled up to a kilogram scale without major problems. Later on when methoxycardanol were ozonolysed, a different technique was developed (See later).

2.2.3.Cleavage of anacardic acids



SCHEME 4 - 18: OZONOLYSIS OF ANACARDIC ACID

Obtaining the aldehyde (**67**) by cleavage of anacardic acids (**1a, 1b, 1c**) was performed by ozonolysis in dichloromethane/methanol (3:1) at room temperature, reduction of the ozonide with zinc/acetic acid, removal of the solvents under vacuum at room temperature, distillation followed by alkaline extraction of the distillate provided (**67**) (42 %) characterized by the expected ^{1}HNMR as could be seen in the figure.[i]

[i] Ozonolysis of anacardic acid was indicated to provide 6-(8 -formylheptyl)-2-hydroxybenzoic acid (**15**) in higher yield (73 %) with heptanal as an impurity, also without column chromatography, but using ethyl acetate as a solvent, performing the ozonolysis at – 60 °C and using Pd/C as a reducing agent of the ozonide.[324] This paper was published after the present work was done.

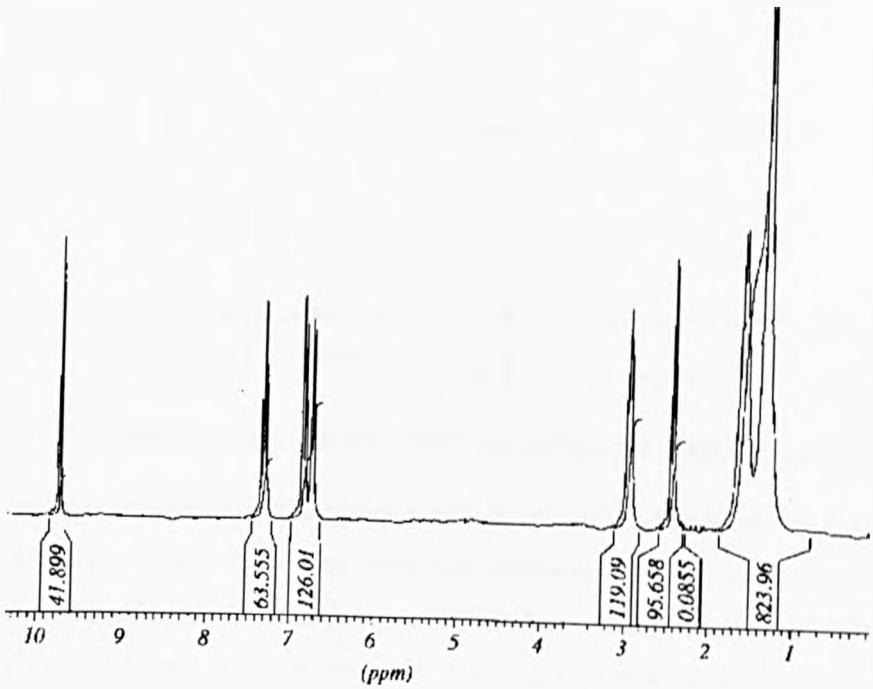


FIGURE 4 - 14: ^{1}H NMR SPECTRUM OF ANACARDIC ALDEHYDE (53)

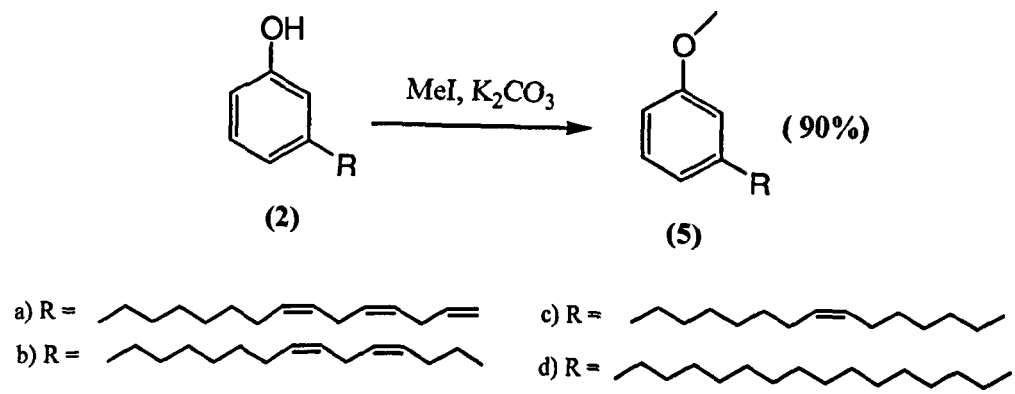
The peak at δ 9.8 indicated an aldehyde proton, the aromatic protons appeared as a multiplet at δ 7.35 - 6.82 (similar to the chemical shift of the aromatic protons of the anacardic acid (**1**)), the chemical shifts of the protons adjacent to the carbonyl group appeared at δ 2.44 - 2.41 while the remaining signals corresponded to the benzylic protons and the remaining alkyl chain.

2.2.4.Production, cleavage and Grignard coupling of methoxycardanols

Production of methoxycardanols

Methoxycardanols were produced previously to provide elements for the analyse of cardanol,[i] and recently as a first step in producing quaternary ammonium salts, via functionalisation of the C8 of the chain.[333] All the published procedures involve the use of column chromatography to purify the reaction mixture.[333]

[i] These analysis were performed at the beginning of the 20th century, when chemical derivatization was routinely used to provide information on the chemical structure of natural compounds. See Chapter 1 for details.

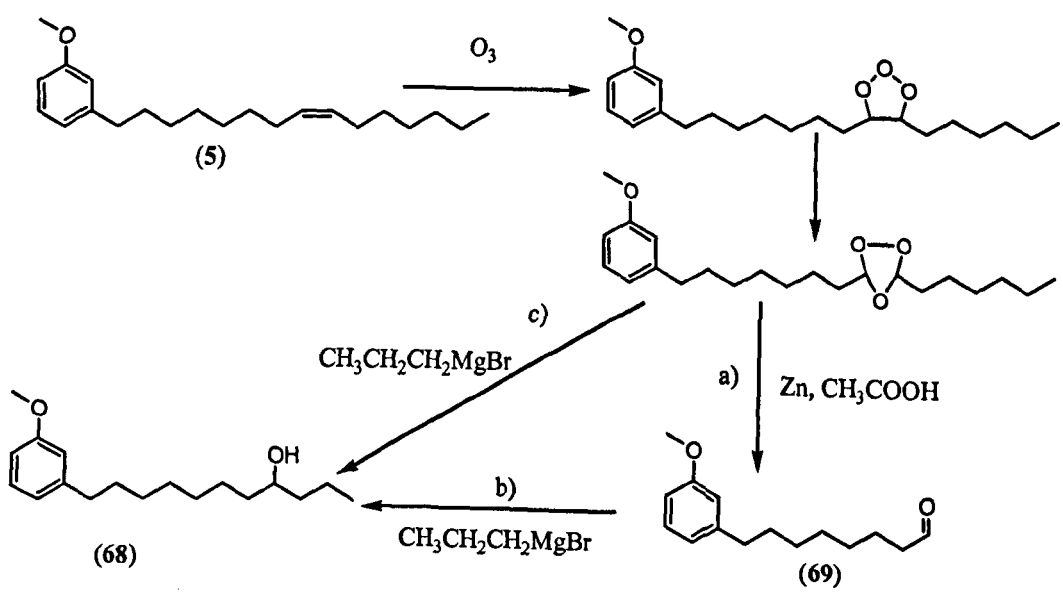


SCHEME 4 - 19: PRODUCTION OF METHOXYCARDANOLS

A method that did not need chromatography was developed in this work, by using cardanols from the previously described solvent extraction procedure, boiling in acetone with sodium bicarbonate under reflux with 10 mol. eq. methyl iodide. This procedure afforded a mixture of methoxycardanols and cardanol, but after removal of the acetone, pouring the reaction mixture on silicagel, and desorbing with petrol afforded methoxycardanol in 90 % yield, (characterised by NMR and MS), cardanol being recovered by washing the silicagel with ethyl acetate.

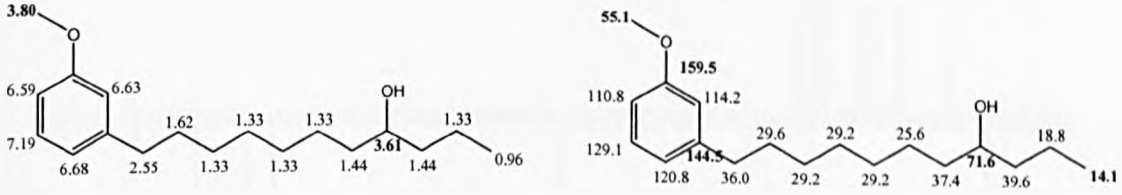
Grignard coupling of methoxycardanols ozonide

An obvious method to obtain 11-(3-methoxy-phenyl)-undecan-4-ol) (**68**) is to cleave the methoxycardanol (**5**) at C_8 by ozonolysis, reduce the ozonide to the corresponding aldehyde (**54**) and add a Grignard reagent (a) and (b) below :



SCHEME 4 - 20: DIRECT REDUCTION OF AN OZONIDE WITH A GRIGNARD REAGENT

Because the methoxycardanol ozonide[1] itself could act as a nucleophile and react with the Grignard reagent n-propylmagnesium bromide, the reaction was performed with 5 eq. of Grignard and without the intermediate reduction of the ozonide, giving in 89 %, the expected alcohol (**68**) as shown in the route c) in Scheme 4-15. This exhibited the expected IR and NMR spectra. The IR spectrum showed a stretch at 3600 cm $^{-1}$, indicating the appearance of a free OH group. The ^{1}HNMR spectrum (presented in the Figure 4-10) showed a broad signal at δ_H 3.61 corresponding to one proton, suggesting a possible secondary alcohol (see Figure 4-16). ^{13}C, and dept (see next page, Figure 4-17) confirmed the structure, as a chemical shift at δ_c 71.6 corresponding to a CH group indicated a secondary alcohol, remaining shifts were assigned as indicated in the Figure 4-9.



a) b)

a) ^{1}HNMR chemicals shifts, b) ^{13} CNMR chemical shifts

FIGURE 4 - 15: NMR CHEMICAL SHIFTS ASSIGNMENTS OF METHOXYCARDANOL ALCOHOL (68)

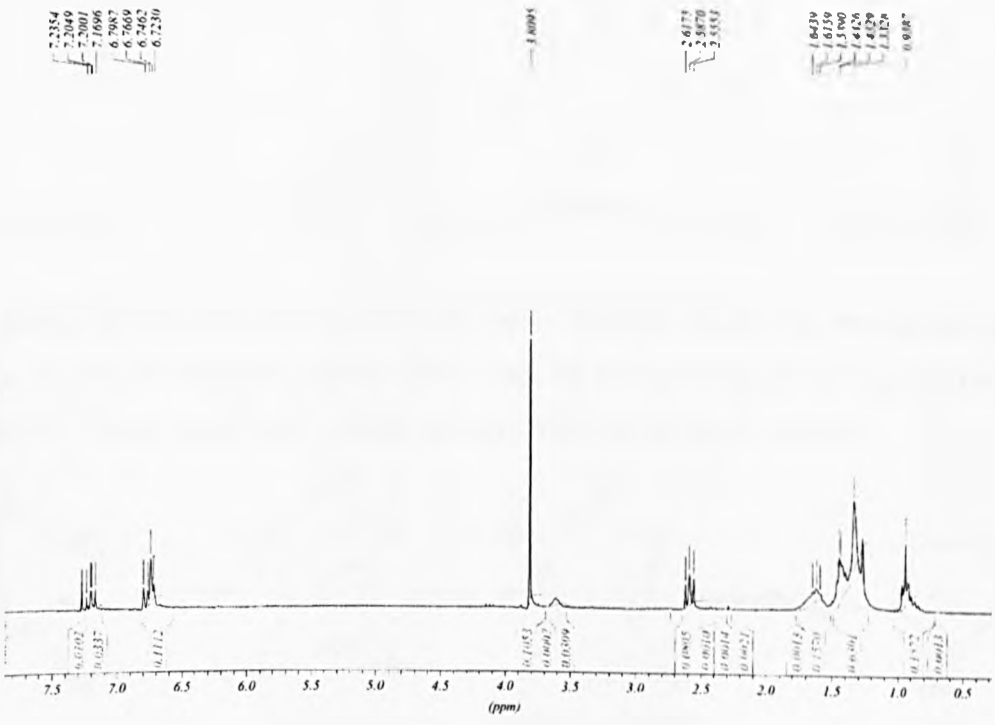


FIGURE 4 - 16: ^{1}H NMR SPECTRUM OF METHOXYCARDANOL ALCOHOL (68)

[1] This experiment was performed in the BioComposites Centre, where other quenching reagents were investigated to produce modified phenolic resins. .Dr.Slava Tveresovsky, personal communication.

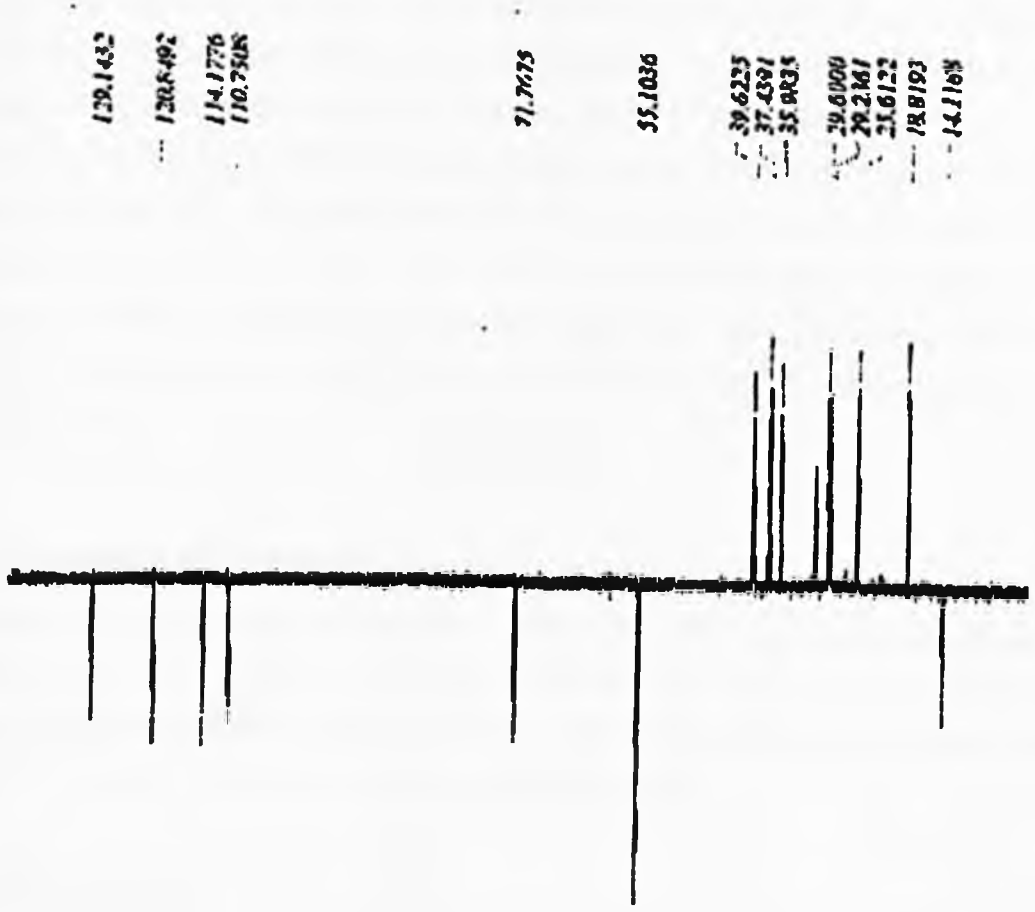
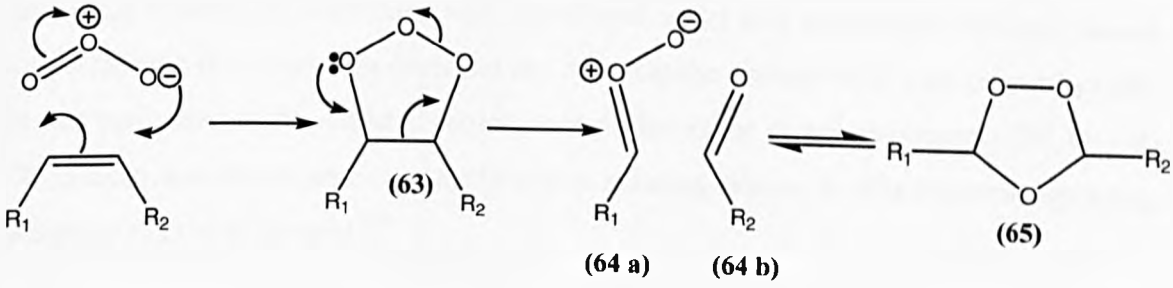


FIGURE 4 - 17: ^{13}C NMR SPECTRUM OF METHOXYCARDANOL ALCOHOL (68)

This shows that it is possible to obtain secondary alcohols directly by treating an ozonide with an excess of Grignard reagent. This could be easily explained as ozonide **(65)** (see scheme 4-21) is in equilibrium with the zwitterion and the aldehyde **(64 a,b)**.



SCHEME 4 - 21: CRIEGEE MECHANISM

The Grignard may simply trap the latter two compounds. Because **(64 a, b)** are in equilibrium with **(65)** their removal from the reaction means that they could be continuously produced until all **(65)** is consumed. Others factors that can influence the equilibrium (pH, temp., coordinative solvents) may influence the rate of this kind of reaction.

It is worth to noticing that reductive cleavage of an ozonide with n-butylmagnesium bromide has been reported.[323] Grignard reagents are too susceptible to oxygen to perform the two reactions in one pot (i.e. to react –in situ- and so to remove continuously the ozonide using a Grignard reaction), but this kind of procedure suggests that others reagents may allow the problem of the low productivity to be solved using non-participative solvents even at room temperature.

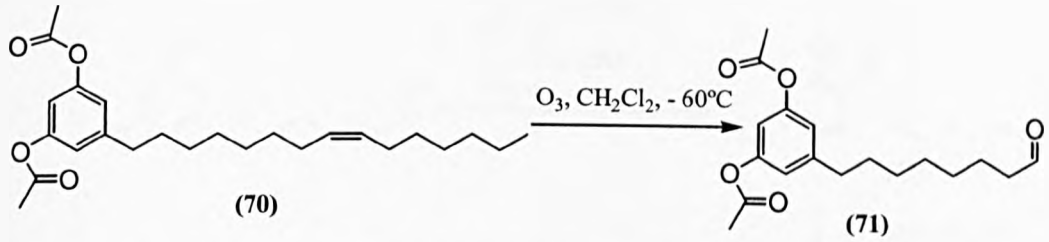
2.2.5.Reactions with Cardols

Having shown with model compounds (anacardic acid and methoxycardanol) that the double bonds of the chain could be cleaved by ozonolysis, and that Grignard addition of n-propylmagnesium bromide could be performed without major problems, the next two steps were to ozonolyse cardol and to obtain its salicylic derivative.

Cleavage of Cardols

8-(3,5-Dihydroxyphenyl)octanal **(57)** has been reported to be obtained by cardol ozonolysis by Itokawa by no experimental details were available,[93] and by Tyman and collaborators, but in this case, a sample was just identified by TLC, and MS, and was reported to have partially polymerised before the submission to NMR, (only weak signals for CHO, HAr, CH_2 could be obtained).[324] In the present work it was not possible to obtain cardols by cleavage of the long chain at carbon C_8 by ozonolysis and reduction with zinc/acetic acid, as even in a very dilute solution at –70 °C, and using 1 equivalent ozone a tar-like fraction was recovered after the reaction.[i] The reaction was therefore performed using an alternative procedure reported by Magalhaes, who ozonolysed cardol after acetylation. However instead of performing the reaction in methanol and reducing the ozonide with sodium borohydride, it was performed with acetylated cardol (exemplified as the monoene congener **70**), at – 60 °C in dichloromethane, with zinc/acetic acid as reducing system, to afford the corresponding aldehyde **(71)** in 92 % yield.[325]

[i] It is worth noticing that Tyman's procedure indicates the use of palladium as a reducing agent that may provide milder conditions than the acetic acid/zinc, present work was performed before Tyman's paper was published



SCHEME 4 - 22: OZONOLYSIS OF ACETYLATED CARDOL MONOENE

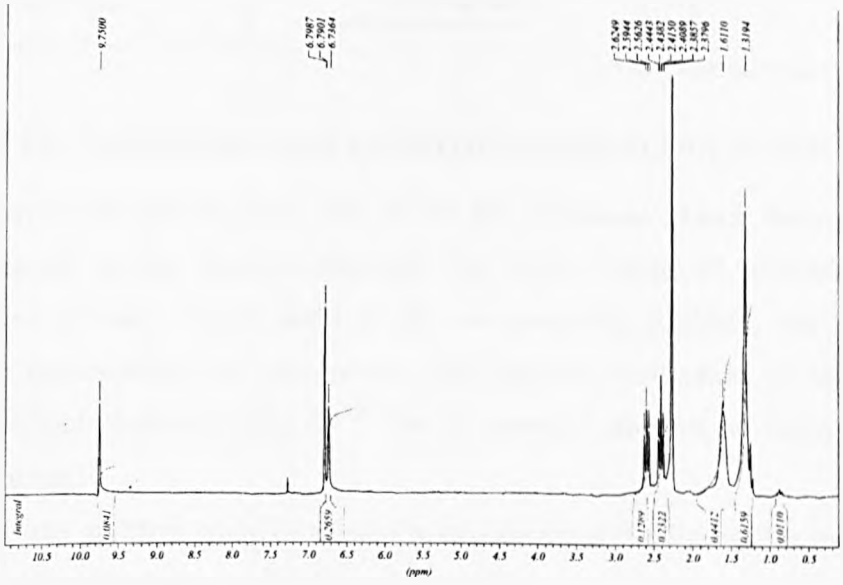
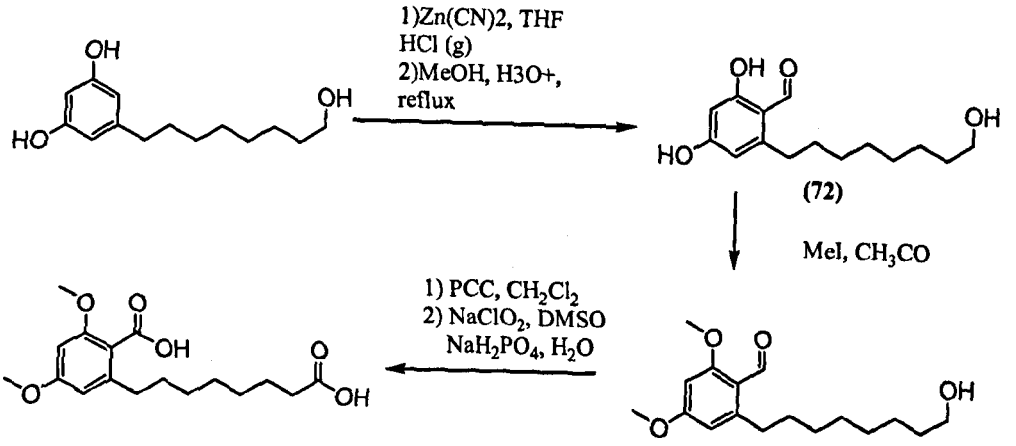


FIGURE 4 - 18: ^{1}H NMR SPECTRUM OF ACETYLATED CARDOL ALDEHYDE (71)

Functionalisation of Cardol

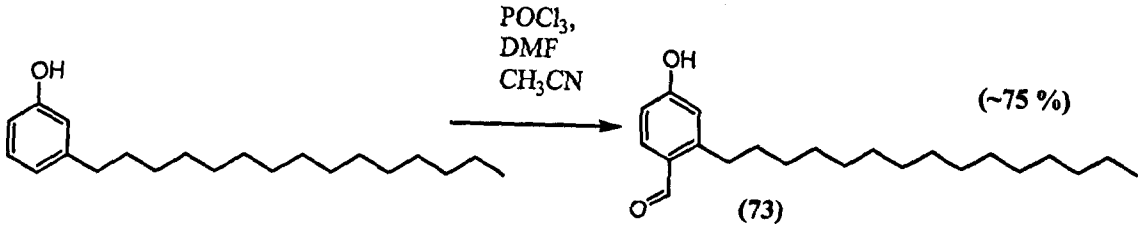
To obtain a salicylic acid derivative of cardol, different approaches are possible. Magalhaes and collaborators (see Scheme 4-17) used a modified Gattermann reaction, with zinc cyanide and anhydrous hydrogen chloride, which provided the salicylic aldehyde (**58**) in high yields. They oxidized it using PCC in methylene chloride followed by treatment with sodium dichlorite-DMSO. [325]



SCHEME 4 - 23: CARBOXYLATION OF A SUBSTITUTED RESORCINOL BY MAGALHAES.[325]

The approach in the present work was to use the Vielsmaier-Haack formylation of the dihydroxyphenols as the literature indicated that with a range of alkylresorcinols this reaction gives not only a high yield of the corresponding aldehyde, but also that the intermediate formamidium salt precipitates, allowing the purification of the formylated resorcinol without chromatography.[326,334] Despite repeated attempts no formylated cardols could be obtained.

To analyse if the problem could be related to experimental conditions, the procedure was tested with cardanol (15:0).



SCHEME 4 - 24: FORMYLATION OF CARDANOL (15:0)

Formylation of cardanol (15:0) gave, in a mixture with the starting material, 2-pentadecyl-4-hydroxy-benzaldehyde (**73**) (approx. 75 %, estimated on the basis of the ratio of the benzylic protons integrals) (see Figure 4-17) suggesting that double bonds in cardols interfere with the reaction, and that formylation may be possible in a saturated compound and therefore a protected resorcinol may be formylated to the corresponding salicylic aldehyde.

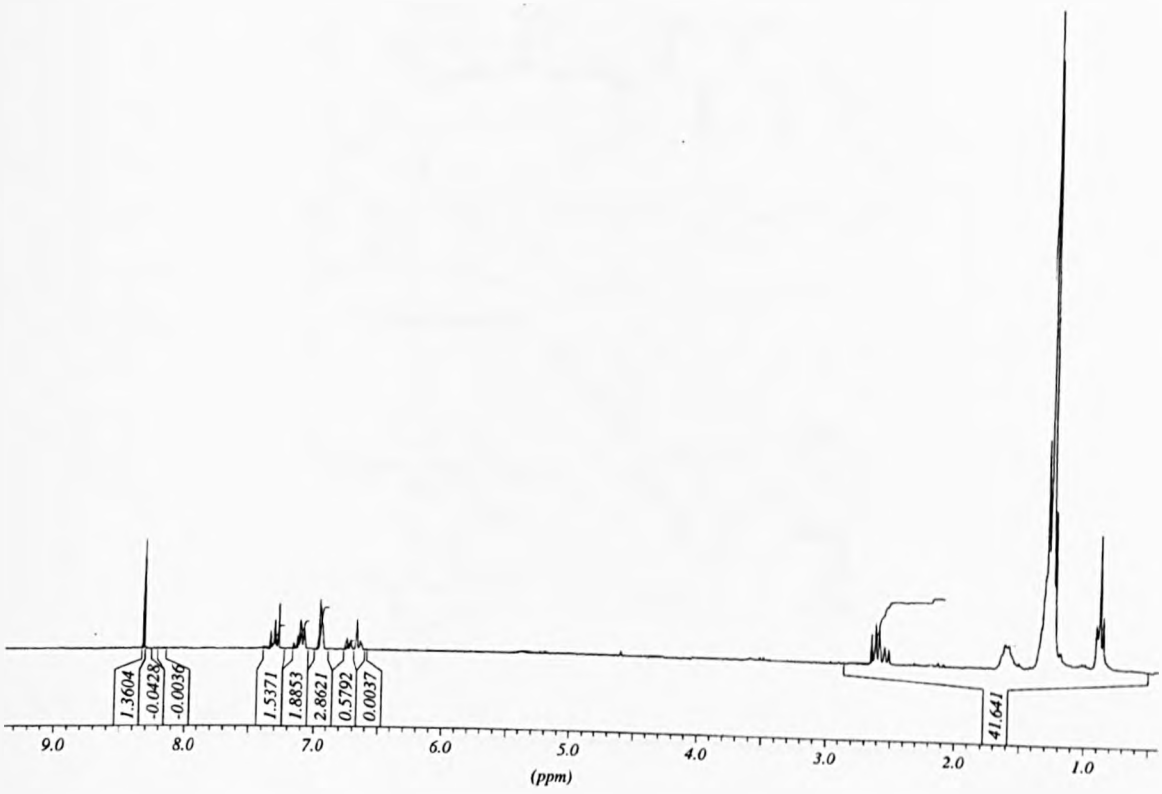


FIGURE 4 - 19: CRUDE ^{1}H NMR SPECTRUM OF THE FORMYLATION OF CARDANOL (15:0)

2.2.6. Synthesis of HIV integrases inhibitors -conclusions

1.In the present work, compounds (**62**), (**69**), (**67**), and (**71**) which are synthons for the production of (**15, 28**) and analogues (**52-55**) have been obtained. The formylation of alkylresorcinols and the chemioselective oxidation of the aromatic ω-hydroxy-aldehyde to the corresponding salicylic acid still need to be performed as a critical step for a successful synthesis of the indicated anti-integrases compounds.

2. It is noteworthy that both 2-hydroxy-6-(8-oxo-octyl)-benzoic acid (**67**), and acetic acid 3-acetoxy-5-(8-oxo-octyl)-phenyl ester (**71**) may provide useful routes for the semi-synthesis of others natural products, as construction of the meta-substituted salicylic acid or meta-substituted resorcinol involve relatively more expensive chemical routes.

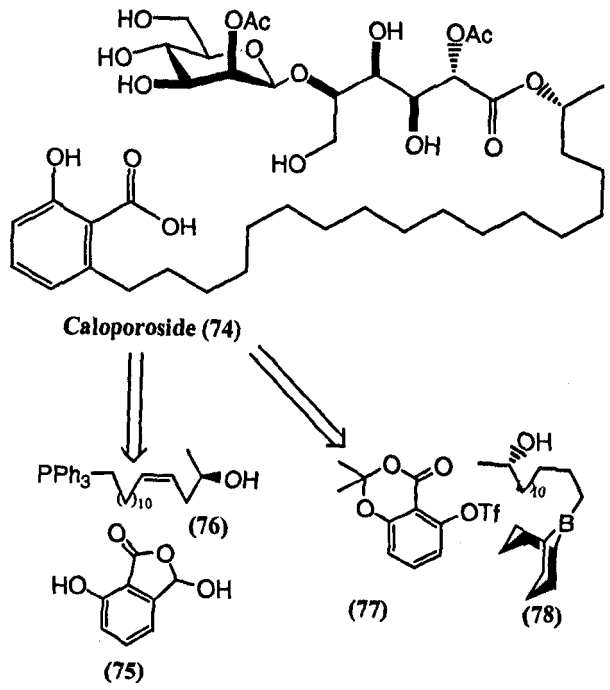


FIGURE 4 - 20: CALOPOROSIDE RETROSYNTHETIC STRATEGIES

2-Hydroxy-6-(8-oxo-octyl)benzoic acid could be used in the synthesis of caloporoside (**74**), a fungal metabolite the synthesis of which, due to its recognised biological interest, has been reported in a number of publications in recent years. Tatsuta constructed the anacardic ring by a Wittig reaction with the hemiacetal (**75**),[327] while Furstner functionalised the aryl triflate (**77**) with 9-alkyl-9-BBN derivative (**78**).[328]

1,3-Diacetoxy-5-(8-oxo-octyl)-phenyl ester (**71**) can be seen as useful synthon for the preparation of a range of cardol derivatives (see Chapter 1 for details on biological activity of cardol).Of interest could also be the production of the resorcinols (analogues $C_{17, 21, 23, 25}$)[i] existent in cereal grains. These may be (in the future) valued as nutritional additive, as they have been associated with anti-tumour, antioxidant,[ii] and antimicrobial properties of wholemeal flour,[iii] and are reported to be missing in refined cereal flour.[330]

3. RECOMMENDATIONS FOR FURTHER STUDIES

1. The conversion of a salicylic alcohol to an oxaspirodienone which can undergo rearrangement to a benzodioxolane provides a rationale for the existence of the latter in

[i] Reported to contain 90 % cardol (mixture of cardol monoene (with a double bond at the 8-position), and the diene (with the second double bond at the 11-position) homologues but no triene, and 10 % 2-ketoalkenylresorcinols. [329] These cardols have 17, 21, 23 and 25 carbons atoms in the chain instead of 15 as CNSL cardol.

[ii] Antioxidant properties of cardol are reported to be poor in comparison with tocopherol in vitro but it has been suggested that they may be metabolised to antioxidant compounds in vivo. [331]

[iii] The US Food and Drug Administration recommends an increased intake of whole grain cereals, and so of alkylresorcinols, reducing the use of refined cereal as a dietetary tool for disease prevention.[332]

nature (were it is a quite common substructure) and eventually an insight into a new biochemical pathway that should be investigated.

2. The synthesis of the HIV integrase inhibitor, and analogues were began in this thesis, and should be performed in later studies as they remain a major target in medicinal chemistry.

3. The Grignard reduction of an ozonide to afford directly a secondary alcohol, without the intermediate reduction providing the corresponding aldehyde need to be investigated as a general procedure.

CHAPTER 5- CONCLUSIONS SUMMARY

As indicated in the introduction of this thesis, the purpose of the present work was to analyse several methods that would allow Cashew Nut Shell Liquid (CNSL) to provide high value compounds, focussing on obtaining synthons for further organic synthesis. Additionally, and as a secondary objective, it was expected to check if the chemistry developed in this work could be applied to a shell oil produced by an other tree from the same family as the cashew tree, Semecarpus Shell Oil (or Bilhawan Shell Oil).

Both Natural CNSL and Technical CNSL (the industrial derivative of the kernel shelling process) from 3 continents were analysed in this work. The composition of both kinds of oil determined by HPLC and ^{1}HNMR confirm that little variation exist as a function of the geographic origin of the samples. Results provided by the latter method were found to be accurate enough to characterise the sample and to provide a quick technique to access different separation methods developed in this work. Semecarpus Anacardium was shown to be a complex mixture, but as previously thought, it contains mainly (more than 74 %) pentadecenylcatechols.

5.1.Novel methods to separate CNSL into its constituents

The lack of availability of individual components of CNSL or even of cardanols, anacardic acids or cardols/methylcardols as families of congeners, led as a prime objective of this work, to the development of separation methods that could be scaled-up to industrial quantities.

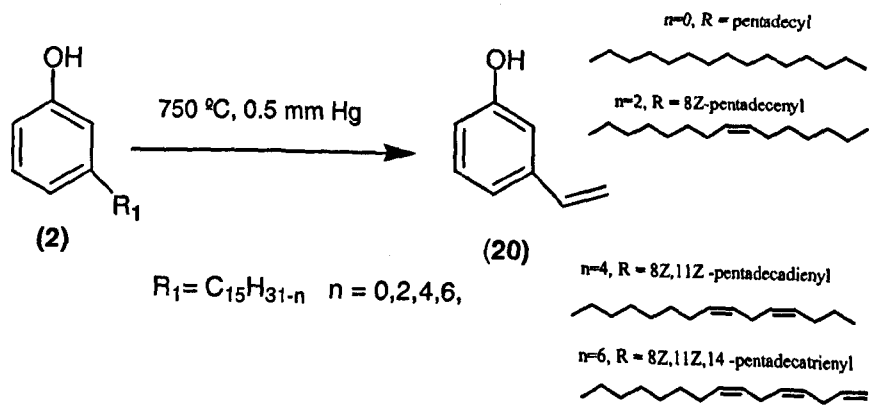
A new and fast technique to search solvents in liquid extraction methods, based on a pre-existing solvent behaviour theory, Kamlet-Taft theory, and the concept of phase modifier, allowed a system to separate cardol (purity 87 %) from cardanol, and cardol (purity 100 %) from anacardic acid to be found. This process has been shown by calculation to be technically suitable for scale up. The method presented is expected to provide both anacardic acid and cardol more cheaply than a previously published method that could eventually be scaled up, a commercial alternative recently patented based on crystallisation.[138,139] On technical grounds, as a raw-material, natural CNSL is preferred, both because of its higher content of cardols, and because it has been possible to obtain a fraction with 100 % purity; however present commercial availability of the natural oil is scarce, so a large scale manufacture of cardols may use technical CNSL.

As a fast laboratory procedure (when the recovery of pure cardols does not matter) a simplified system could be used. Washing a petroleum solution of Technical CNSL with

acetonitrile gave a high yield (30 % of the oil) of cardanols, with a purity of 100 % (by HPLC). A similar procedure for the recovery of anacardic acid has been developed.
The equivalent of the commercially available "technical cardanols"/"distilled CNSL" could also be obtained by flocculating the above mentioned aggregate with petrol-nitromethane.
In the case of Technical CNSL, a range of other methods (alkaline extraction, complexes with solids, partition phase chromatography, filtration on silica) have been shown to be non-competitive with the former procedure as they provide cardanols in lower yields.

5.2.Meta-vinylphenol

Meta-substituted phenols are costly to obtain through synthesis, because alkylation in the m-position of a phenol is not favoured; a cheap way to reduce the chain length of CNSL would be an interesting route to short chain m-substituted phenols from a renewable source.



SCHEME 5 - 1 : CARDANOL PYROLYSIS

Previous research has shown that it was possible to obtain meta-vinylphenol by pyrolysis of cardanols in a tubular reactor, but with less than 30 % yield. Present work shows that it is possible to increase this yield up to 64 % using vacuum and copper tubes. As vaporisation is a crucial question in the pyrolysis process, and because vacuum could ensure smooth vaporisation of the cardanols, this was a justified premise of the study. In this work copper has been shown to inhibit secondary, coke producing reactions. This behaviour was rationalised as being the result of a low hydrogen chemisorbtion. A preliminary economic analysis, based on the experimental results, in the cost of the equipment estimated by Selas, and others costs estimated on the basis of current values in Wales, indicated that with the new approach presented in this thesis, the value of the products is higher than the commercial value of 3-hydroxybenzaldehyde, the nearest chemical synthon commercially available.

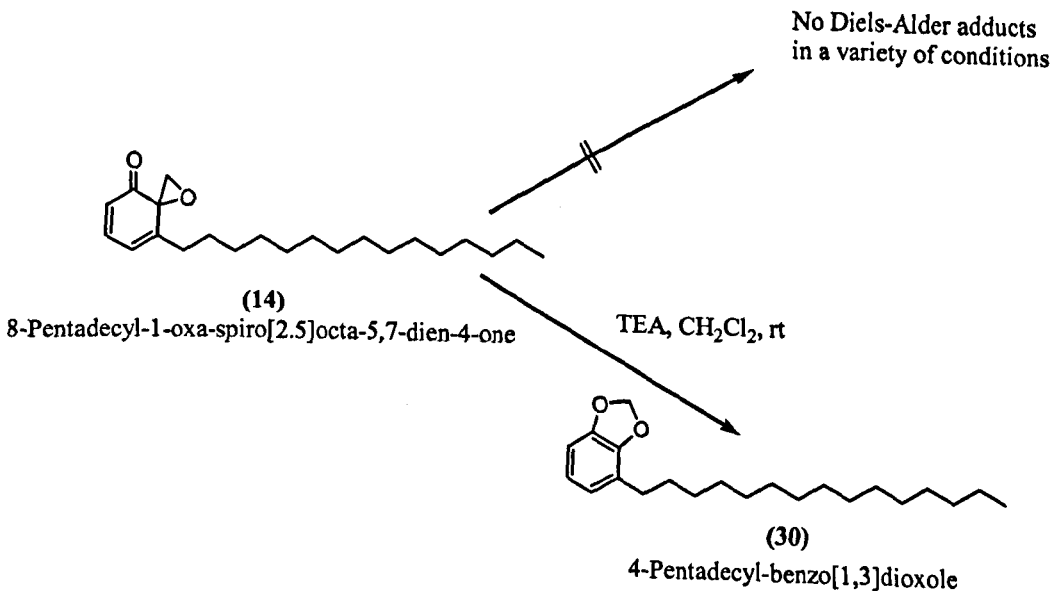
Pyrolysis of cardanols follows the same characteristic pattern as the pyrolysis of alkylaromatics, i.e. giving as the main products 3-vinylphenol/3-cresol in place of

styrene/toluene. Yields of minor compounds are a function of operational conditions. FVP of cardanol (15:0) in the same apparatus and conditions as the one used for mixed cardanols, gave a smaller conversion. This is consistent with the possibility that reaction is initiated by homolytic scission of a carbon-carbon bond which is simultaneously α to a double bond and β to another one in the alkyl chain.

In the conditions of this study, FVP of cardols, and bhilawanol did not give vinyl compounds.

5.3.Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one chemistry

The chemistry of the oxaspirodienone (**14**), a derivative of anacardic acid, was explored as a possible new way to obtain an array of new products.



SCHEME 5 - 2 : PENTADECYL-1-OXA-SPIRO[2.5]OCTA-5,7-DIEN-4-ONE CHEMISTRY

Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (**14**) was obtained in a two step reaction; by reducing anacardic acid (mixture of congeners) to 2-hydroxymethyl-3-pentadecyl-phenol, followed by the oxidation of the latter with sodium metaperiodate. (**14**) was shown to be unreactive in a range of Diels Alder reactions, but undergoes a rearrangement to 4-pentadecyl-benzo[1,3]dioxole (analogues to vinylcyclopropane to cyclopentene rearrangement) under a variety of conditions investigated. A quantitative yield could be obtained by treating the oxaspirodienone with a mild base, triethylamine.

The same procedure has been shown to be applicable to the mixture of unsaturated congeners of anacardic acid allowing a mixture of benzodioxolane with an unsaturated carbon chain to be obtained.

5.4.HIV-integrase inhibitors

The discovery of efficient integrase inhibitors (targets of novel anti-HIV therapies) having a substructure related to cardols led us to analyse routes to obtain this compound and a range of analogues from CNSL. By ozonolysis of the double bond of the carbon chain of each of the CNSL constituents, synthons for the proposed synthesis were obtained.

5.5.General

The concomitant availability of CNSL, a commercially important source of natural phenols, and the commercial/scientific need of compounds with phenolic template, is the main justification to investigate the possibility to use this phenolic oil as a source of fine chemicals.

In the present work, a new system to purify/separate the constituents of the oil, and that could be scaled up has been developed. Vacuum pyrolysis was used as a technique to take advantage of the rather unusual meta substitution of cardanol, and to produce 3-vinylphenol. Using the proposed process, the latter may be produced at lower cost than the present price of 3-hydroxybenzadehyde, its nearest equivalent synthon. Both anacardic acid and cardol have key biological properties, and could provide template for more complex biologically active molecules. Preliminary functionalisation of these molecules by simple ozonolysis –that could also be scaled up, has been performed.

Different new methodologies (use of Kamlet Taft to optimise solvents in liquid extraction, use of FVP on copper to pyrolyse low volatility compounds, and the possibility to use ozonides in aldehyde-like reactions without intermediate reduction) have been developed during the present work, and may be applicable to others chemical studies. Detailed conclusions and recommendations have been made at the end of the precedent chapters.

CHAPTER 6- EXPERIMENTAL DETAILS

1. GENERAL

Chemicals

All solvents were purchased from *Aldrich*, or *Lancaster*. The silica gel used for column chromatography was from *Fluorochem* (silica gel 60, particle size 0.2-0.5 mm).

HPLC solvents were degassed prior use. Reactions requiring anhydrous conditions were performed using dry solvents. In particular dichloromethane was distilled over calcium hydride; diethyl ether and tetrahydrofuran from potassium and benzophenone. Organic solutions were dried using anhydrous magnesium sulphate and solvents were removed on a Buchi rotary evaporator at 14 mmHg. Reactions were carried out at room temperature unless otherwise stated. Ozone was produced using an Ozcon 133 generator, calibrated at the BioComposites Centre, Bangor.

Spectroscopic analysis

NMR spectra were recorded on a Bruker AC250 spectrometer, in $CDCl_3$ and referenced to the solvent signal. An Unicam 610 series Gas Chromatograph equipped with a 15-m, 0.53-mm i.d., fused capillary column (diphenyl (5%)-dimethylpolysiloxane (95%)), and a flame ionisation detector was used for the GC with helium as carrier gas. IR spectra were obtained as KBr discs (solids) or as liquid films on a Perkin-Elmer 1600 spectrometer. UV was recorded on a UV/VIS spectrometer UV4 from Fisher Scientific. Elemental analysis (C, H, N) was performed with a Carbo-Erba Model 1106 CHN analyser. Semi-quantitative ICP analysis was performed at IES at Bangor on Jobim Yuom 138 Ultratrace. MSGC-EI, was recorded on Finnigan Mat 1020, coupled with a Restek TOK 5MS column 30 m 0.21 id, with helium carrier gas, using electron impact spectrum at 70 eV. Results are quoted as m/z (% most important fragment). HPLC chromatography used a Kontron 525 pumping system, a Kontron HPLC560 autosampler, with a 20-µl loop, a Phenylhexyl Phenomenex column, and an UV-variable spectrometer detector (Kontron HPLC535), coupled to a computing integration system.

2. CNSL & BSL SEPARATION TECHNIQUES

Characterisation of CNSL samples

General characterisation of unpurified technical CNSL

CNSL Bras is a black viscous oil which showed (see ^{1}HNMR in Figure 2-1), δ_H ($CDCl_3$), 7.18-7.09 (m, 0.95 H), 6.81-6.63 (m, 2.85 H), 6.33-6.21 (bs, 0.024 H), 5.92-5.78 (ddt, 0.3 H), 5.52-5.35 (m, 2.7 H), 5.13-4.97 (m, 0.6 H), 2.87-2.75 (m, 2.6 H),2.68-2.56 (t, 1.9 H; J= 7.4 Hz), 2.56-2.40 (bs, 0.024 H), 2.17-1.93 (m, 3.8 H), 1.71-1.51 (bs, 2.6 H),1.50-1.20 (m, 14 H), 0.98-0.95 (m,2.5 H), ν_{max} 3400, 3010, 2925, 2856, 1487 cm^{-1}. HPLC analysis was carried out by taking an aliquot (25 mg) and adding 4-hexylresorcinol (5 mg) as internal standard. The mixture was dissolved in THF and filtered through a nylon Aldrich cartridge. The cartridge was eluted with further THF (3 x 3 ml), and the combined eluant was made up to 50 ml into a volumetric flask. TLC analysis of the extract of the cartridge with ether showed that no cardanol or cardol was retained. The solvent (acetonitrile-water-acetic acid (78:20:5) for 30 min followed by gradient elution with THF-water over an additional 30 min) was pumped at 1 ml/min. The sample was introduced automatically, allowing 20 µl analyte to be injected into a guard column before passing through a Phenomenex Luna HPLC column, 4.6 x 150 mm, packed with 5 µ PhenylHexyl silica. The detector was set at 280 nm.

Pure constituents of cardanols and cardols, and their hydrogenated congeners were obtained using the method described later. The relative response factor of cardanols to cardol was 1.09.

For different CNSL samples the areas from the chromatograms are presented in the Results and Discussions, Table 2-4.

General characterisation of natural CNSL

Extraction

Experiment 1 Extraction by percolation

Cashew nuts from India (0.9 kg) were stored overnight in a freezer to make the shells brittle. The nuts were then bisected by light hammering with a Swiss knife along the junction of the halves of the shell. The internal kernel testa lining was then separated, and parts of the testa still in the shell were removed by knife and brushing. Cleaned shell (710 g) was powdered in a home coffee mill, and the ground shell was extracted by

percolation of successively dichloromethane (3 x 1 l), ethyl acetate (3 x 1 l), and methanol (3 x 1 l) over a column filled with the powdered shells. The combined extracts were filtered on a celite/silicagel pad and evaporated to constant weight, under vacuum, at room temperature giving a reddish oil (174 g); λ_{max} at 308 nm (ϵ=1520, based on average MW 339); ν_{max} 3400, 3010, 2925, 2856, 1487, 1262 cm^{-1}; MS (DI), M 328, 346, 396 (minor peak), HNMR spectrum. See Figure 2-7 in the discussion.

Experiment 2 Extractions of ground shells with soxhlet

Samples of ground cashew nut shell (3 x 10 g) obtained by the procedure described in Experiment 1, were extracted separately with 3 solvents (petrol, acetone, and methanol) using a soxhlet for 6 h, in the solvent indicated. Yields and ratios of cardol/anacardic acid are provided in Table 2-5 in the Results and Discussion.

Experiment 3 Extractions of clean unground shells by churning

Cashew nuts (10g) were plunged into a liquid nitrogen bath to make the shells brittle, and were then bisected by light hammering with a Swiss knife along the junction of the halves of the shell. The kernel and the internal kernel testa lining was then separated, and parts of the testa still in the shell were removed by knife/ and brushing.

Oil extraction was then performed on the clean shells by stirring (in separate experiments) in 3 solvents (petrol, acetone, or methanol) (50 ml) for one week. Yields and ratios of cardol/anacardic acid are provided in Table 2-5, in the Results and Discussion.

Quantitative analysis of natural CNSL by HPLC

Pure constituents of anacardic acid and cardol, and their hydrogenated congeners were obtained using the method described later. HPLC analysis was carried out by taking an aliquot (25 mg) of the extract and adding 4-hexylresorcinol (5 mg) as internal standard. The mixture was dissolved in acetonitrile and filtered through a nylon Aldrich cartridge. The cartridge was eluted with further acetonitrile (3 x 3 ml), and the combined eluant was made up to 50 ml in a volumetric flask. The solvent (acetonitrile-water-acetic acid (78:20:5) was pumped at 1 ml/min for 30 min. The sample was introduced automatically, allowing 20 µl to be injected into a guard column before passing through a Phenomenex Luna HPLC column, 4.6 x 150 mm, packed with 5 µ PhenylHexyl silica. The detector was set at 280 nm.

For different CNSL samples, areas from the chromatograms are presented in the Table 2-4 in the Results and Discussion.

Technical CNSL separations-screening procedures

Acid-base extractions of CNSL

Aqueous sodium hydroxide (5 % solution, 0.15 ml) was added dropwise to CNSL-Bras (0.5 g) (with 8 % cardol estimated by NMR (0.08 g, 0,13 mol)), dissolved in ether (4.5 ml). The mixture gave an emulsion which was separated after washing with brine (3 x 10 ml). The ether layer was dried over magnesium sulfate, and concentrated under vacuum to give a brown-reddish mixture (0.41 g) (molar ratio cardanol/cardol by HNMR 12/1). The aqueous layer was acidified to pH 1 with HCl (37 %) extracted with ether (2 x 10 ml), dried over magnesium sulfate, and concentrated under vacuum to give a yellow oil (0.2 g). NMR and TLC show that both oils contained both cardanol and cardol (molar ratio cardanol/cardol by HNMR 9.5 /1). The procedure was repeated changing the organic solvent to dichloromethane, ethyl acetate, petrol (same volume as ether) changing the base to sodium bicarbonate (2 ml, 1 % solution). Types of solvents, bases, yields and ratios of cardanol/cardol in both layers, are provided in Table 5-1.

TABLE 6 - 1: ALKALINE EXTRACTION OF CNSL

Solvent	Base	Yield organic layer (%)	Cardanol/cardol in the organic layer (by HNMR)	Yield from the aqueous layer (%)	Cardanol/cardol from the second organic layer (by HNMR)
Dichloromethane	NaOH	a)	a)	a)	a)
Ethyl acetate	NaOH	44	10	13	9.5
Petrol	NaOH	38	12	18	8.3
Petrol	$NaHCO_3$	41	10	16	10

(a) when treated with NaOH, this solution provided a foam and was discarded

Titration

A solution of CNSL (1 g) in methanol 20 ml) was titrated, at room temperature, with aq. ammonia (25%) and the pH of the solution was recorded (see Figure 2-5).

Adsorbtion

Column chromatography

In a 2.5 cm ID column, silicagel (30 g) was packed by the slurry method, and CNSL (0.56 g) dissolved in pentane (1 ml) was added. Elution (c.a. 3 ml / min) was performed in 3 steps using mixtures (each 200 ml) of n-pentane + ethyl acetate + acetic acid, i.e (i) 90 + 10 + 1 (ii) 80 + 20 + 1 and (iii) 50 + 50 + 1. Fractions 5-7 (each 10 ml) were recombined, yielding cardanols (0.22 g) while fractions 36-56 yielded cardols (0.02 g).

The cardanol mixture showed:

δ_H ($CDCl_3$), 7.18-7.09 (t , 1 H, 7.7 Hz), 6.81-6.63 (m, 3 H), 5.92-5.78 (m, 0.3 H), 5.42-5.35 (m, 2 H), 5.13-4.97 (m, 0.6 H), 2.87-2.75 (m, 1.6 H), 2.56 (t, 2 H; 7.4 Hz), 1.59-1.20 (m, 27 H), 0.98 (m, 3 H) (see Figure 2-2); required m/z 304.276 for the saturated congener, cardanol (15:0), found m/z= 304.2, 302.1, 300.1, 298.9 one peak corresponding to each congener); λ_{max} (MeOH) (nm) = 232 (ϵ =13450), 273 (ϵ =1120) (four peaks in the HPLC assay used for technical CNSL and described previously).

The cardol mixture showed:

δ_H (^1H $CDCl_3$), 6.43 (s, 1H), 6.34-6.31 (m, 2 H), 5.92-5.78 (m, 0.3 H), 5.42-5.35 (m, 2H), 5.13-4.97 (m, 0.6 H), 2.87-2.75 (m, 1.6 H), 2.56 (t, 2H; J, 7.4 Hz), 1.59-1.20 (m, 27 H), 0.98 (m, 3 H) (see Figure 2-3); required m/z: 320.271 (for the saturated congener), found m/z= 320.2, 318.1, 316.1, 314.1(one peak for each congener); λ_{max} (MeOH) (nm) = 238 (ϵ = 12650), 273 (223) (four peaks in the HPLC assay used for technical CNSL and described previously).

Separation by adsorbtion on silica and desorbtion with solvents with different polarity

A solution of CNSL (1.00 g) in petrol (20 ml) was mixed with silicagel (20 g), and the solvent was removed on the rotary evaporator.

a) The resulting mixture (21.00 g) was dissolved in petrol (200 ml) and stirred overnight. The petroleum extract was then filtered and concentrated under vacuum to give a clear yellow oil (0.05 g) identified by ^{1}HNMR as cardanol.

b) The above procedure was repeated to obtain the CNSL-silicagel suspension.

It was then stirred with petroleum (200 ml) for 18 h, under reflux; the same work-up gave a clear oil (0.08 g) identical by ^{1}HNMR to that above.

c) The procedure was repeated to obtain the CNSL-silicagel suspension, which was then stirred for 2 h in a mixture of petrol (180 ml) and toluene (10 ml). TLC showed that the resulting solution contained cardanol with trace of cardol (0.12 g).

Complexes with $CaCl_2$, $AlCl_3$, $CaSO_4$, $MgSO_4$, and molecular sieves

To CNSL (1.00 g) dissolved in petroleum (10 ml), was added absolute ethanol (0.4 ml) and finely ground calcium chloride (0.33 g). The disappearance of the cardol spot on TLC (eluted with petrol-ether 5-2) was complete after 3 days. Filtration of the resulting suspension, and evaporation of the petroleum gave a black oil (0.35 g) identified as cardanol by NMR. The procedure was repeated using toluene instead petrol giving also cardanols (0.33 g) as a black oil. It was then repeated using petrol but modifying the concentration of the complexing agent (calcium chloride), or substituting it with others as indicated in the Table.

TABLE 6 - 2: USES OF COMPLEXES TO SEPARATE CARDANOL FROM CARDOL

Complexing agent	Concentration of complexing agent (g/g CNSL)	Yield of cardanols (%) (pure by NMR)
Calcium chloride	0.33	35
Calcium chloride	0.35	18
Calcium chloride	0.27	Not selective a)
Aluminium chloride	0.30	15
Calcium sulfate	0.30	Not selective a) b)
Magnesium sulfate	0.30	Not selective a) b)
Molecular sieves	0.30	Not selective a) b)
B_2O_3	0.18	12

a) TLC analysis showed that both cardanol and cardol were present in solution b) HNMR indicate that the ratio of cardanol/cardol is similar to the one in CNSL

Attempts to regenerate the complexed cardanol-cardol-calcium chloride

The complexed cardanol-cardol-calcium chloride (0.4 g) was washed with methanol (5 ml), filtered and dried to give a grey gel (0.35 g), insoluble in $CDCl_3$. The procedure was repeated using acetone instead of methanol giving a similar grey gel. Attempts to boil the methanol suspension before filtering it gave also a gel.

Complexes with urea

(a) By percolation on a column CNSL (1.00 g) diluted in petrol (1 ml) was added to a column packed with urea (10 g) by the slurry method and this was eluted with petrol (10 ml). ^{1}HNMR of the black oil recovered (0.35 g) was similar with CNSL ^{1}HNMR.

(b) In a batch system CNSL (1.00 g) diluted with methanol (20 ml), was mixed with aq. urea (6M) and allowed to settle. The heterogeneous mixture was filtered and the resulting solution was evaporated to give a brown oil (0.35 g). TLC and ^{1}HNMR suggest that both cardol and cardanol were present. ^{1}HNMR suggested that the oil had the same degree of unsaturation as the starting material, and that the proportion of cardol was the same.

Petrol-glycol partition

CNSL (1000 mg) was dissolved in petrol (10 ml) to which was added diethylene glycol (10 ml). After shaking, the petrol and the diol layers were allowed to separate. Removal of the solvent from the non-polar layer gave of pure (^{1}HNMR identical to that above) cardanol (65 mg). The glycol layer was diluted with water (2 x 10 ml) and re-extracted with ethyl acetate (3 x 10 ml) to give, after drying over magnesium sulfate, a mixture of cardanol-cardol (812 mg) with ^{1}HNMR similar with the one of CNSL.

Other Petrol-Diol partitions

The same procedure was repeated using instead of glycol, other diols (1,3-propanediol, 1,2-butanediol, 1,4-butanediol and 1,5-pentanediol) in separate experiments. The results are presented in Table 2 - 7.

Continuous extraction Petrol-diol system

By shaking and decanting, in a separating funnel, CNSL (10.00 g), petrol (100 ml) and 1,4-butanediol (100 ml), the top layer afforded cardanol (0. 65 g), while the bottom polar layer was submitted to continuous extraction in a standard laboratory apparatus. The polar phase was thus introduced into the top reservoir, with petrol (100 ml) in the lower flask. The petrol was then evaporated, and condensed (at a rate of ca. 1 drop/sec.) to flow through the polar phase. The top of the condenser was closed with a rubber septum, topped with a argon filled balloon. The petroleum flask was changed each 4 h, and the solvent was removed *in vacuo* to allow isolation and characterisation of the extract. Pure cardanol (3.23 g) was obtained after 60 h. The polar layer was dissolved in water (2 x 100 ml), and re-extracted with ethyl acetate (3 x 100 ml) to give, after drying on magnesium sulfate, a mixture of cardanol-cardol (5.12 g) (ca.. 10/1 by NMR).

The procedure was repeated with using 1,5-pentanediol instead of 1,4-butanediol. The top layer from the separating funnel afforded cardanol (0.79 g), while the continuous extraction after 60 h afforded more cardanol (3.21 g) and a mixture of cardanol-cardol (4.7 g) (ca. 10/1 by NMR).

Petrol-amino derivatives partition

CNSL (1000 mg) was dissolved in petrol (10 ml) to which was added diethanolamine (10 ml). After shaking, the petrol and the amine layers were allowed to separate. Removal of the solvent from the non-polar layer gave of pure (^{1}HNMR identical to that above) cardanol (92 mg). The polar layer was diluted with water (2 x 10 ml) acidified with aqueous HCl (10 %) until pH = 1 and re-extracted with ethyl acetate (3 x 10 ml) to give, after drying on magnesium sulfate, a mixture of cardanol-cardol (580 mg) with ^{1}HNMR similar with the one of CNSL. The procedure was repeated, using instead of monoethanolamine, diethylenetriamine, diethylenetetramine, or t-butylamine. Yields are reported in Table 2 - 8 .

Non-diol, non-amino solvent partition

CNSL (1000 mg) was dissolved in petrol (10 ml) to which was added acetonitrile (10 ml). After shaking, the layers were allowed to separate. Both solvents were removed *in vacuo*. The non-polar layer afforded cardanol (with ^{1}HNMR identical to that above) (193 mg), while the polar layer afforded a cardanol-cardol mixture (640 mg, ratio 10:1, by ^{1}HNMR). A black resinous material (163 mg) flocculated in the separating funnel, (recovered by washing the glassware with dichloromethane) with ^{1}HNMR identical to that of CNSL, but broader, IR similar to the one of CNSL though the relative intensity of the peaks at 988, 945, and 910 cm^{-1} was smaller, MS-DI spectrum similar than the one of cardanol, but with a small additional peak at m/z 352.

This procedure was repeated using instead of acetonitrile, trifluoroethanol, methanol or dimethylformamide. With this last solvent, the polar layer was diluted with water (2 x 10 ml) and re-extracted with ethyl acetate (3 x 10 ml) to give, after drying over magnesium sulfate, a mixture of cardanol-cardol (625 mg) with ^{1}HNMR similar with the one of CNSL. Others results are indicated in Table 2 - 9.

Petrol-dimethylsulfoxide, petrol-nitromethane solvents partition

The above procedure was repeated using nitromethane instead of acetonitrile and dimethylsulfoxide instead of dimethylformamide. The results are given in Table 2 - 10.

Back extraction

P.TFE back extraction

CNSL (1000 mg) dissolved in heptane (1ml) was extracted with TFE (1 ml x 40). Removal of the heptane gave cardanol (752 mg), while the combined TFEs layers gave, after removal of the solvent, a cardanol and cardol mixture rich in cardols (0.13 g). This mixture was

redissolved in TFE and after re-extraction with heptane (1 ml x 20) gave cardol with TFE (0.034 g, ca. 83 % solvent by ^{1}HNMR).

Petrol-acetonitrile back extraction

CNSL (10.00 g) was dissolved in a mixture of petrol-acetonitrile (1:1), (200 ml). Separation of the two layers, and removal of the solvents under vacuum gave cardanols (1.95 g) from the non-polar layer, a mixture of cardols-cardanols (5.90 g) (cardanols 91%) from the polar layer, and a sticky material (2.00 g) that flocculated in the flask. The acetonitrile layer was redissolved in ACN (100 ml) and re-extracted with petrol (100 ml). This operation was repeated four times; the weights, and purity accessed by HPLC assay are indicated in the Table.

TABLE 6 - 3: YIELDS AND PURITY IN PETROLEUM- ACN MULTISTEP EXTRACTION

re-extraction	Petroleum layer			ACN layer		
	Weight	Purity Cardanols (%)	Purity Cardols (%)	Weight	Purity Cardanols (%)	Purity Cardols (%)
1	1.02	100	0	4.90	87	13
2	0.70	99.4	0.6	4.20	82	18
3	0.52	n.a.	n.a.	3.6	n.a.	n.a.
4	0.35	98.5	1.5	3.2	75	25

n.a.: no available data

Continuous extraction

Continuous extraction with P-TFE

CNSL (1.00 g) in petrol (10 ml) was introduced was into the top reservoir, while TFE (100 ml) was put in the lower flask. The TFE was then refluxed, and condensed (at a rate of approx. 1 drop/sec.) to flow through the petroleum phase. The top of the condenser was closed with a rubber septum, topped with a argon filled balloon. After 3 h, a two-phase product appear in the TFE receptor. TLC shown that both phases contained cardanol and cardol and the experiment was stopped.

Continuous extraction with petrol-acetonitrile system

CNSL (20.00 g) dissolved in a mixture of petrol-ACN (1:1, 200 ml), gave cardanols (5.53 g) after separation of the petrol layer, an enriched mixture of cardols (8.3 g) after separation of the acetonitrile layer and a sticky material (5.76 g) that flocculated in the flask. The acetonitrile layer was redissolved in ACN (100 ml), introduced in a continuous extraction device and re-extracted with petrol for 36 h. Hourly samples of the petroleum layer, and the

final ACN layer were analysed by ^{1}HNMR and results are reported in the table. The viscosity of the oil obtained after evaporating the ACN layer was very high.

TABLE 6 - 4: YIELDS IN THE PETROLEUM-ACN CONTINUOUS EXTRACTION OF 20 G OF CNSL

Time after the Petroleum layer was recovered (h)	Extracts weights (g) a)	Cardols /Cardanols (^{1}HNMR)
0-1	5.53	0
1-6	3.49	0.1
6-12	1.87	
12-24	1.35	
24-30	0.56	
30-36	0.13	
Final ACN layer sample	1.2	1.87

a) The mass of all these fraction is 14.30 g, remaining material account for the sticky flocculate (5.76 g).

TFE-cosolvent, multiple extraction of the petroleum layer to afford pure cardanol

a) TFE- acetonitrile (10:1, v/v)

CNSL (1.00 g) in petrol (10 ml) was extracted with TFE –acetonitrile (3 x (10 ml-1 ml)). The non-polar layer afforded cardanols (0.62 g) while the combined polar layers afforded, after removal of the solvent, a mixture of cardanols/cardols (1:1, by NMR) (0.28 g). A resinous black solid (0.08 g) with a broad NMR spectrum similar to the one of crude CNSL, was recovered after washing the separating funnel with THF.

b) TFE- nitromethane (10:1, v/v)

The procedure used in a) was repeated using nitromethane instead of acetonitrile. The non-polar layer afforded cardanols (0.58 g), while the polar layer afforded a mixture of cardanol-cardol (1.1:1, by NMR, 0.22 g). A resinous black solid (0.10 g) was obtained upon washing glassware with THF. The cardanols were pale yellow coloured.

Cardol recovery

Continuous extraction with P-TFE-ACN system

CNSL (4.00 g) dissolved in petrol-TFE-ACN (10:10:0.5) (82 ml), gave after separation of the layers, cardanol (1.98 g) from the petroleum layer, a cardol rich fraction (0.97 g) from the polar layer, and a sticky material together with some solvent (1.52 g) that flocculated on the flask. The fraction from the polar layer was redissolved in TFE-ACN (10:0.5) (42 ml), introduced into a continuous extraction device and re-extracted with petrol for 12 h. Hourly samples of the petroleum layer, and the final TFE-ACN layer were analysed and results are

reported in the table. In the Petroleum-TFE-ACN continuous extraction of CNSL, the ratio of cardols/cardanols obtained in the final polar layer, accessed by HPLC was over 9/1.

TABLE 6 - 5: YIELDS IN THE PETROLEUM-TFE –5 %ACN CONTINUOUS EXTRACTION OF 4 G OF CNSL

Time after the Petroleum layer was recovered (h)	Weights (g)	Cardol /Cardanol (by ^{1}HNMR)
0-1	2.0	0.05
1-2	0.32	0.1
2-3	0.18	
3-4	0.10	
4-5	0.06	
5-6	0.02	
TFE ACN layer after 6h [a)]	0.24	9 a)

a) The ratio of cardol-cardanol and the concentration of extract in the TFE layer was constant for the following 2 h and then fell. It is not known why this happened.

Multistep back extraction with petrol-TFE-ACN systems

CNSL (1000 mg) was dissolved in petrol-TFE- ACN (10:10:0.5, 20.5 ml). Separation of the petrol layer, and evaporation of the solvent gave cardanols (570 mg), while the polar layer, gave, after evaporation of the solvent, a mixture of cardols-cardanols (190 mg). A sticky material (300 mg with some solvent) that flocculated on the flask was recovered by washing the glassware with dichloromethane. The fraction from the polar layer was redissolved in TFE-ACN ((10:0.5), 10.5 ml) and re-extracted with petrol (10 ml). This operation was repeated four times and the petrol layer were recombined for analysis. The weights, and purity are indicated in the Table.

TABLE 6 - 6: YIELDS IN MULTISTEP BACK EXTRACTION WITH PETROL-TFE-ACN SYSTEMS

	Weight (mg)	Cardols/cardanol (by ^{1}HNMR)
Combined petroleum layers	135	0.05
Final TFE-ACN layer	55	3.71

Reproducibility of the method

Samples of different CNSLs (see Table for details) (1.00 g) were each dissolved in a mixture of petrol-TFE- ACN (10:10:0.5, 20.5 ml). Separation of the petrol layer, and evaporation of the solvent gave cardanol with traces of cardols (amount indicated in the Table), while the polar layer, gave, after evaporation of the solvent, a mixture of cardols-cardanols (amount and ratio of cardanol/cardol indicated in the Table). When a sticky material (see Table, in

the Observation column) flocculated on the flask, it was recovered by washing with dichloromethane, and the weight was recorded.

TABLE 6 - 7: EXTRACTION OF CNSL WITH DIFFERENT ORIGINS WITH PETROLEUM-TFE-ACN.

CNSL name	Cardanol (from petrol layer) (g)	Cardanol/cardol (from the Polar layer)		Observations
		Weight (g)	(by ^{1}HNMR)	
Moz	0.58	0.17	1.95 /1	Sample gave 0.2 g of flocculate
Ajay	0.78	0.21	1.99/1	1) sample refluxed with sulphuric acid/hydrochloric acid by the manufacturer 2) no flocculate in the separating funnel 3) Both phases were dark and it was difficult to see the interface.
Cardolite	0.77	0.22	2.12/1	1) no flocculate in the separating funnel
Marlin	0.78	0.20	2.05/1	1) no flocculate in the separating funnel

Equilibrium data

CNSL Bras (9100 mg) was partitioned in a two-phase system (petrol (100 ml), TFE (100 ml) and ACN (5 ml)). The petrol layer gave, after removing the solvent, an oil (5621 mg), as well as the flocculated solid (2010 mg) (with traces of solvent). The TFE-ACN layer was also evaporated to give an oil (1560 mg). A sample of the polar layer was removed for HPLC characterization, and the remainder was dissolved in TFE-ACN. This layer was re-extracted with same volume of petrol, and after removing the solvents, both fractions were weighed. HPLC analysis was performed using the same methodology for technical CNSL analysis previously described.

The results are presented in the following table.

TABLE 6 - 8: EQUILIBRIUM DATA OBTAINED BY CNSL PARTITION IN PETROLEUM-TFE-ACN

layer type	Extraction step	amount (mg)	area cardanols "(1)	corrected cardanols area "2"	area cardols methylcardols "3"	total area "2" + "3"	cardanols HPLC (%)	cardanols Qty (mg)	cardols HPLC (%)	cardols Qty (mg)
non-polar	1	5621								
polar	1	1780	677	738	371	1109	67	1184	**33**	596
non-polar	2	816	706	770	113	883	87	**712**	13	104
polar	2	753	1178	1284	723	2007	**61**	458	**36**	271
non-polar	3	88	1303	1420	192	1612	88	**78**	12	10
polar	3	507	1177	1283	735	2018	**60**	306	**36**	185
non-polar	4	15	1612	1757	266	2023	87	**13**	13	2
polar	4	340	230	251	297	548	46	156	52	177
non-polar	5	3.8	971	1058	520	1578	67	**3**	33	1
polar	5	200	235	256	1051	1307	**20**	39	**80**	161
non-polar	6	3	623	679	681	1360	50	**1**	50	2
polar	6	180	151	165	1070	1235	13	24	**87**	156
non-polar	7	2.8	418	456	1294	1750	26	**1**	74	2
polar	7	170	149	134	850	984	14	**23**	**86**	147

a) The area of cardols is area of cardols+ methylcardols

Additional information collected in the development of Technical-CNSL extraction

A) Analysis of a published procedure

Experiment 1

To technical CNSL (1000 mg) in methanol (6.6 ml) was successively added water (0.32 ml), and ammonia (25 %, 6.6 ml). The mixture was stirred for 30 min and extracted with hexane/ethyl acetate (98:2) (3 x 6 ml). The combined organic layer was washed with NaOH solution (2.5 %, 6 ml), followed by aq.HCl (5 %, 3 ml). The organic layer was dried over magnesium sulphate and concentrated to give a pale brown oil characterized by HNMR. The methanolic ammonia solution was then extracted with ethyl acetate-hexane (80:20) (6 ml). The organic layer was washed with HCl (5 %, 3 ml) followed by distilled water (3 ml). The organic layer was dried over magnesium sulphate and concentrated to give a pale brown oil characterized by HNMR.

TABLE 6 - 9: TEST OF A PUBLISHED PROCEDURE TO SEPARATE CARDANOL/CARDOL

Sample ID	Estimated cardanols/cardol (mol/mol) by NMR	Estimated cardanols (wt/wt (%))	Amount used/recovered (mg)
Technical CNSL	9.31	90	1000
Hexane-ethyl acetate (98:2) layer a)	13	95	290
Ethyl acetate-hexane (80:2) layer b)	No resolution, broad HNMR spectra	No resolution	412

a) after NaOH, HCl treatment b) after HCl, distilled water treatment

Experiment 2

Technical CNSL (1000 mg) was dissolved in methanol (32 ml) and ammonium hydroxide (25 %, 20 ml) and stirred for 15 min. The solution was extracted with petrol (4x 20 ml). The organic layer was concentrated to get cardanols (pure by HNMR, 62 mg). The methanolic ammonia solution was extracted with ethyl acetate. The resulting organic layer was concentrated under vacuum to give a mixture of cardanols-cardols very similar to the starting material (534 mg) by ^{1}HNMR.

Experiment 3

Cardol (100 mg) (obtained by column chromatography), was dissolved in methanol (3 ml) and aq.ammonium hydroxide (25 %, 2 ml). This solution was extracted with ethyl acetate (4x 2 ml), to afford, after removal of the solvent cardol, pure by HNMR (45 mg).

New procedure to obtain Technical CNSL

Treatment of cardanols with CH_3NO_2

Cardanols (10.00 g) obtained from previous CNSL-acetonitrile-petrol (1:10:10) partition were dissolved in petrol (20 ml) and washed with nitromethane (30 x 5 ml), and provided, after the evaporation of solvent, clear brown-reddish cardanols (6.90 g) and a black flocculate (3.01 mg). The treated cardanols gave a U-tube viscosity of 65.5 cps.

Treatment of CNSL with CH_3NO_2

CNSL (10.00 g) was also submitted to the same procedure and provided a mixture of cardanols-cardols (6.40 g) and a black solid (3.20 g). The mixture gave a U tube viscosity of 73.1 cps.

Black resinous flocculate

CNSL (50.00 g) was dissolved in a mixture of petrol-acetonitrile (10:10) (1000 ml). Separation of the two layers, and removal of solvent, provided cardanol (9.76 g) from the petroleum layer, and a mixture of cardanol-cardol (29.75 g) from the acetonitrile layer, while a sticky black material (10 g) flocculated in the separating funnel and was recovered by washing with THF. The NMR spectrum of the resinous black material was broad, and its MS-EI and IR spectra were similar to the ones of the crude CNSL.

Ash composition of the flocculate & the acid washed flocculate

A sample of the black solid (4.55g), in a porcelain cup, was heated in air for 6 h at 800 °C. The recovered brown ash (0.15 g) was diluted in nitric acid (10%) to a concentration of 4 g/l and analysed by ICP. Results are reported in Table A1-01 in Annex 1.

Standards for HPLC analysis

3-Pentadecylphenol

Cardanol (10.32 g, 32.1 mmol) was dissolved in methanol (100 ml) and mixed with 5 % palladium on charcoal (1.5 g) in a low-pressure hydrogenation flask. This suspension was shaken in the presence of hydrogen (1680 ml) for 8 h, filtered, and evaporated to dryness under reduced pressure to give the title compound as a white powder (9,80 g, 95 %); δ_H

($CDCl_3$), 7.18-7.09 (t , 1 H, 7.7 Hz), 6.81-6.63 (m, 3 H), 2.53 (t, 2 H,J 7.4 Hz), 1.33-0.89 (m, 29 H) (The spectrum was similar to that reported in the literature);[133] requires m/z 304.514; found m/z= 304.2; the product gave one peak on HPLC; mp 51.5 - 52 °C, lit.51 - 52 °C.[20]

5-Pentadecylresorcinol

Cardol (10.00 g, 31.22 mmol) was dissolved in ethyl acetate (100 ml) and mixed with 5 % palladium on charcoal (1.5 g) in a low-pressure hydrogenation flask. This suspension was shaken in the presence of hydrogen (1680 ml) for 8 h, filtered, and evaporated to dryness under reduced pressure to give a beije solid, which was recrystallized from petrol to give 5-pentadecylresorcinol as a white powder (7.80 g, 77 %) mp 95 - 95.5 °C, lit.95.5 - 96 °C,[43] which showed δ_H ($CDCl_3$) 6.34-6.31 (m, 2 H), 5.92-5.78 (m, 0.3 H), 2.56 (t, 2 H, J 7.4 Hz), 1.33-0.89 (m, 29 H) (The ^{1}HNMR was similar to that reported in the literature);[133] requires m/z = 320.272, found m/z = 320; this gave one peak on HPLC.

Natural CNSL separation

(i) Chromatography on triethylamine- treated silica

Petrol-soxhlet extracted CNSL (10.2 g) (from experiment 2, p. 161) was dissolved in petrol (10 ml), and triethylamine (2.87g; 0.028 mmol). The viscosity of the solution increased, and it became a dark brown paste. This was poured through a pad of silica gel (30 g), previously wetted with petrol and 5 % triethylamine. The filter was then eluted with petrol and 5 % triethylamine. The filtrate was washed with conc. HCl (10 ml) to give, after drying over magnesium sulfate and solvent removal, a brown-yellow oil (2.27 g, 22.5 % of the natural CNSL). Analysis by HNMR showed that it consisted mainly of cardols/methylcardols with a trace of anacardic acid. The filter was then washed with 95:5 methanol - formic acid, until the dark paste deposited on the top of the silicagel pad was removed. Washing the methanolic filtrate with conc. HCl (30 ml), and extraction of the resulting aqueous solution with ethyl acetate (100 ml), then removal of the solvent afforded a brown oil, identified as pure anacardic acids (7.1 g, 70 %); δ_H ($CDCl_3$), 7.37-7.35 (t, J = 8 Hz, 1 H), 6.87-6.81 (dd, J =8.1 Hz, 1 H), 6.75-6.68 (dd, J= 8.1 Hz, 1 H), 5.92-5.78 (m, 0.3 H), 5.42-5.35 (m, 2.7 H), 5.13-4.97 (m, 0.6 H) 3.12-2.87 (t, J = 7.5 Hz, 2 H), 2.90-2.70 (bs, 2 H), 2.01 (bs, 2 H), 1.59-1.20 (bs, 27 H), 0.98 (m, 3 H); ν_{max}(film, cm^{-1}) 3400, 3010, 2925, 2856, 1487; λ_{max} (MeOH) (nm) (ϵ) = 206 (50118), 303 (5021).The data are similar to those in the literature.[120]

(ii)Filtration over amine-treated silicagel

A column (3.5 cm id) was prepared by slurrying silica gel (50 g) in hexane containing 2 % triethylamine. A solution of natural CNSL (10.2 g) mixed with hexane (10 ml), with triethylamine (2.87 g; 0.028 mol), was poured on to the column which was then washed with petrol-ethyl acetate (3:1; 800 ml) with triethylamine (12 ml). The eluant was evaporated under reduced pressure yielding cardol (2.72 g) (with no traces of anacardic acid), identified by HNMR. The column was then washed with formic acid (400 ml) yielding, after evaporation under reduced pressure, anacardic acid (7.1 g) (identified by HNMR) with a trace of triethylamine.

Alkaline extractions

(i) Separation using sodium bicarbonate

To natural CNSL (1.00 g) dissolved in ether (5 ml) was added sat.aq. sodium bicarbonate (10 ml). After drying over magnesium sulfate and removal of the solvent, the ethereal layer gave an oil (0.23 g, 23 %) which ^{1}HNMR showed to be a mixture of anacardic acid and cardol (ratio 4:1) The aqueous layer gave, after reacidification with concentrated HCl (10 ml), re-extraction with ether (3 x 10 ml), drying over magnesium sulfate and removal of the solvent, a clear oil (372 mg, 37 %) which HNMR showed to be a mixture of anacardic acid with cardol (ratio 7:1).

(ii) Calcium hydroxide

a) Procedure A

Acetone-extracted CNSL (50.00 g) was dissolved in ethanol (200 ml), and filtered through a bed of celite. A slurry was made with calcium hydroxide (10 g) and water (20 ml) added in small portions. This was suspended in ethanol (100 ml) and added slowly, with continuous stirring to the filtered CNSL solution. Stirring was continued overnight. The mixture was then allowed to settle and the insoluble solids (calcium anacardate plus excess calcium hydroxide) filtered off and washed with acetone. The filtrate was concentrated under vacuum, extracted with butyl acetate (2 x 10 ml), dried over magnesium sulfate, and reconcentrated under vacuum to give a cardol rich fraction (3.75 g, 7.5 %). The corresponding water layer, with a strong yellow colour, was discarded. The residual solid (calcium anacardate plus excess calcium hydroxide) was suspended in water (100 ml) and concentrated hydrochloric acid (40 ml) was added. The mixture was heated in a boiling water bath for 30 min., the regenerated anacardic acid separating as an upper layer. After cooling, saturated brine (10 ml) and butyl acetate (10 ml) were added. The aqueous layer was re-extracted with butyl acetate and the combined organic layers were dried over magnesium sulphate, and the solvent removed under reduced pressure. The residual oil

crystallised as a waxy solid at room temperature within few minutes (35.51 g, 71 %), and gave an HNMR corresponding to anacardic acid (purity 98.5 %) (mp 23 °C) with a trace of cardol.

b) Procedure B

The same technique was used as in procedure A but using anhydrous calcium hydroxide and acetone. No reaction could be observed after 2 days.

c) Procedure C

The same procedure was used as in procedure A but using CNSL without solvent. The viscosity of the mixture with aq. calcium hydroxide increased in such a way that agitation was difficult, and the experiment was stopped.

(iii) Copper hydroxide

Natural CNSL (1 g) dissolved in butyl acetate (5 ml) was shaken with an aqueous solution (10 ml of water) of copper hydroxide (212 mg). The organic layer, obtained after drying, and concentrating under vacuum gave a green oil (1060 mg). The aromatic signals corresponding to anacardic acid had changed into one broad signal. This sample was totally soluble in water. The aqueous layer, acidified with concentrated HCl until pH 1, and re-extracted with butyl acetate (10 ml), gave an oil (235 mg). NMR analysis show that cardols and anacardic acids were present in both layers.

Liquid-liquid extraction

Petrol-Acetonitrile solvent system

Natural CNSL (10.00 g) was injected to a separating funnel containing petrol (10 ml) and ACN (10 ml). Immediately after shaking, two liquid phases separated. After evaporation of the solvents, the petroleum layer gave a brown oil (1.93 g, 19 %) (anacardic acid by NMR), while the ACN layer gave also a brown oil (8.02 g, 80 %) (mixture of anacardic acid/cardol (ratio by NMR : 2.1 (mol/mol). An aliquot of the brown oil from the petroleum layer was then dissolved in diethylether (2 ml) treated with diazomethane (2 ml) to gave a mixture of methylated anacardic acid. δ (^{1}H $CDCl_3$), 7.37-7.35 (t, J = 8 Hz, 1 H), 6.87-6.81 (dd, J =8.1 Hz, 1 H), 6.75-6.68 (dd, J= 8.1, 1 H), 5.92-5.78 (m, 0.25 H), 5.42-5.35 (m, 2 H), 5.13-4.97 (m, 0.25 H), 3.98 (s, 0.0.75 H), 3.3.94 (s, 0.6 H), 3.80 (s, 1.5 H), 3. 3.12-2.87(t, J = 7.5 Hz, 2 H), 2.90-2.70 (bs, 2 H), 2.01 (bs, 2 H), 1.59-1.20 (bs, 27 H)., 0.98 (m, 3 H).

Petrol-Methanol solvent system

The same procedure was used as in the previous experiment, but using petrol:methanol 7:1 instead of petrol acetonitrile (1:1). The petrol layer afforded a brown oil (6.82 g) identified by HNMR as a mixture of anacardic acid and cardol (5:1), while the methanol layer afforded (3.10 g) of a mixture of anacardic acid and cardol in a similar ratio.

Optimal ratio using Petrol-TFE-ACN

Natural CNSL was injected into a separating funnel containing different amounts of petrol, ACN, and TFE indicated in the Table. After separation of the phases, both layers were evaporated under vacuum, and analysed by NMR. Data obtained are shown in the Table:

TABLE 6 - 10: OPTIMAL SOLVENT RATIO IN NATURAL CNSL SEPARATION

	Solvent system			Polar layer		Non-polar layer	
Natural CNSL (mg)	TFE (ml)	ACN (ml)	Petrol (ml)	Cardol/ Anacardic (mol/mol) (by NMR)	Quant. (mg)	Cardol/ Anacardic (mol/mol) (by NMR)	Quant. (mg)
1000	5	5	10	0.276	644	0.01	356
1000	3	7	10	0.247	780	0.016	280
1000	8	2	10	0.645	629	0.034	371
1000	9	1	10	1.096	316	0.077	684
1000	9.6	0.4	10	1.736	282	0.170	652
1000	9.88	0.02	10	1.177	9	a)	91
1000	9.5	0.5	10	1.766	173	0.112	827

a) no available data.

Multistep extraction of Natural- CNSL using Petrol-TFE-ACN

Natural CNSL (860 mg) was injected into a separating funnel containing petrol (10 ml), TFE (10 ml) and ACN (0.5 ml), and was separated into two layers (extraction 1). The polar layer, corresponding to the TFE-ACN solvents, was re-extracted with petrol (4 x 10 ml, extractions 2 , 3, 4 & 5). Yields and NMR ratios are indicated in the Table:

TABLE 6 - 11: MULTISTEP EXTRACTION OF NATURAL- CNSL USING PETROLEUM-TFE-ACN

Extraction	Layer	Mass Yield (mg)	Anacardic acids/ Cardols (mol/mol) by NMR
1	Non-polar	700	12
2	Non-polar	62	3.5
3	Non-polar	15	2.6
4	Non polar	10	a)
5	Non polar	5	1.2
6	Polar	60	0 b)

a) no data
b) 100% cardols by NMR and HPLC

Back extraction of the petroleum layer

The petroleum layer from the previous experiment (corresponding to line 1 from the Table) (500 mg) was extracted with TFE-ACN (5%) (3 x 10 ml) to give, in the petrol layer, anacardic acid (256 mg) with no cardols.

Equilibrium data for the partition of CNSL with P-TFE-ACN (5%).

a) Natural-CNSL (8750 mg), was partitioned in a two-phase system (petrol (100 ml), TFE (100 ml) and ACN (5 ml), to afford a petroleum layer (7030 mg) and a TFE-ACN layer (1681 mg). An aliquot of the polar layer was removed for ^{1}HNMR, and HPLC (see Table). HPLC analysis was performed using the same methodology as for Natural CNSL analysis previously described .

b) The remainder was dissolved in TFE (100 ml) and ACN (5 ml). This layer was re-extracted with petrol (100 ml). After removing the solvents, both fractions were weighed and aliquots collected for ^{1}HNMR, and HPLC characterization.

c) The polar layer was then redissolved in TFE (100 ml) and ACN (5 ml), and the procedure described in b) was repeated more 3 times

The results are presented in the table.

TABLE 6 - 12: EQUILIBRIUM DATA FOR THE PARTITION OF CNSL

Extraction & layer polarity	amount (wt.,mg)	NMR information		HPLC Preliminary information								Obs.
		Anacardic acids (%)	Cardols (%)	Anacardic acids area (%)				Cardols area (%) a)				
				15:3	15:2	15:1	Tot.	15:3	15:2	15:1	Tot	
1, non polar	7030	92	8	36	16	33	86	9	3	2	14	
1, polar	1681	81	19									
2, non polar	742	83	17	44	14.7	24.8	87	12	1	-	13	
2, polar	930	28	72	12	-	-	12	65	17	6	88	b)
3, non polar	153	63	37	37	11	14	63	27	10	-	37	
3, polar	781	23	77 b)	7	-	-	7 b)	69	18	6	93	b)
4, nonpolar	123	n.a.	n.a.	-	-	-	-	-	-	-	-	c)
4, polar	664	18	82	22	-	-	22	60	18	-	78	
5,non polar	48	43	57									
5, polar	601	0	100	-	-	-	0	81	18	-	100	

a) cardols+ methylcardols
b) HPLC samples too diluted.
c) sample too dilute and gave only one peak for anacardic acids by HPLC

Anacardic acid content in cashew kernels

Cashew kernels (9.00 g), obtained from a supermarket, were extracted in a soxlhet with petroleum to afford a pale yellow oil (0.34 g, 38 %).

$\delta_H(CDCl_3)$, 5.5 (m, 6.5 H), 4.15 (m, 4 H), 2.7 (t, 0.5 H, J 7.4 Hz), 2.25 (t, 6 H, J 7.4 Hz), 2.1-1.9 (m, 9 H), 1.6 (m, 4 H), 1.3 (m, 60 H), 0.9 (m, 9 H).

HPLC sample and conditions

Analysis was carried out by using a Phenomenex Luna HPLC column, 4.6 x 150 mm, packed with 5 μ PhenylHexyl silica with acetonitrile-water-acetic acid (78:20:5) at a flow rate of 1 ml/min and the UV detector set at 280 nm. Areas and retention times corresponding to the chromatogram of a sample of the kernel oil (200 mg) and 4-hexylresorcinol (0.196 mg) in petrol (1 ml) are reported in the Table. Identification of the peaks was performed using a sample of the kernel oil (200 mg) with 4-hexylresorcinol (0.196 mg) spiked with (0.5 mg) anacardic acids in petrol (1ml). From the later chromatogram anacardic acids (0.1 mg) was found to correspond to 88.81 mV min.

TABLE 6 - 13: ANACARDIC ACID CONTENT OF CASHEW KERNEL AND CASHEW KERNEL OIL

Compound name	Cashew kernel oil			Cashew kernel
	Retention time (min)	Area (mV/min)	Anacardic acid concentration (ppm)	Anacardic acid concentration (ppm)
4-HR	3.62	573.58	----	---------
Anacardic acid (15:3)	7.10	48.3	270	104
Anacardic acid (15:2)	8.95	18.64	105	40
Anacardic acid (15:1)	12.05	7.88	45	16
Unknowns	others	305.02	------	-------
Total anacardic	----------	**74.78**	**420**	**160**

Semecarpus oil composition

Semecarpus nuts (56 nuts, 105.00 g) were cut transversally and the kernels (23.50 g) recovered manually from the shells (81.50 g). The latter were then milled in a coffee mill. The powdered shell was extracted with methanol-ethyl acetate-dichloromethane (3 x 100 ml, 10:10:10), to afford upon elimination of the solvent under vacuum, a dark reddish oil (7.16 g, 30.5 % of the shells) characterised by δ_H ($CDCl_3$) (see ^{1}HNMR in Figure 2-22), 6.7 (s, 3 H); 5.4 (m, 5.2 H), 2.82 (m, 1.8 H) 2.62 (t, 2 H, J= 7.4 Hz), 2.07 (bs, 4 H) , 1.65 (bs,1.5 H),

1.35 (m, 22 H), 0.93 (m, 3 H). ; ν_{max} 3400, 3010, 2925, 2856, 1487, 740 and 770 cm^{-1}; λ_{max} at 292 nm (ϵ=1118, based on average MW 316), MS (DI) M 316 (minor peak).

HPLC analysis (see Figure 2-25) was carried out with a Phenomenex Luna HPLC column, 4.6 x 150 mm, packed with 5 µ PhenylHexyl silica, using 4-hexylresorcinol (5 mg in 25 mg of oil) as internal standard and a detector at 292 nm. Water-acetonitrile-acetic acid (40-60-10) was pumped for 55 min at 1 ml/min and the oil showed 18 peaks

An aliquot of the oil (1.2 g) was separated by chromatography on silicagel using petrol-ethyl acetate acetic acid (5:2:0.1), to afford, as a major fraction, a pale yellow oil (0.88 g) characterized by δ_H ($CDCl_3$) 6.7 (s); 5.4 (m), 2.82 (m) 2.62 (t, J= 7.4 Hz), 2.07 (bs) , 1.65 (bs), 1.35 (m), 0.93 (m) and which on silver nitrate TLC (see Figure 2-24) showed 3 spots. The oil (0.80 g) dissolved in ethyl acetate (25 ml) was hydrogenated in a Parr hydrogenator over 4 h, to afford 3-pentadecylcatechol (0.79 g) identified as δ_H ($CDCl_3$) 6.7 (s, 3 H); 2.62 (t, 2 H, J= 7.4 Hz),1.62 (bs, 2 H) 1.35 (bs, 22 H), 0.93 (m, 3 H); (found C, 78.7; H, 11.3 %; $C_{21}H_{36}O_2$ requires: C 78.69, H 11.32 %). The data were similar to the ones in the literature.[114]

3. SHORT-CHAIN PHENOLS BY PYROLYSIS

Typical procedure

The apparatus is shown schematically in the "Results and Discussion".

The cylindrical reaction chamber (0.75 cm id x 30 cm long) was a quartz tube (A) mounted in an electrical tube furnace (B) fitted with alumina ends plugs.

The starting material was introduced using a syringe through a rubber septum (C), at one end of the reactor were it was vaporized, transported to the reaction zone and cracked. In the firsts runs, the reaction temperature was measured continuously during the reaction by a probe (D) in the reactor. The variation of temperature, followed by the digital thermometer (E) during a typical run was around 1 - 3 °C. At both extremities (the first and last 5 cm) of the tube, the temperature was 250 - 270 °C lower than at centre. As the value obtained by the temperature probe in the middle of the reactor was similar to the one displayed by the control system in the oven, in subsequent runs the temperature was followed using just the oven display. The temperature indicated is the one of the internal wall of the reactor, as the radial temperature gradient is unknown.

The products and unconverted feed were trapped in a 25 ml flask (F), immersed in a cold fluid (liquid nitrogen unless stated otherwise, see details) and connected to the vacuum (G) produced by a vacuum pump (or in some specific cases, by a water pump (see details in each particular experiment)).

On completion of the experiment, the product was allowed to reach room temperature, and volatile fraction eliminated (at liquid nitrogen temperature, the reaction mixture is an icy solid, which bubbles when reaching room temperature, allowing the elimination of the "incondensable" compounds which are gases at normal temperature and pressure). The condensable fraction was weighed, an analysed by NMR. At the end of each run, the apparatus was dismantled, and the reactor tube was visually inspected, then reheated for 3 h at 650 °C with the two ends open to allow a free flow of air (to burn all coke deposits)

The % MVP by NMR in the product indicated in the Tables was calculated from the spectra as a ratio between the area of one vinyl proton and one fifth of the area of the aromatic protons.

Pyrolysis of CNSL in a small diameter quartz pipe

CNSL (1.030 ml, 1000 mg) was injected in small aliquots, using a 250 microliter GC syringe, into a 6.5 mm i.d. quartz tube reactor. The tube was heated in a Carbolite-type tube oven, at an angle of 30°, allowing a downward flow of the pyrolysed gas, at constant temperature in each run (range 680 - 800 °C).

The injection rate was maintained at ca 0.05ml / 3 sec.

At the outlet, the tube was connected to a reduction adaptor, which led to a flask cooled in a liquid nitrogen/methanol mixture at a temperature of –85 °C. The system was maintained at low pressure (between 0.1 and 0.5 mm Hg). A first set of experiments (650 and 850 °C) (run A) was repeated (run B). All the samples were characterised by HNMR and by GC. The results are presented on the Table.

TABLE 6 - 14: PYROLYSIS OF CNSL IN A SMALL DIAMETER QUARTZ PIPE

	Run A			Run B							
Temp (°C)	Pres. (mm Hg)	Mass recovery (mg liquid fraction/ g CNSL)	MVP (%) by NMR	Pres. (mm Hg)	Mass recovery (mg liquid fraction/ g CNSL)	MVP (%) by NMR	cardanol (%) by GC	cresol (%) by GC	EP b) (%) by GC	PP c) (%) by GC	MVP (%) by GC
650	0.2	402	31	0.1	425	30	13.5	8	3	4	28
680	0.3	369	33	0.2	367	38	5	13	4	4	36
700	0.4	344	40	0.5	358	40	3	16	0	8	41.5
730	0.2	270	39	0.3	274	41	-	-	-	-	-
750	0.4	188	46	0.3	192	44	0.0	14	0	1.	43
770	-	-	-	0.3	173	40	0.0	8	0	0	40
800	0.2	152	37	0.2	151	35	0.0	5	0	0	35
850	0.3	78	23	0.1	82	26	0.0	0	0	0	29

a) GC analysis was performed by comparison of the retention time and peak area of pure compounds. 3-Cresol, and 3-ethylphenol were obtained from Aldrich and 3-propylphenol and MVP were synthesized; b) EP ~ 3-ethylphenol; .c) PP ~ 3-propylphenol.

Samples of run B obtained at 650 and 730 °C, were characterised by DI-MS.

(m/z) found (at both 650 °C and 730 °C) 136, 122, 120, 108; propylphenol requires 136, ethylphenol requires 122; metavinylphenol requires 120; and cresol requires108.

3-Vinylphenol

Butyl lithium (1.5 M, 6.2 ml) was added dropwise to methyl triphenyl phosphonium bromide (5.24 g) dissolved in THF (15 ml), cooled to –78 °C. The resulting deep orange mixture, was stirred for 0.5 h, then allowed to reach room temperature. The solution was cooled to –50 °C, and 3-hydroxybenzaldehyde (0.76 g, 6.3 mmol), in THF (5 ml) was added dropwise, when the mixture became light orange. After 3 h, the reaction was quenched with water (10 ml) and extracted with ether (3 x 30 ml). The extract was washed with brine (10 ml), to afford, after "in vacuo" solvent removal, a yellowish solid which was separated by column chromatography on silicagel with petrol-ethyl acetate (5:2) to afford the title compound as a pale yellow oil (0.33 g, 2.7 mmol, 43 %). The ^{1}H-NMR and EI-MS were identical to those reported in the literature.[254] δ_H ($CDCl_3$) 7.1-6.61 (5 H, m), 5.61 (1 H, d, J 17.9 Hz), 5.18 (1 H, d, J 10.9 Hz); m/z 120, C_8H_8O requires 120.058.

3- (1-Hydroxypropyl)-phenol

Ethyl-magnesium bromide (80 ml, 37 mmol) was added dropwise to 3-hydroxybenzaldehyde (2 g, 16.39 mmol) in dry THF (20 ml), cooled in a nitrogen-ethanol bath at – 40 °C. After 20 min, the product was quenched with HCl (5 %) to pH 1, extracted with ethylacetate (3 x 20 ml), repurified with brine (20 ml), dried over magnesium sulfate, and concentrated "in vacuo", to afford a pale yellow oil (2.57 g).This was purified by column chromatography to afford the title compound (2.2 g, 13.25 mmol, 81 %). The ^{1}H-NMR was identical to that reported in the literature,[253] δ_H ($CDCl_3$) 7.1-6.9 (4 H, m), 4.5 (1 H, bs),1.81 (2 H, bs), 0.94 (3 H, t, J 7 Hz).

3-Propylphenol

3-(1-Hydroxypropyl)-phenol (1.4 g, 9.21 mmol), in methanol (20 ml) was acidified with acetic acid (5 ml) and HCl (33 %,1 ml), and the resulting mixture was hydrogenated, over 4 h, in a Parr hydrogenator, with palladium on carbon (5 %) (0.4 g). The product was filtered over celite, re-extracted with ether (3 x 20 ml) and concentrated "in vacuo" to afford the title compound (1.1 g, 8 mmol, 87 %).The ^{1}H-NMR was identical to that reported in the literature,[253] δ_H ($CDCl_3$) 7.1-6.9 (4 H, m), ,2.55 (2 H, d, J 7 Hz),1.66 (2 H, bs), 0.94 (3H, t, J 7 Hz).

Pyrolysis of cardanols in a clean quartz ring filled reactor

General

Quartz rings where obtained by cutting 2 mm internal diameter quartz tube in 15 mm length rings. Cardanols (1ml, 870 mg, 2.72 mmol) were injected (at a constant rate of approx. 0.05

ml / 3 sec.) as before, using a 1 ml syringe, with a 14 cm needle, into the hot zone of a quartz tube reactor filled with 40 quartz rings (with a global surface area of 283 mm^2) between two small quartz wool pads. The first pad was located 11 cm from the septum. The tube was held at a constant temperature in each run (range of 680 - 800 °C), (between 0.1 and 0.5 mm Hg). At the outlet of the quartz tube reactor, and before the collecting flask, a whitish cloud was visible some seconds after the cardanols were injected in the reactor. During the reaction, the outlet tube become gradually black. The vacuum was maintained during the heating and the cooling of the tube; 5 min after finishing the injection, the tube was cooled stepwise, reducing the temperature with an automatic control system by 100 °C and maintaining at this new temperature for 20 min and repeating the operation until reaching room temperature. The product was analysed by ^{1}HNMR. The black tar deposited on the tube wall between the end of the quartz filling and the collecting flask was weighed in each run, and one sample was characterized by HNMR (see Figure 3-15). The black tar deposited between the injection point and the quartz filling was also weighed at the end of each run, then washed with $CDCl_3$, and the extract analysed by HNMR. The results are presented in the Table

TABLE 6 - 15: PYROLYSIS OF CARDANOLS IN A CLEAN QUARTZ RING FILLED REACTOR

Temp (°C)	Press. (mmHg)	Time til no more product was collected (s)	Mass recovery (mg liquid fraction/ g cardanol)	MVP (%) by NMR	Tar (a) (mg liquid fraction/ g cardanol)
680	0.3	43	570	19	24
700	0.2	43	453	27	12
720	0.1	45	116	42	11
740	0.5	18	272	43	13
740	0.4	38	214	12	10
740	0.1	271	510	28	5
740	0.3	34	220	24	11
740	0.5	43	137	18	13
760	0.1	39	120	26	9
780	0.1	55	92	40	12
800	0.3	54	90	37	7

a) Tar collected between the quartz wool pad at the end of the quartz filling and the collecting flask.

HPLC assay of the pyrolysed products

Each analysis was carried out by taking an aliquot (25 mg) of the extract and adding the internal standard (5 mg). The mixture was dissolved in THF (5 ml) and filtered through a nylon Aldrich cartridge. The cartridge was eluted with further THF (3 x 3 ml), and the combined eluant was made up to 100 ml in a volumetric flask. Solvent (acetonitrile-water-

acetic acid, 78:20:5) was pumped at 1 ml/min for 30 min. The sample (20 µl) was injected into a guard column before passing through a Phenomenex Luna HPLC column, 4.6 x 150 mm, packed with 5 µ PhenylHexyl silica. The UV detector was set at 204 nm (the absorption maximum for MVP). An overlap of the chromatograms is presented in the Figure 3-14.

Pyrolysis on a de-activated quartz ring filled reactor

Deactivation of the quartz tube and of the quartz rings

Cardanols (20 ml, 17.4 g), obtained by the petrol/ TFE (5% ACN) method were injected, at a rate of approx. 0.05 ml / 3 sec., into the hot zone of a quartz tube reactor filled with 40 quartz rings between two small pads as previously described. The temperature was maintained at 700 °C and the vacuum was maintained with a water pump. The vacuum was maintained during the cooling and the resulting quartz tube was covered by an internal, shiny black carbonaceous layer (with a very bad smell). This was used as the deactivated quartz reactor.

FVP on the deactivated quartz reactor

Cardanols (1 ml, 870 mg, 2.72 mmol) were injected into the deactivated quartz reactor using the same method as for the clean quartz pipe reactor. ^{1}HNMR and HPLC analysis was performed as before. The results are presented in the Table.

TABLE 6 - 16: YIELDS IN FVP ON THE DEACTIVATED QUARTZ REACTOR

Temp (°C)	Press. (mmHg)	Mass recovery (mg liquid fraction/ g cardanol)	MVP (%) by NMR
700	0.1	612	12
720	0.2	567	35
740	0.3	526	25
760	0.1	516	14

An overlap of the HPLC chromatograms is presented in Figure 3-17.

Oxypyrolysis

Cardanols (amount indicated in the Table) were co-injected simultaneously, with air (amount indicated in the Table), using two syringes with long needles, through a rubber septum, directly into the hot zone of a quartz ring filled reactor, at a constant temperature (indicated in the Table). The results are presented in the Table:

TABLE 6 - 17: YIELDS IN CARDANOL OXYPYROLYSIS

Temp (°C)	Pressure (mmHg)	Air (ml / g cardanols)	Mass recovery (mg liquid fraction/ g cardanol)	GC data		NMR data
				MVP (%)	EP (%)	MVP (%)
720	3	20	183	40	7.	34
650	5	40	56	----	----	5
726	7	20	180	41.3	7.5	31

Pyrolysis on stainless steel, iron sponge filled reactor

Pyrolysis on mild steel

Mild steel nuts (30) (with a total an external surface of 232 mm^2) were introduced into the quartz pipe tube in place of the previously used quartz rings. Cardanols (5.00 g) then (1.00 g), where then successively FVP using the standard procedure (see page 180). Data are presented in the Table below.

Pyrolysis on iron sponge

An iron sponge (used for cleaning in the workshop) (20 g) was introduced into the quartz reactor in place of the quartz rings. Cardanol (1 g) was then pyrolysed using the standard procedure. Data are presented in the Table below.

Pyrolysis in a stainless steel tube

Stainless steel nuts (30) (with a total an external surface of 156 mm^2) were introduced into a stainless tube reactor in the place of the previously used quartz tube. The tube was connected at one end to a GC injection probe (this is the device, recovered from a scrap GC where the probes were injected to a column) and at the other end to a metal-glass fitting which led to a 5 ml flask cooled by a nitrogen/methanol mixture at – 40 °C. The tube was heated in the oven, with an angle of 30°, at constant temperature 740 °C. The injection rate was maintained constant of approx. 0.05ml / 3 sec. The recovered pyrolysed product presented a complicated ^{1}HNMR. The results are presented in the Table below GC was not performed due to concerns that the pyrolysed samples would block the column,

TABLE 6 - 18: YIELDS IN FVP ON METALLIC SUPPORTS

Temp (°C)	Press. (mmHg)	Type of filling	Mass recovery (mg liquid fraction/ 1000 mg cardanol)	MVP (%) c)
746 a)	0.1	Mild steel	280	11
746 a) & b)	0.1	Mild steel	110b)	7
766	0.1	Mild steel	269	7
740	0.5	Iron sponge	123	0
740	0.5	Stainless steel	230	17

a) all mild steel was covered with coke at the end of the experiment, b) the value refers to the recovery after the 5 th successive injection of cardanol (1g) c) HNMR was very complicated and GC was not performed due to concerns that it would block the column, so the others compounds have not been identified.

Pyrolysis in a copper ring filled reactor

Method development

Copper rings were obtained by cutting a 1.5 mm diameter copper pipe into 15 mm length rings; 40 rings with a surface area of 235.5 mm^2 were introduced into the quartz reactor. Cardanols (1 g) were then pyrolysed using the same procedure as the one used in a clean quartz reactor. Data are reported in the Tables below.

TABLE 6 - 19: METHOD DEVELOPMENT

Temp (°C)	Press. (mmHg)	Injection time (sec)	Mass recovery (mg liquid fraction/ g cardanol)	MVP (%) (by HNMR)
740	0.05	60	462	45
740	0.05	360	462	45

Influence of pressure

TABLE 6 - 20: INFLUENCE OF PRESSURE IN FVP ON COPPER

Temp (°C)	Pressure. (mm Hg)	Mass recovery (mg liquid fraction/ g cardanol)	MVP (%) by NMR data
740	0.1	460	50
740	0.1	457	50
740	10	423	36
740	0.5	447	39
740	0.5	423	31
740	70	418	30
740	110	411	33

Influence of temperature

This was carried out with 30 copper rings

TABLE 6 - 21: INFLUENCE OF TEMPERATURE IN FVP ON COPPER

Temp (°C)	Press. (mmHg)	Mass recovery (mg liquid fraction/ g cardanol)	GC data				NMR data
			MVP (%)	EP (%)	C b) (%)	P c) (%)	MVP (%)
656	3	610	a)	a)	a)	a)	29
736	3	588	45	13	5.9	3.2	45
746	1	521	51	15	3.6	3.8	30
766	0.9	482	38.9	13.5	3.4	3.9	26
786	0.8	410	38.8	24.7	6.9	5.5	45 a)
806	1	331	45	18	5.5	4.3	40
826	1	310	46.3	19.6	6.5	5.6	38
846	1	253	50	16.3	7.8	5.5	34

a) not available- this sample was more viscous than others and there was concern it would block the GC.

b) C- 3-cresol c) P- phenol

Influence of contact area

This was carried on 60 copper rings.

TABLE 6 - 22: INFLUENCE OF CONTACT AREA

Sample ID	Temp (°C)	Press. (mmHg)	Copper ring (nr)	Mass recovery (mg liquid fraction/ g cardanol)	GC data				NMR data
					MVP (%)	EP (%)	C (%)	P (%)	MVP (%)
65/1	746	1	60	452	44.8	15	4.8	3.4	40
65/2	786	1	60	276	45.7	16.0	5.6	3.8	42
65/3	826	1	60	205	49.9	15.3	8.3	5.8	41

Separations of the products from the FVP on copper rings

Vacuum distillation

Cardanol (1.00 g) was pyrolysed on copper (30 pieces, 735 °C, 0.1 mm Hg). The resulting mixture was then distilled .The results are provided in the Table:

TABLE 6 - 23: YIELDS IN VACUUM DISTILLATION OF THE PRODUCTS FROM THE FVP

Distillate			Residue		Observations
Mass recovery (%)	MVP by NMR (%)	MVP by GC (%)	Mass recovery (%)	MVP by NMR (%)	Boiling point of MVP at 20 mm Hg is 120 °C [27]
12	50	------	85	0	The sample used was a one to two days old pyrolysed product. Distillation was performed at 10 mm Hg and 110 °C by using a Kugelrohr apparatus
78	50	-------	15	0	Sample used were a fresh sample, heated for 10 minutes to 125 °C, and subsequently put under vacuum (at 10 mm Hg); the distillate gave a pale yellow oil in very good yield.
77	52	------	16	0	
78	54	55	17	0	

FVP of the distillation residue

The distillation residue, corresponding to the experiment reported in the last row of Table 5-17, was re-pyrolysed on copper using the standard procedure. The results are presented in the Table.

TABLE 6 - 24: YIELDS FROM FVP OF THE DISTILLATION RESIDUE.

Starting material	Temp (°C)	Press. (mm Hg)	Filler (type, nr)	Mass recovery (mg/g) a)	MVP by NMR (%)	MVP by GC (%)
Distillation residue	740	0.3	copper, 30	453	45	48

a) mg liquid fraction/g starting material

Pyrolysis in an aluminium cylinder filled reactor

Aluminium cylinders where obtained by sawing aluminium cylinders, into 15 mm lengths. In a range of experiments, cardanols were flash vacuum pyrolysed (between 650 - 786 °C) in a quartz reactor over 60 aluminium cylinders using the standard procedure. The results are presented in the Table 5-25.

TABLE 6 - 25: YIELDS IN FVP IN AN ALUMINIUM CYLINDER FILLED REACTOR

Temp (°C)	Pressure. (mmHg)	Mass recovery (mg liquid fraction/ g starting material)	NMR data MVP (%)	GC data	
				MVP (%)	EP (%)
746	0.1	247	28	42	12
766	0.5	203	40	59	11
786	0.5	186	51	64	13
756	0.5	223	50	51	11
690	n.a.	440	30	34	11
650	1	461	34	n.a.	n.a.
580	1	512	7.5	n.a.	n.a.

Pyrolysis of cardanol (15:0) on copper ring filled pipe reactor

Cardanol (15:0), was melted in a water bath, and injected into the quartz tube (filled with 40 copper rings), following the pyrolysis methodology indicated given on page 183. Because the viscosity of the sample was higher the injection time was 0.05 ml / 12 sec. The results are provided in the Table below.

TABLE 6 - 26: YIELDS IN FVP OF CARDANOL (15:0)

Temp (°C)	Press. (mm Hg)	Mass recovery (mg liquid fraction/ g starting material)	MVP (%) by NMR
826	1	653	18
846	1	540	23
866	1	485	35

FVP of anacardic acids

Anacardic acid (1.00 g, 1.15 ml) was pyrolysed over 40 copper rings using the standard procedure (page 184). Results are presented in the Table 5-27.

TABLE 6 - 27: YIELDS IN FVP OF ANACARDIC ACID

Temp (°C)	Pressure (mmHg)	Mass recovery (mg liquid fraction/ g starting material)	NMR data MVP (%)
730	3	290	24
745	7	257	41
746	6	253	40
746	7	258	43
766	5	238	51 a)

a) by GC this sample contained 48 % MVP and 9.0% EP.

FVP of cardols

Cardol (1000 mg) were pyrolysed over 40 copper rings at 550 - 600 °C using standard procedure (page 184). The results are given in the Table 5-22.

TABLE 6 - 28: YIELDS IN FVP OF CARDOL

Temp (°C)	Pressure (mmHg)	Mass recovery (mg liquid fraction/g starting material)	vinyl compounds (%) by HNMR
600	1	36	0
550	1	42	0

FVP of Bilhawanol

Crude semicarpus oil (Bilhawanol) (1000 mg) was pyrolysed on copper rings, using the same procedure used for cardanol (page 184) . The results are presented in the Table below.

TABLE 6 - 29: YIELDS IN FVP OF BILHAWANOL

Temp (°C)	Press. (mmHg)	Mass recovery (mg liquid fraction/g starting material)	vinyl compounds (%) by HNMR
400	1	570	0
500	1	410	0
600	1	270	0
700	1	120	0
800	1	80	0

CNSL pyrolysis

CNSL was pyrolysed on copper (30 rings) using the standard procedure (see page 183). The data are shown on the Table below.

TABLE 6 - 30: YIELDS IN CNSL PYROLYSIS

Starting material	Temp (°C)	Press. (mmHg)	Mass recovery (mg liquid fraction/ g starting material)	GC data		NMR data
				MVP (%)	EP (%)	MVP (%)
CNSL Bras	760	0.1	352	48.3	6.1	46
CNSL Treated a)	760	0.3	421	47.5	6.1	45
CNSL cardolite	760	0.2	440	48.5	6	48

a) CNSL (1 g) was dissolved in dichloromethane (10 ml) washed with HCl (5 %, 5 ml x 2) vacuum dried to obtain treated CNSL (0.94 g) which was then pyrolysed on copper using the standard procedure.

4. OXASPIRODIENONE CHEMISTRY

Anacardic acid (15:0) (1a)

Anacardic acids (mixture) (obtained by petrol-acetonitrile partition, see details page 172) (10.00 g) was added to 5 % palladium on carbon (1 g) suspended in ethyl acetate (100 ml), and the mixture was hydrogenated in a Parr hydrogenator. After the consumption of hydrogen (1120 cm^3, uncorrected value) the suspension was filtered on a small celite pad and the solvent was removed using a rotary evaporator to afford anacardic acid (15:0) (9.80 g, 27.7 mmol) as a white solid (m.p. 87.5 - 88 °C, lit. 87 - 91.5 °C).[43] This showed: δ_H ($CDCl_3$) 7.1 (1 H, dd, J = 8.3 Hz, 7.6 Hz), 6.9 (1H, d, J = 8.3 Hz), 6.8 (1H, d, J = 7.6 Hz), 3.1 (2H, t, J = 7Hz), 1.6 (2H, bs), 1.3 (26 H, s), 0.94 (3H, t, J 7 Hz); δ_C ($CDCl_3$) 176.1, 163.54, 147.54, 135.3, 122.74, 115.80, 110.59, 36.43, 34.08, 31.93, 29.79, 29.63, 29.47, 29.35, 29.23, 29.05, 24.64, 22.68, 14.10; ν_{max} 3600, 2800, 1585 cm^{-1}. Data were identical to those reported.[120]

2-Hydroxymethyl-3-pentadecylphenol.(13)

Anacardic acid (15:0)(5.3 g, 15 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.68 g, 18 mmol) in THF (5 ml) under argon. The mixture was refluxed for 2 h, under a calcium chloride drying tube. It was cooled to 8 - 10 °C with an ice bath, and quenched by dropwise addition of water (10 ml), followed by hydrochloric acid (5 %, 30 ml) and dichloromethane (100 ml). The addition of the acid was carried out in such a way as to control the temperature below 15 °C. After stirring for 0.5 h, the suspended solids had dissolved, and the layers were separated. The aqueous layer was re-extracted with dichloromethane (40 ml) and the combined dichloromethane layers gave, after drying over magnesium sulphate and removal of the solvent under reduced pressure, a reddish oil (4.9 g). This was dissolved in hot acetonitrile (20 ml). On cooling 2-hydroxymethyl-3-pentadecylphenol. (4.5 g, 13.5 mmol, 90 %) precipitated as a white powder, mp 61.5 - 62 °C(lit. 65 - 66 °C)[120] which gave δ ($CDCl_3$) 7.1 (1 H, dd, J 8.3, 7.6 Hz,), 6.7 (2 H, m), 4.9 (2 H, s), 2.6 (2 H, t, J 7 Hz), 1.5 (2 H, bs), 1.3 (28 H, bs), 0.94 (3 H, t, J 7 Hz). The ^{1}HNMR spectrum agreed with that reported (CCl_4). [120]

8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (14)

(a) A solution of 2-hydroxymethyl-3-pentadecylphenol (2.00 g, 6 mmol) and cetrimide (200 mg) in dichloromethane (12 ml) were added to a stirred solution of sodium metaperiodate (2.81 g, 13 mmol) in water (8 ml). The reaction was followed by TLC (petroleum-ethyl acetate, 5:2) which showed one major product (R_f 0.32). After 3 h. the dichloromethane

layer was separated and the whitish aqueous layer was re-extracted between brine (5 ml) and dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and evaporated under vacuum to give a black solid (1.97 g). This was recrystallised from petrol to give a suspension. Filtration gave 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (0.96 g, 2.88 mmol, 48 %) as a white solid. Evaporation of the filtrate gave a black oil (1.01 g) with no trace of aromatic signal by HNMR. The white powder provided the following data: mp : 79 - 79.5 °C (lit. 78.5 - 80 °C),[118] δ_H ($CDCl_3$) 7.1 (1H, m), 6.7 (2 H, m), 3.2 (2 H, m), 2.6 (2 H, m), 1.5 (2 H, bs), 1.3 (28 H, s), 0.94 (3 H, t, J 7 Hz); δ_C ($CDCl_3$) 196.2, 152.9, 142.5, 123.8, 122.7, 59.2, 31.9, 29.7, 29.6, 29.5, 29.4, 28. 4, 22.7, 15.2; ν_{max} 2860, 1650, 1630 cm^{-1}. The data were similar to the ones in the literature.[118]

(b) 2-Hydroxymethyl-3-pentadecylphenol (2.00 g, 6 mmol) was added to a stirred solution of sodium metaperiodate (2.81 g, 13 mmol), in aq. THF (water: THF (2 : 8)), the reaction being followed by TLC. Stirring was stopped after 6 h and the reaction mixture was extracted between brine (5 ml) and dichloromethane (3 x 20 ml). The organic layers were combined, dried over magnesium sulphate and evaporated under vacuum to give a black solid (1.38 g), which was recrystalised from petrol to give a white solid characterised by HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (0.76 g, 38 %). Evaporation of the filtrate gave a black oil (0.43 g) with no trace of aromatic signals by HNMR.

(c) A solution of sodium metaperiodate (2.80 g, 13 mmol), in water (8 ml) was added to a stirred solution of 2-hydroxymethyl-3-pentadecylphenol (2.0 g, 6 mmol) and cetrimide (200 mg) in dichloromethane (12 ml). The mixture was stirred for 3 h , and then separated as in procedure a) to give a black-reddish oil (1.32 g) which was cooled in a fridge, in petrol to give the spirodienone characterised by HNMR as a white solid (0.80 g, 28.6 %). Evaporation of the filtrate gave a black solid (0.97 g) with no trace of aromatic signals by HNMR.

4-Pentadecyl-benzo[1,3]dioxole (30)

Methyl lithium (as a complex with lithium bromide, 1.5 M, 0.4 ml) was added dropwise to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg, 0.3 mmol) stirred in THF (30 ml) under an argon atmosphere at – 40 °C. The mixture was stirred for 1 h at room temperature, and then quenched with cold HCl (5 %, 10 ml) and re-extracted between brine (10 ml) and dichloromethane (3 x 10 ml). The combined dichloromethane layer after drying over magnesium sulphate and removal of the solvent under reduced pressure, gave a reddish oil (88 mg). This was separated by column chromatography with petrol-ethyl acetate (5:1) as eluting solvent, to give 3-pentadecyl-benzo[1,3]dioxole (55 mg, 55 %), identified by δ_H ($CDCl_3$) 6.7 (3 H, m), 5.92 (2 H, s), 2.60 (2 H, t, J 7 Hz), 1.60 (2 H, bt), 1.25 (24 H, bs), 0.88 (3 H, t, J= 7 Hz); δ_C ($CDCl_3$) (quaternary C, 146.9, 145.4, 124.4) , (tertiary C, 122.5, 121.2,

106.2), (secondary C, 100.3, 32.6, 31.9, 29.7, 29.4 (broad peak), 29.4, 22.8), (primary C, 14.1); ν_{max}(film, cm^{-1}), 2719, 1724, 1650-1670, 1610, 1460, 1240, 1140, 920, 830cm^{-1}; m/z (M^+ 332, $C_{22}H_{36}O_2$ requires 332); (found: C, 79.49; H, 10.9 %; $C_{22}H_{36}O_2$ requires C 79.46 %, H 10. 91 %).

Reaction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with butyl lithium

Butyl lithium, (1.6 M in hexane, 1.3 Eq, 0.4 ml) was added using a 1 ml syringe to the 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (160 mg, 0.48 mmol) in THF (30 ml), at – 40 °C. The mixture was cooled at room temperature and after 10 min, it became reddish. After 2 h, it was quenched with water (2.5 ml) and re-extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over magnesium sulphate and evaporated to give a reddish oil (155 mg). This was then separated by column chromatography with petrol-ethyl acetate (5:1) as eluting solvent to give 4-pentadecyl-benzo[1,3]dioxole (45 mg, 28 %). The ^{1}HNMR spectrum was similar to that above.

Reaction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with LiBr

To 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) in THF (10 ml) was added LiBr (13 mg, 0. 165 mmol) under reflux over 4 h. The mixture was quenched with water, and re-extracted with CH_2Cl_2 (10 ml). The organic layer was dried over magnesium sulphate and evaporated to give a reddish oil (41 mg). This was separated by chromatography with petrol-ethyl acetate (5:1) as eluting solvent to give 4-pentadecyl-benzo[1,3]dioxole (39 mg, 78 %) which gave an ^{1}HNMR spectrum that was similar to that above.

Reaction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with imidazole

To 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) dissolved in ether (5 ml) was added imidazole (10.2 mg, 0.15 mmol). As no reaction could be detected by TLC, the mixture was heated under reflux during 4 h, and still no new compound could be seen.

Reaction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with LDA

To 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) dissolved in ether (5 ml) was added lithium diisopropylamide (0.1 ml, 0.1 M in THF). After 2 h the mixture was quenched with water (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over magnesium sulphate and evaporated to give a brown oil which was separated by column chromatography using petrol-ethyl acetate (5:1) as eluting

solvent, to afford 4-pentadecyl-benzo[1,3]dioxole (39 mg, 78 %) the ^{1}HNMR spectrum of which was the same as that above.

Reaction of the oxaspirodienone t-butylchlorodimethylsilane

8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) and t-butylchlorodimethylsilane (0.22 mmol, 1.5 eq.) were dissolved in dimethylformamide (5 ml) and triethylamine (0.22 mmol, 1.5 eq). The solution was heated under reflux for 4 h. The reaction was quenched with water (10 ml), and HCl (15 %) to pH 1, and extracted with ethyl acetate (2 x 20 ml) to recover a yellowish oil (56 mg) (with solvent) which was purified by column chromatography using petrol-ethyl acetate (5:1) as eluting solvent, to afford 4-pentadecyl-benzo[1,3]dioxole (12 mg, 24 %) the ^{1}HNMR spectrum of which was the same as that above.

Amine reactions with 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

a).The 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (200 mg, 0.6 mmol) was added to a stirred solution of piperidine (50 mg, 0.6 mmol) in dichloromethane (10 ml). The mixture become violet. When, after 3 h no more starting material could be detected by TLC, the dichloromethane layer was evaporated, to give a violet oil (211 mg). An aliquot (180 mg) was purified by column chromatography using petrol-ethyl acetate (5:1) as eluting solvent, to afford 4-pentadecyl-benzo[1,3]dioxole (153 mg, 85 %), which by ^{1}HNMR was the same as that above.

b) DEA (3 mg) was added to a solution of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg) in dichloromethane (5 ml), the reaction being followed by TLC. Stirring was stopped after 24 h and the mixture was concentrated under vacuum to afford 4-pentadecyl-benzo[1,3]dioxole (with some solvent) (95 mg, 95 %) which by ^{1}HNMR was the same as that above. No others products were present in the reaction mixture.

c) The same procedure as in b) using TEA (3 mg) instead of DEA gave of a pale beije oil identified as 4-pentadecyl-benzo[1,3]dioxole (98 mg) which by ^{1}HNMR was the same as above.

d) The same procedure as in b) using IPA (3 mg) instead of DEA gave of pale beije oil identified as 4-pentadecyl-benzo[1,3]dioxole (95 mg, ca 95 %) which ^{1}HNMR was the same as above.

Morpholine reaction with 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

Morpholine (26.25 mg, 0.3 mmol) was added to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg, 0.3 mmol) in ether (5 ml) After 25 min the mixture became bright red, and was quenched with HCl (5%),(10 ml). The ether layer was then removed and the aqueous layer was extracted with ether (2 x 10 ml). The organic layers were then dried over magnesium sulphate, and the solvent was removed in vacuo to afford a reddish oil (82 mg) Crude ^{1}HNMR spectrum showed that the major compound was 4-pentadecyl-benzo[1,3]dioxole (approx. 80 %).

Potassium t-butoxide reaction with 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

Potassium t-butoxide (7 mg, 0.06 mmol) was added to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg, 0.3 mmol) stirred in THF (5 ml). After 1 hr, the mixture was quenched with water (5 ml) and re-extracted with CH_2Cl_2(10 ml). The organic layer was dried over magnesium sulphate and evaporated to give a resinous black mixture (35 mg) with a very complicated ^{1}HNMR, which was not separated.

Acetic acid reaction with 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) was dissolved in acetic acid (10 ml) and left under stirring for 6 h. TLC showed that no new products were formed. The solution was diluted with water (30 ml), extracted with ethyl acetate (3 x 10 ml). The combined organic layers, washed with aq. $NaHCO_3$ (20 ml), brine (10 ml), dried over magnesium sulfate, and the solvent was removed to afford 4-pentadecyl-benzo[1,3]dioxole (32 mg, 64 %).

Zinc dibromide reaction with 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one

$ZnBr_2$ (37 mg, 0.165 mmol), was added the 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (50 mg, 0.15 mmol) in CH_2Cl_2 (10 ml) giving rise to a brownish solution. After 60 minutes the mixture was quenched with aq. $NaHCO_3$ (20 ml), followed by the addition of a 10 % solution of NH_4OH (4 ml). The solution was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic layers were dried over $MgSO_4$ and the solvent removed under vacuum to afford a brown oil (41 mg) which by ^{1}HNMR was ca. 50 % 4-pentadecyl-benzo[1,3]dioxole. The reaction mixture was not separated.

8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one reactions with amine in HNMR tubes

a) 8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg, 0.06 mmol) was added to triethylamine (30 mg, 0.30 mmol). dissolved in $CDCl_3$ (4 ml). The reaction was followed by HNMR, and it was possible to follow the formation (complete after 36 h) of 4-pentadecyl-benzo[1,3]dioxole as the only product.

b) The reaction was repeated as in a) but isopropylamine was used instead triethylamine. Reaction was complete after 48 h. 4-Pentadecyl-benzo[1,3]dioxole was the only product.

Attempted reduction of 8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with aluminium isopropoxide

8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (500 mg, 1.5 mmol) was added to a suspension of aluminium isopropoxide (30.6 mg, 0.15 mmol) in isopropanol (10 ml) at 60 °C. The mixture was stirred for 1h, then worked up with ethyl acetate (30 ml) and saturated

aqueous chloride (30 ml), to give a brown oil (458 mg). The mixture was not purified but ^{1}HNMR showed to contain 4-pentadecyl-benzo[1,3]dioxole (approx 80 %).

Attempted reduction with dimethylcuprate

Methyl lithium (as a complex with lithium bromide, 1.5M, 0.8 ml, 0.66 mmol) was added dropwise to a suspension of CuI (62.9 mg, 0.33 mmol) in THF (40 ml) in an argon atmosphere at a –40 °C, and stirred at room temperature for 1 h. To this mixture, was added dropwise a solution of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg, 0.3 mmol) in THF (10 ml), giving rise to a greenish black solution. After 15 min the mixture was quenched sat.aq. $NaHCO_3$ (20 ml), followed by the addition of a 10 % solution of NH_4OH (4 ml). The blue solution was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic layers were washed with brine (10 ml) dried over $MgSO_4$, and the solvent removed under vacuum. The oily residue gave an ^{1}HNMR spectrum which contained approx 75 % 4-pentadecyl-benzo[1,3]dioxole.

Attempted diimide reduction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with potassium azodicarboxylate

Potassium azodicarboxylate (1 g) was added to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg), and tetrahydrofuran (15 ml). under a nitrogen atmosphere The stirred mixture was cooled in an ice bath, and acetic acid (200 mg in 10 ml of THF) was dropwise added over 6 h. The mixture was filtered on a sinter funnel and dried in vacuo to afford an oil (with some THF) (140 mg) which was columned to give of a white solid identified by ^{1}HNMR as 4-pentadecyl-benzo[1,3]dioxole (52 mg, 52 %).

Reduction of 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one with palladium

8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (100 mg) was added to palladium (5%) on carbon (20 mg) suspended in ethyl acetate (100 ml) and the mixture was hydrogenated in a Parr Hydrogenator. After 3 h, the suspension was filtered through a small celite pad and the ethyl acetate was removed using a rotary evaporator to afford 2-hydroxymethyl-3-pentadecylphenol (100 mg, 99.4 %), which ^{1}HNMR was identical than the one above.

Mixture of substituted benzodioxolanes with an alk(en)yl chain with different degrees of unsaturation

Anacardic acid (mixture) (5.00 g, 15 mmol) in dry THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.68 g, 18 mmol) in THF (5 ml) under argon. The mixture was refluxed for 2 h, under a calcium chloride drying tube. It was cooled

to 8 - 10 °C with an ice bath, and quenched by dropwise addition of water (10 ml), followed by hydrochloric acid (5 %, 30 ml) and dichloromethane (100 ml). The addition of the acid was carried out in such a way as to control the temperature below 15 °C . After stirring for 0.5 h, the suspended solids had dissolved, and the layers were separated. The aqueous layer was re-extracted with dichloromethane (40 ml) and the combined dichloromethane layers gave, after drying over magnesium sulphate and removal of the solvent under reduced pressure, a reddish oil (4.95 g). This was dissolved in dichloromethane (45 ml) and to the solution were added both cetrimide (0.5 g) and sodium metaperiodate (7.00 g, 32 mmol) in water (20 ml). The reaction was followed by TLC (petroleum - ethylacetate 5:2) which showed one major product (R_f 0.32). After 3 h, the dichloromethane layer was separated and the whitish aqueous layer was re-extracted between brine (5 ml) and dichloromethane (3 x 20 ml). Triethylamine (1 ml) was added to the combined organic layers, which were left for 24 h. Removal of the solvent afforded a black oil (4.98 g). Purification by chromatography with petrol - ethyl acetate (5:1) afforded (as a mixture) 4-(8'-pentadecenyl)-benzo[1,3]dioxole, 4-(8'-11'-pentadecadienyl)-benzo[1,3]dioxole, and 4-(8'-11'-14'-pentadecatrienyl)-benzo[1,3] dioxole, identified by HNMR (see Figure 4-6) ; δ_H (in $CDCl_3$) 6.7 (3 H, m), 6.0-5.0 (7 H, m), 2.60 (2 H, t, J 7 Hz), 1.60 (2 H, bs), 1.25 (24 H, bs), 0.90 (m, 3 H).

Attempted Diels Alder reactions

a) Acrylonitrile (16 g, 300 mmol) was added to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (2 g, 60 mmol) in ethyl acetate (20 ml). The reaction was allowed to stand at 20 °C for 3 days and then refluxed for 6 h. No new products could be detected by TLC (petrol-ethyl acetate 5: 2). Solvent removal under vacuum afforded a white powder, identified by HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (2 g).

b) 8-Pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (2 g, 60 mmol) was dissolved in acrylonitrile (16 g, 300 mmol) at room temperature. The reaction was followed for 2 h refluxed for 2 h, but no new products could be detected by TLC (petrol - ethyl acetate 5:2). Solvent removal under vacuum gave a white powder, identified by HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (2 g).

c) Acrylonitrile (70 mg, 1.3 mmol) was added to 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg, 0.06 mmol) dissolved in $CDCl_3$ (1 ml). The reaction was followed by HNMR for 4 days then refluxed for 6 h, and dried under vacuum to give a white powder, identified by HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg).

d) Same as above, using dihydrofuran (177 mg, 2.2 mmol) instead of acrylonitrile. Product was identified by ^{1}HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg).

e) Same as above, using allyl alcohol (542 mg, 9.2 mmol) instead of acrylonitrile. Product was identified by ^{1}HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg).

f) Same as above, using 2,5-diphenyl-3,4-benzofuran (120 mg, 0.44 mmol) instead of acrylonitrile. Product was identified by ^{1}HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg).

g) Same as above, using styrene (60 mg, 0.5 mmol) instead of acrylonitrile. Product was identified by ^{1}HNMR as 8-pentadecyl-1-oxa-spiro[2.5]octa-5,7-dien-4-one (20 mg).

h) Same as above, using dimethyl maleate (70 mg, 0.48 mmol) instead of acrylonitrile. This reaction mixture was not however refluxed. Removal of the solvent afforded 4-pentadecyl-benzo[1,3]dioxole (20 mg).

i) Same as above, using tetracyanoethylene (70 mg, 0.54 mmol) instead of dimethylmaleate. Removal of the solvent afforded 4-pentadecyl-benzo[1,3]dioxole (20 mg).

5. C_8 CHAIN CLEAVAGE

8-(3-Hydroxy-phenyl)-octanal (62)

Procedure A.

Ozone (308 mmol, 2 equivalents (equipment calibrated by the BioComposites Centre)) was bubbled into a solution of cardanol (20 g, 66 mmol), dissolved in methanol (100 ml) in a three-neck flask provided with a condenser and an ice-bath cooling. After purging the reaction mixture with nitrogen (for 5 min.), the mixture was cooled in an ice bath, and dimethylsulfide (30 ml) was slowly added. The resulting mixture was stirred for 4 h. The suspension was then filtered and the inorganic residue washed with light petroleum. The combined washing and filtrate were then concentrated under reduced pressure, to provide a brown oil, which was separated by column chromatography using petrol-ethyl acetate (5-1) to provide 8-(3-Hydroxy-phenyl)-octanal (1.72 g, 12 %) identified by ν_{max}(film, cm^{-1}), 3300, 2980, 2719, 1700 cm^{-1}; δ_H (ppm) ($CDCl_3$), 9.8 (s, 1 H), 7.15 - 7-13 (t, 1 H, J 7.6 Hz), 6.85 - 6.82 (m, 3 H), 2.57 - 2.54 (pseudo-t, 2 H, J 7.3, 7.6 Hz), 2.47 - 2.41 (dt, 2 H, J 1.5, 7.3 Hz), 1.61 (br, 2 H),1.32 (br, 7.5 H); δ_c ($CDCl_3$, ppm), 204.1,175.5, 163.4, 147.4,135.2, 122.7, 115.8, 110.7, 43.8, 36.4, 31.8, 29.5, 29.0, 29.0, 22.0; m/z (M^+ 220, $C_{14}H_{20}O$ requires 220). Data are similar to the ones indicated in the literature, except ^{13}CNMR spectrum which has not been reported.[324]

Procedure B Same as A but acetic acid (30 ml) and zinc (30 g) were used instead of dimethylsulfide (30 ml). This provided 8-(3-Hydroxy-phenyl)-octanal (4.45 g, 31 %)

Procedure C Same as B but with only 2 g of cardanol instead of 20 and THF (100 ml) was used instead of methanol; and the temperature in the reaction flask was maintained at – 78 °C using a cooling bath with methanol-liquid nitrogen instead of ice. This provided 8-(3-Hydroxy-phenyl)-octanal (13.92 g, 97 %).

Procedure D Same as C but dichloromethane (100 ml) was used instead of THF. This provided 8-(3-Hydroxy-phenyl)-octanal (13.95 g, 97 %)

Procedure E Same as B but dichloromethane-methanol (1:1) was used instead methanol This provided 8-(3-Hydroxy-phenyl)-octanal (6.50 g, 45 %)

Procedure F Same as B but dichloromethane-methanol (1:4) was used instead methanol This provided 8-(3-Hydroxy-phenyl)-octanal (5.00 g, 34 %)

2-Hydroxy-6-(8-hydroxy-octyl)-benzoic acid (67)

Ozone (43 mmol, 2 equivalents,(equipment calibrated by the BioComposites Centre)) was bubbled into a solution of anacardic acids (3 g, 8.6 mmol), dissolved in methanol (50 ml) - dichloromethane (50 ml), in a three-neck flask provided with a condenser and an ice-bath

cooling. After purging the reaction mixture with nitrogen (for 5 min.), the mixture was cooled in an ice bath, and acetic acid (5.3 g , 10 equivalents) and zinc (5.5 , 10 equivalents) were slowly added. The resulting mixture was stirred for 4 h. The suspension was then filtered and the inorganic residue washed with light petroleum. The combined washing and filtrate were then concentrated under reduced pressure, to provide a brown oil, which was distilled at 1 mm Hg, and 120 °C. The distillate was dissolved in ethyl acetate (10 ml) and washed with sodium bicarbonate (saturated solution) (3 x 10 ml).The aqueous layer was then acidified to pH 1 with a solution of HCl (5 %) and re-extracted with ethyl acetate to provide the title compound (1.02 g, yield = 46 %) identified by ν_{max}(film, cm^{-1}) 3300, 2980, 2719, 1724, 1650-1670, 1610, 1460, 1240, 1140, 920, 830; δ_H (ppm) ($CDCl_3$) 9.8 (s, 1 H, CHO), 7.35 - 7.28 (t, 1 H, H-Ar, J 7.2 Hz), 6.85 - 6.82 (d, 1 H, H-Ar, J 8.2 Hz), 2.98 - 2.92 (pseudo-t, 2 H, J 7.3, 7.6 Hz), 2.44 - 2.41 (dt, 2 H, CH_2CO, J 1.5, 7.3 Hz), 1.61 (br, 2 H, $ArCCH_2$),1.32 (br, 7.5 H, CH_2); δ_c ($CDCl_3$, ppm), 204.1, 175.6, 163.4, 147.4, 135.2, 122.7, 115.8, 110.6, 43.7, 36.4, 31.8, 29.5, 29.0, 22.0; m/z (M^+ 264, $C_{15}H_{20}O_4$ requires 264); (found C, 68.14, H, 17.64 %, requires C 68.06, H 17.63 %). Data are similar to the ones indicated in the literature .[324]

Methoxycardanols (5)

Cardanols (10 g, 32.9 mmol) obtained by petrol-acetonitrile partition (page 168) were added to a stirred solution of potassium carbonate (45 g , 10 equivalents) in dry acetone (125 ml). Methyl iodate (20.7 ml, 10 equivalents) was slowly added to the cold suspension. When the addition was completed, the ice-bath was removed and the mixture was heated under reflux for 4 h, then cooled at room temperature and stirred for a further 4 h. Acetone was then removed under vacuum, and the resulting mixture was dissolved in ethyl acetate-water (10:10). The organic layer was then removed, and the aqueous layer was re-extracted with ethyl acetate (2 x 10 ml). Both organic layers were combined, dried over magnesium sulphate, mixed with silicagel (20 g) and concentrated under reduced pressure. To the dried silicagel-oil mixture was added petrol. The suspension was then filtered, and the solvent removed to provide methoxycardanols (9.4 g, 90 %) as a colourless oil (the reaction between cardanol and methyl iodate afforded a mixture of cardanol-methoxycardanol, but cardanol stayed on the base line when eluted with petrol) identified by ν_{max}(film, cm^{-1}) 1630, 1604, 1588, 1498, 1261 cm^{-1}; δ_H: ($CDCl_3$) 7.2 - 6.7 (m, 4 H, H-Ar), 5.4 (m, 4.5 H, CH=), 3.8 (s, 3 H, CH_3O), 2.8 (br, 2.5 H, =C-CH_2-C=), 2.6 (t, 2 H, CH_2-Ar, J 7.3 Hz), 2.1 (bs, 2.6 H, CH_2-C=), 1.4 (bs, 7.5 H, CH_2,), 0.9 (m, 2.4 H); required m/z 316 for the monounsaturated congener, found m/z 316. Data were similar to the ones reported in the literature.[333].

Washing the petroleum washed silicagel with ethyl acetate gave after solvent removal, cardanol (0.09 g) identified by its ^{1}HNMR spectrum and MS spectra.

11-(3-Methoxy-phenyl)-undecan-4-ol (68)

Procedure 1

a) Preparation of propylmagnesium bromide (1 mmol/ml). Propyl bromide (6 g, 50 mmol) in dry THF (30 ml) was added dropwise with a syringe to magnesium flakes (1500 mg, ca. 60 mmol), agitated under an argon atmosphere, in a 3 neck-flask cooled in an iced bath. An exothermic reaction followed and the mixture was stirred for 2 h, before use. b) Preparation of the ozonide. Ozone (45 mmol, 2 equivalents, apparatus calibrated by the BioComposites Centre) was bubbled into a solution of methoxycardanols (3 g, 9.9 mmol), dissolved in THF (200 ml), and cooled with an ice-bath at 5 °C. c) Quenching the ozonide with propylmagnesium bromide. After purging the reaction mixture with nitrogen, for 30 min at room temperature, the reaction was cooled in an ice bath, and the previously prepared solution of propyl magnesium bromide (50 mmol) was dropwise added. The mixture was stirred under reflux during 4 h, and then cooled in an ice bath and quenched with water (10 ml) and 96 % sulphuric acid (10 ml). The mixture was extracted with ethyl acetate (3 x 100 ml), and the combined organic layers were dried over magnesium sulphate, and concentrated under vacuum to give a reddish oil (2.6 g) which was chromatographed on silica eluting with petrol-ethyl acetate (5-2) to afford 11-(3-methoxy-phenyl)-undecan-4-ol (2.2 g, 84 % yield) as a colourless oil identified by ν_{max} (film, cm^{-1}): 2719, 1724, 1604, 1587, 1498, 1261 cm^{-1}; $\delta_H(CDCl_3)$: 9.7 (s, 1 H, HCO), 7.2-6.7 (m, 4 H), 3.8 (s, 3 H), 2.6 (t, 2 H, J 7.2 Hz), 2.3 (bs, 2 H), 1.6 (bs, 2 H), 1.6 (bs, 7.5 H); $\delta_C(CDCl_3)$ 159.5, 144.5, 129.1, 120.85, 114.2, 110.8, 71.8, 55.1 , 39.6, 37.4, 37.0, 31.3, 29.6, 29.5, 29.2, 25.6, 18.8, 14.1; m/z M^+ 278 ($C_{18}H_{30}O_2$ requires: 278); (found: C, 77.6; H, 10.8 %; requires C 77.65; H 10.86 %).

Procedure 2

The ozonide, prepared as earlier, was slowly added to propylmagnesium bromide, prepared as indicated in the preceding procedure. The reaction was highly exothermic. Similar work-up as above afforded the title alcohol (2.01 g, 80 %) which was identical by ^{1}HNMR with the previous one.

Attempted ozonolysis of cardols

Ozone (21.5 mmol, 1 equivalent) was bubbled into a solution of cardols (3.00 g, 9.4 mmol), dissolved in dichloromethane (100 ml), in a three-neck flask provided with a condenser and an liquid nitrogen-bath cooling (-70 °C). After purging the reaction mixture with nitrogen (during 25 minutes), acetic acid (10 ml) and zinc (5 g) were slowly added, and the mixture was stirred for 4 h then washed with sodium bicarbonate (saturated solution) until no more

gas was evolved, then distilled water (10 ml). The water layer twas re-extracted with dichloromethane (2 x 25 ml), and the combined organic layers were dried over magnesium sulphate and concentrated under vacuum to give a reddish oil (0.62 g). The crude ^{1}HNMR of which did not show any signals in the aromatic region of the spectrum.

Acetylated cardols(70)

To a solution of cardol (2.75 g, 8.6 mmol) in acetic anhydride (10 ml) , was added pyridine (1.5 ml). The mixture was stirred at room temperature for 2 h, until the reaction was shown to be complete by thin layer chromatography (petrol-ethyl acetate, 4:1). Water (10 ml) was then added and the mixture was extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with 5% hydrochloric acid solution (2 ml), brine (5 ml), dried over magnesium sulphate and evaporated. The residue was chromatographed over silicagel (petrol-ethyl acetate, 4:1) to furnish the acetylated cardol as a colourless oil (3.2 g, 92 %) which showed: ν_{max}(film, cm^{-1}): 3010, 2928, 2855, 1772, 1619, 1592, 1451, 1369, 1197, 1123, 1022; δ_H: ($CDCl_3$) 6.75 (m, 3 H), 6.1 - 4.8 (m, 4.5 H), 2.9 - 3.6 (m, 2.5 H), 2.55 (pseudo-t, 2 H, J 7.3 Hz, 7.6 Hz), 2.15 (s, 6 H), 2.2 - 1.8 (m,2.6 H), 1.8 - 1.1 (bs, 7.5 H), 0.85 (m, CH_3, 2.5 H). The data were similar to the ones reported in literature.[325]

Acetic acid 3-acetoxy-5-(8-oxo-octyl)-phenyl ester(71)

To a solution of the acetylated cardols (1.88 g, 4.75 mmol), dissolved in dichloromethane (100 ml) in a two-neck flask, was bubbled ozone (21.5 ml, 2 equivalents). The temperature was maintained at - 70 °C with a liquid nitrogen/ IMS cooling bath. After purging with nitrogen (for 5 min), acetic acid (5 ml) and zinc (5 g) were added, and the mixture was stirred for 4 h. The suspension was then washed in sequence with aq. sat. sodium bicarbonate until no gas was evolved, and distilled water (5 ml).The aqueous layer was re-extracted with dichloromethane (3 x 10 ml).The combined organic layers were dried over magnesium sulphate and concentrated under vacuum to give a reddish oil (2.2 g) which was purified by chromatography on silicagel (petrol-ethyl acetate, 4:1) to provide the title compound as a colourless oil (1.4 g, 92 % yield), ν_{max}(film, cm^{-1}): 2719, 1724, 1604, 1587, 1498, 1261; δ_H($CDCl_3$) 9.7 (s, 1 H), 7.2 - 6.7 (m, 3 H), 2.62 - 2.56 (pseudo-t, 2 H, J 7.3, 7.6 Hz), 2.44 - 2.41 (dt, 2 H, J 1.5, 7.3 Hz), 2.15 (s), 1.61 (bs, 2 H,), 1.32 (bs, 7.5 H,); δ_C($CDCl_3$) 202.9, 169.1 (2C), 150.8 (2C), 145.2 (2C), 118.9, 112.63, 77.6, 77.0, 76.5, 43.8, 35.6, 30.7, 29.1, 22.0, 21.1; m/z: M^+ 320 ($C_{18}H_{24}O_5$ requires 320); (found C 67.5 ; H, 7.5 %; requires C 67.58, H 7.55 %).

Vilsmeier-Haack reaction of cardols with phosphorous oxychloride

To DMF (0.493 g, 6.75 mmol) and acetonitrile (15 ml), cooled in an ice bath, was slowly added $POCl_3$ (0.88 g, 5.75 mmol) dissolved in acetonitrile (10 ml) in such a way that the temperature was maintained below 12 °C. The mixture was then stirred at room temperature for 2 h to ensure the complete conversion of the Vilsmeier reagent, and the reagent was cooled with a liquid-nitrogen-methanol bath to – 40 °C, and a solution of cardol (obtained by the Petrol-TFE-ACN partition previously described) (1.1 g , 3.4 mmol) in acetonitrile (15 ml) was slowly added maintaining the temperature at –30 °C. The mixture was agitated for an additional 2 h at – 30 to –2 °C, and then overnight at room temperature. The reaction mixture was then cooled at – 40 °C, but no crystals appeared (note: with small chain alkylresorcinols, the Vilsmeier salt is reported to precipitate under these conditions)[334], and the product was dried at room temperature and 10 mm Hg to constant weight to afford a dark yellow solid (1.3 g) which was dissolved in water (15 ml). The aqueous solution was heated at 50 °C for 0.5 h, and stirred at room temperature for a further 1 h, then treated with sat.aq. sodium bicarbonate to pH 7, and extracted with dichloromethane (3 x 50 ml). Removal of the solvent after drying over magnesium sulfate afforded a reddish oil (0.35 g) with no signs of aromatics by ^{1}HNMR.

Vielsmeier-Haack reaction of 3-pentadecylphenol with phosphorous oxychloride

The same procedure as above was used, but using pentadecylphenol (98.8 % Aldrich product) (1.00g, 3.4 mmol) instead of cardols. When reaction mixture was cooled at – 40 °C, a white clear solid precipitate appeared in the acetonitrile solution. It was filtered and redissolved in water (10 ml). The aqueous solution was heated at 50 °C for 0.5 h, stirred at room temperature for more 1 h, and treated with sat. sodium bicarbonate until pH 7, and extracted with dichloromethane (3 x 50 ml). Removal of the solvent after drying over magnesium sulfate afforded a yellow oil (1.10 g) identified as a mixture of cardanol (15:0) and 4-hydroxy-2-pentadecyl-benzaldehyde by the ^{1}HNMR spectrum shown in Figure 4-17.

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APPENDICES

Appendix 1 Preliminary analysis of the flocculate

The solid resinous material obtained by flocculating CNSL Bras in petrol-acetonitrile had a zero R_f on TLC on silicagel eluting with petrol-ether (5-2), a very broad ^{1}HNMR, with peaks with chemical shifts similar with the ones of cardanol, and IR and MS spectra very similar to those of crude CNSL. [1]

(i)Ash content

The solid resinous material was calcinated, and the resulting ash (10 % of the flocculated solid), was dissolved in nitric acid and analysed by ICP. The results, presented in the Table A1-1 show the presence of considerable amount of metals including potassium.

TABLE A1-1: Metals from ash of the flocculated solid

Element	K	Ca	Fe	Si	Al	P	Mn	Others
%	44.95	17.5	10.75	7.25	6	3.75	1.95	2.6

The high potassium content suggested that the solid would be a salt or a mixture of salts, and therefore a method to eliminate the metallic elements was devised. Freshly obtained solid was dissolved in dichloromethane, the resulting solution was mixed with dilute HCl, separated from the aqueous layer, dried over magnesium sulfate, and the dichloromethane layer was evaporated *in vacuo*. This gave a dark coloured solid which was not tacky.[2] The recovered solid was reduced to 2 % of the initial CNSL. When dissolved in dichloromethane, this acid washed solid gave three main spots on TLC with dichloromethane-methanol (10-0.5). Column chromatography, gave one main compound identified as cardanols (27 %), and two yet unidentified fractions (respectively 0.06 and 0.4 %).

The latter two had broad ^{1}HNMR spectra similar to CNSL. The major one had MS-DI-CI corresponding to cardanols plus an oxygen. The fact that ^{1}HNMR showed similar chemicals shifts to cardanol in the aromatic region of the spectrum suggested that the oxygen would be located in the chain.

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[1] After several days in air and light, this black solid become rubbery. After two weeks it was not totally soluble in most of the usual laboratory solvents, just in THF.

[2] An alternative procedure was tested diluting the solid in dichloromethane and treating it with very dilute sulphuric acid (which caused gas evolution and a very bad smell), The corresponding IR spectrum showed a reduction of the OH stretching signal. For this reason, this method was abandoned.

(ii)Compatibility with earlier studies on the solid

The experimental results obtained in this work fits quite well with the results presented by others researchers:

a) The solid flocculates with acetonitrile and pentane but it is soluble in THF.

Tyman (1984) detected the so-called "polymer" by HPLC when they eluted it with THF. Shobba et al (1991) used acetonitrile as solvent in HPLC and did not find the peaks attributable to the "polymer".

b) On treatment with HCl, the solid gives at least three fractions, one being cardanol, and two yet not identified, but one of the three is non-volatile, and not detected by GC-MS. Tyman (1994) found, that the fraction that he named "polymer", obtained by HPLC, eluted on TLC with chloroform /ethyl acetate, and produced 3 spots with the Rf of cardanol, 6-methylcardol, and cardol.

c) Tyman (1978) reports that the GC-MS of the trimethylsilyl derivatives of the fractions obtained by molecular distillation (at around 220 °C) of the oil correspond to peaks attributable to dimeric and trimeric substances. In the present study, the DI-MS of the hydrogenated CNSL and of the acetylated fractions showed no peaks in the regions corresponding to dimeric and trimeric region.

Both these two last results are subject to questions. As the CNSL isolated dimer and trimer (characterized only by TLC) were isolated by molecular distillation and as previous experiments have proved that the known constituents of the oil can react by heating at high temperature, it is difficult to know if the fractions obtained by distillation are artifacts of the laboratory separation process or are genuine constituents of industrially-extracted oil.

Conclusions and recommendations

1) A fraction that contains the non-volatile constituents of CNSL, and has been detected in previous studies, has been separated by non-published method, but its full characterization still needs to be done. It has been shown that it contains a significant amount of metals, one of them being potassium. Mass spectra didn't show any major fractions of dimer and trimer, while the IR is similar to the one of cardanol.

2) One of the main commercial applications of CNSL is the manufacture of brake liners. Published information indicate that brake liners obtained with CNSL have superior performance in relation with the ones obtained with distilled cardanol, suggesting that this may be due to non-cardanol fraction of CNSL. The existence of the flocculate may be

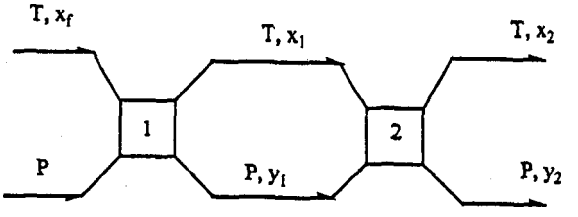
related with these characteristics and therefore a better understanding of its role in brake liners structure may help to design better materials.

Appendix 2 McCabe Thiele method

to calculate the number of theoretical stages in a immiscible liquid-liquid solvent extraction process

Co-current extraction

The case is illustrated in the Figure.

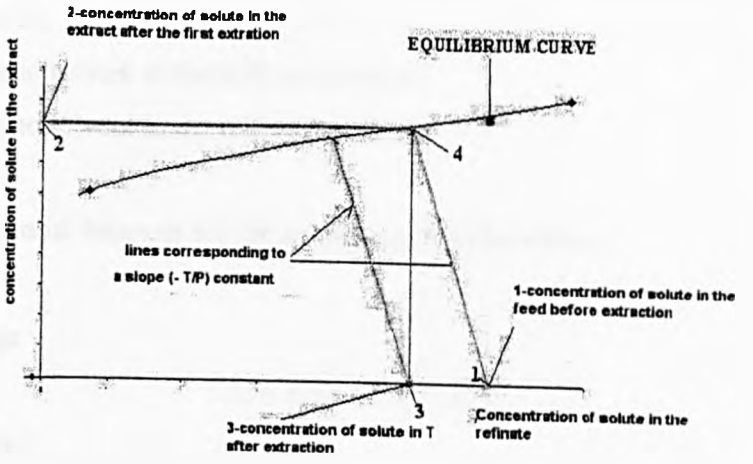


The solution to be extracted contain t kg of solvent T with a mass ratio x_f of solute C.
The selective solvent to be added will be a mass p of solvent P. On mixing and separating, a raffinate is obtained with the solvent T containing a mass ratio x_1 of solute, and an extract with the solvent P containing a mass ratio y_1 of solute. C material balance on the solute gives.

$$T.x_f = T.x_1 + P.y_1$$

$$y_1/(x_1 - x_f) = - (T./P)$$

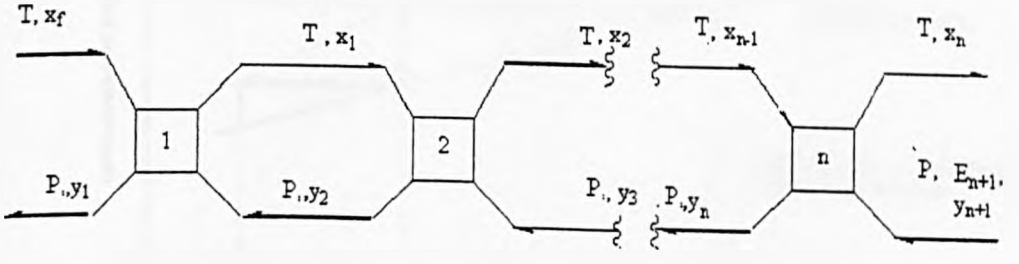
This is the equation representing a straight line of slope (- T/P) which passes through. the point 1-(x_f , 0), and the point 4 (x_1, y_1). "4" could therefore be found as the point of intersection between the equilibrium curve and a line of slope (- T/P), which passes through the point "1".



If a further stage is then carried out by the addition of solvent T to the stream C x_1, then the point 5 is found on the equilibrium curve by drawing "3" "5" of slope (- P/T). "5" coordonates gives the compositions of the second extract and raffinate, x_2 and y_2. This system can be used for any number of stages, with any assumed variation in the proportion of solvent P to raffinate from stage to stage.

Counter-current extraction

If a series of mixing and separating operations are executed in such a way that the flow is countercurrent, then the conditions of flow can be represented as in Figure.



The initial solution F of the solute C in solvent T is fed to the first unit and leaves as raffinate R_1. this stream passes through the units and leaves the nth unit as stream R_n. The

fresh solvent P enters at the nth unit and passes in the reverse direction through the units, leaving as extract E_1.

X_i- ratio of solute to solvent in the raffinate stream i

Y_i- ratio of solute to solvent in the raffinate stream i

The following material balances for the solute may then be written

(a) for the 1st stage

$$T.x_f + P.y_2 = T.x_1 + P.\ y_1$$

(b) for the nth stage

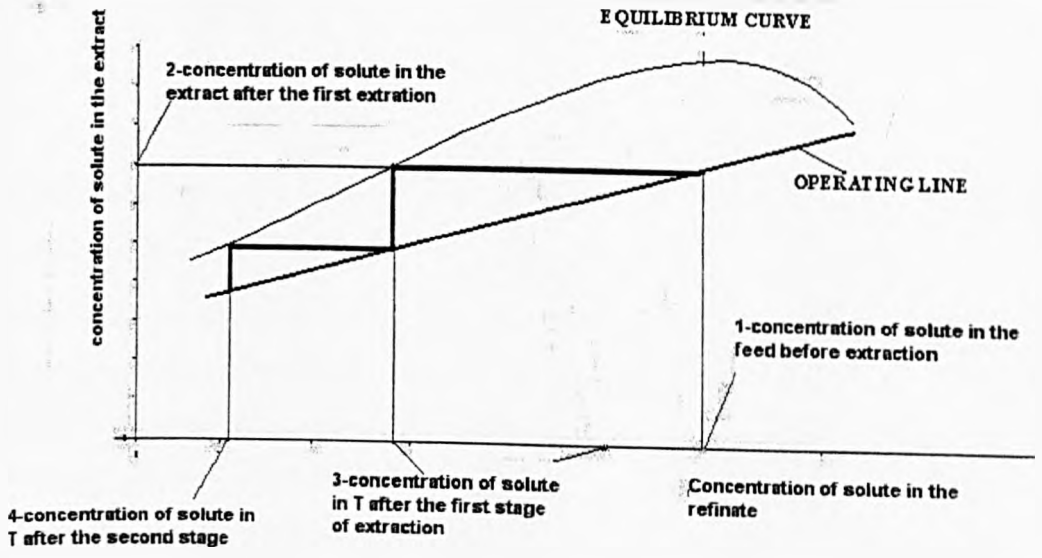
$$T.x_{n-1} + P.y_{n+1} = T.x_n + P.\ y_n$$

(c) for the whole unit

$$T.x_f + P.y_{n+1} = T.x_n + P.\ y_1$$

$$y_{n+1} = T/P.(.x_n - .x_f) + y_1$$

This is the equation of a straight line of slope, known as the "operating line", from the above equalities it is shown to pass trough the points (x_n, y_{n+1}) and (x_f, y_{n+1}). In the figure is draw the equilibrium line (i.e, the relationship between y_n and x_n), and the operating line.



The number of stages required to pass from x_f to x_n is found by drawing in steps between the operating line and the equilibrium curve. In the example shown two stage are required.

Appendix 3 General information on liquid-liquid extractors

There are three systems of continuous extraction used in industry, mixer-settlers, un-agitated and agitated columns.

Mixer settler systems are of simple construction but are economic up to five theoretical stages. Un-agitated columns (which are typically 1-1.5 m in height per theoretical plate) have the lowest capital and operating cost, but are less efficient than agitated columns (which can smoothly create bubbles of one phase inside the other and increase the area of mass transfer, and are typically 0.12-0.5 m in height per theoretical plate). There are several types of agitated extractors available in the market. From these there are three types which have been reported to be used by fine chemical industries: centrifugal extractors, reciprocating plate extractors (RPE), and rotary-agitated extractors (RAE).

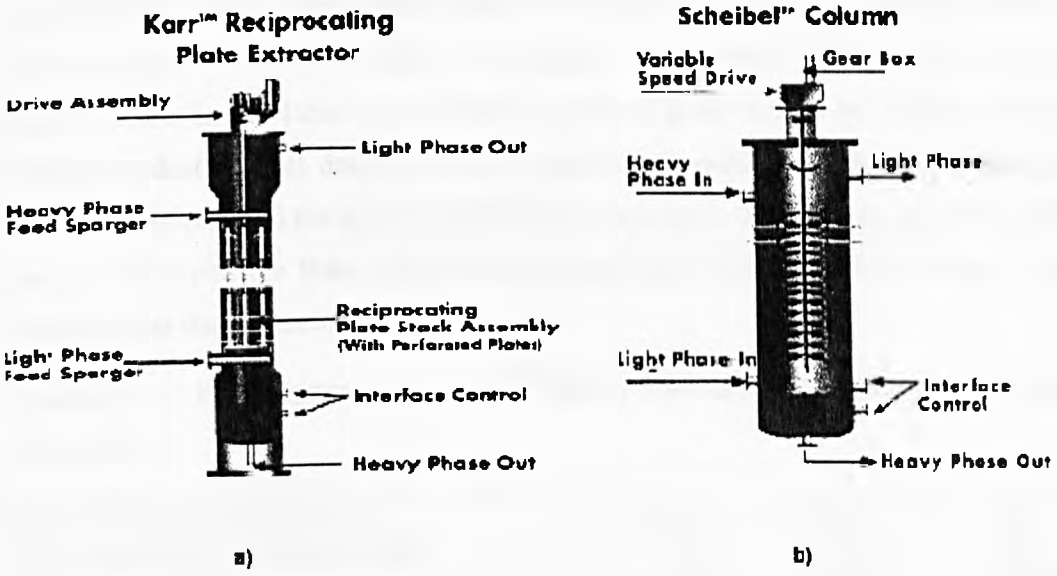


FIGURE A3 1:EXAMPLE OF A) RECIPROCATING PLATE EXTRACTOR (CHEM PRO. CO) AND B) ROTARY AGITATED EXTRACTOR (E.G.SCHEIBEL CO)

Centrifugal extractors are the most expensive; their use is recommended for short contact times for unstable material or when the density difference between the phases is smaller than 25 kg/m^3, so could not be recommended to perform CNSL separation. From the two remaining classes of extractors the rotary agitated column can be operated at higher throughput, but the reciprocating plates columns have the lowest height equivalent to one theoretical plates. In the pharmaceutical industry, RPE extractors have been reported to be used in the production of ephridine, erythromycin, unidentified nitroaromatic derivatives, and waste water treatment.

Ultimate sizing of an extractor needs to be performed on the basis of bench scale and pilot-plant experiments, on the chosen model of extractor. The main purpose of these experiments is to determine the flooding velocity, pulse amplitude and frequency, optimum plate design and spacing, in a range of operational conditions similar to the ones at which the industrial plant will work, and ultimately to have a figure for the maximum allowable superficial velocity and for the height of an equivalent theoretical plate, and elements for the mechanical design of the unit.

For a given capacity, some rough idea of the size of an extractor can be obtained as a function of the physical properties of the solvents, operating conditions and the equilibrium data information. On the basis of the available information, the possibility of using the Petrol-TFE-ACN solvent system to separate CNSL was analysed the dimensions of a small RPC extractor (Karr™ RPC) able to separate one gallon of cardols / 6 hrs shift. [3] The dimensions of the extractor were obtained on basis of empirical relationships stated by the manufacturer. Using these relationships, the values of the critical parameter (the flooding velocity) are very similar to those values obtained using a more elaborate value publicized in the literature. In the Table A3-1, different ratios of polar/ non polar solvent were analysed because industrial unit design would be based on a minimum cost of production of the extraction system and the associated distillation to remove the solvents, and TFE-ACN is not only more expensive than petrol, but also has higher boiling point (solvents need to be remove after the extraction).

TABLE A3 1 : PARAMETERS OF A KARR™ RPE TO SEPARATE ONE GALLON OF CARDOLS / 6 HRS SHIFT.

TFE-ACN/Petrol ratio (v/v)	0.25	0.5	2
Nr theoretical equilibrium stages	16	5	2
Diameter (m) (a)	0.25	0.27	0.39
HETP (m)	0.33	0.34	0.39
Total height (m) (b)	5.31	1.72	0.78
Volume of petrol in the column (m^3)	0.21	0.07	0.03
Volume of polar solvents in the column (m^3)	0.05	0.03	0.06

a) at 75 % of the flooding velocity; b) HETP height equivalent to a theoretical plate; c) total height = (nr stages x HETP) + Height for solvent holding.

The capacity of a Karr extractor could be increased to a maximum cumulative throughput (of both phases) of 80 m^3/hr (for higher capacities, others kind of extractors need to be used).

[3] This capacity was chosen because a company was interested in one gallon of cardols.

Additional data to design of this type of installation would require a pilot plant, to a) correlate the flooding point of the extraction column and the flow ratio over a range of conditions, and b) determinate the effective height a transfer unit.

This, in conjunction with the equilibrium data, allows the determination the dimensions of the equipment required for a given separation in the full sized column.

However because no markets for cardols have been yet developed this work was not considered a priority.

Appendix 4- Economical prefeasibility of the CNSL pyrolysis process

Typical flow sheet

As has been seen MVP could be obtained by CNSL pyrolysis in a copper tube at 750 °C. On a larger scale, a typical flow-sheet for this process would correspond to the one presented in the figure.

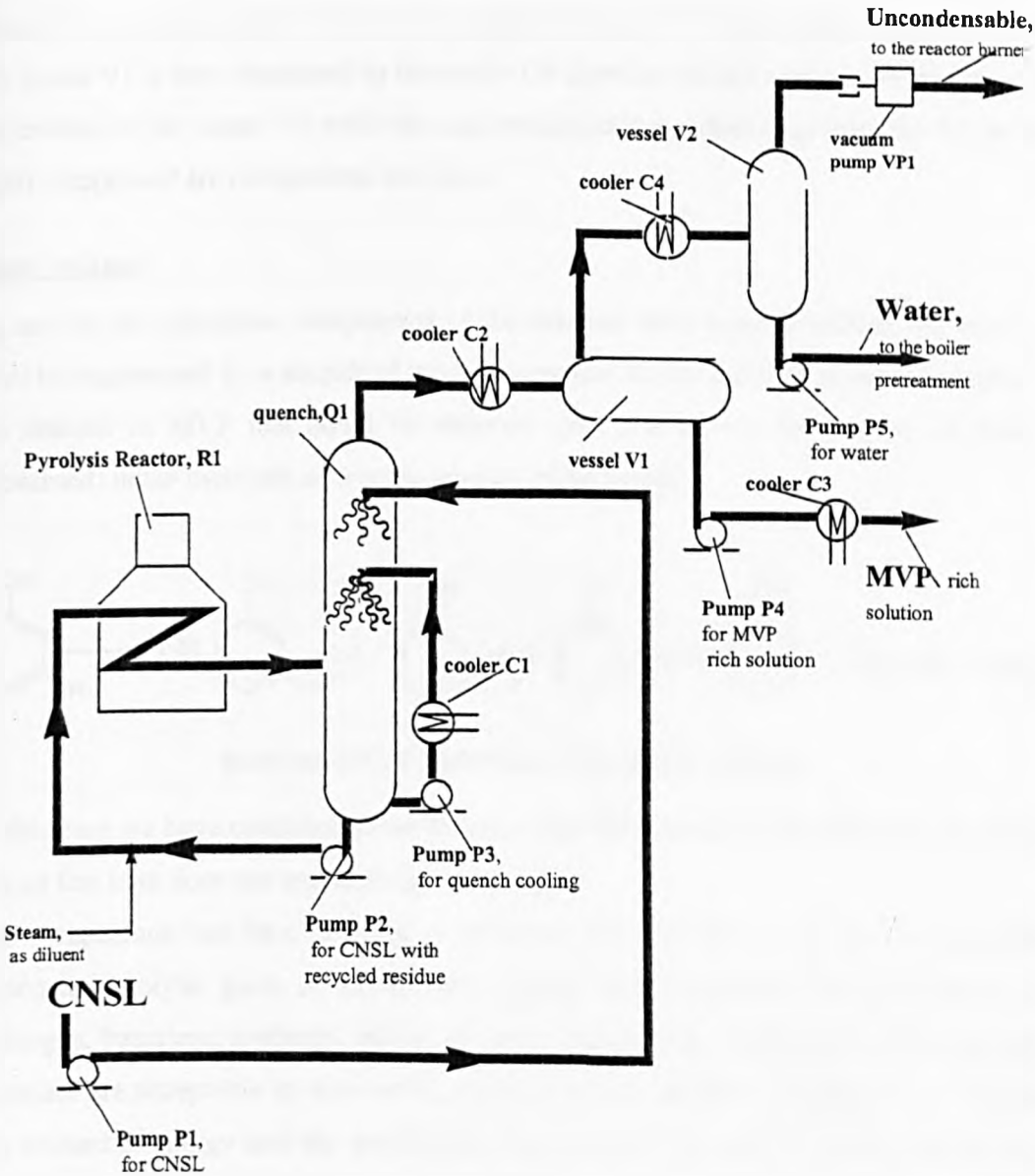


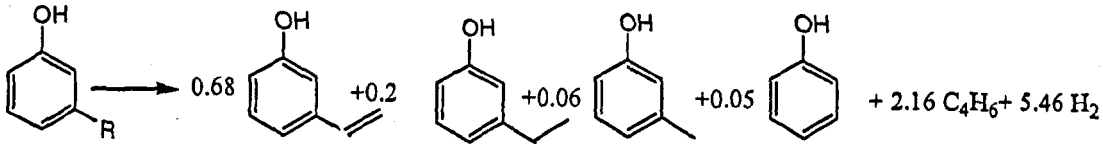
FIGURE A4 1--CNSL PYROLYSIS FLOW SCHEME

Fresh CNSL, is pumped through the pump P1 to the quench Q1 where it is mixed with products of the reaction. It condenses (at the bottom of the quench) with a recycled fraction (rich in C_{3+} alkenylphenols), and both streams are pumped through P2 to the pyrolysis furnace R1. In the inlet of the furnace, steam is added (to reduce the partial pressure of the effluent). The resulting mixture is then totally vaporized and pyrolysed.

The non-condensable gases and the condensable vapours generated in the reactor are discharged in the quench Q1, where a spay of fine oil droplets quenches the reaction and condenses the fraction heavier than MVP, which is recycled to the furnace. To maintain a constant temperature a fraction of the liquid fraction is recycled to the quench Q1 through the pump P3 and cooled in the heat exchanger C1. The gases, leaving the quench unit, are partially cooled in the heat exchanger C2 and the fraction rich in MVP is condensed in the vessel V1, and is pumped to the store through the pump P4. The vapour fraction leaving the vessel V1 is then condensed in the cooler C4 allowing the hot water to be recovered in the bottom of the vessel V2 while the non-condensable gas drawn up from the V2 by the main compressor are compressed and fired.

Mass balance

As not all the individual components of the reaction have been identified, the reaction must be represented by a simplified model acceptable for the purpose of the calculation of the amount of MVP that could be obtained (and respectively the amount of energy consumed) in the pyrolysis of a given amount of cardanols.



SCHEME A4 1 CARDANOLS PYROLYSIS SCHEME

In this case we have considered that the non-identified aromatic fraction is re-pyrolysed, and so this term does not appear in the calculation.

Gas composition has been assumed to hydrogen and butadiene. This fact is chemically wrong as pyrolytic gases of olefins and alkanes contain typically beside ethylene and hydrogen, butadiene, methane, ethane, propane, 1-propylene, 2-propylene. However these premises are acceptable in view of the purpose of this calculation (which is to calculate the amount of energy and the specification of the pyrolysis reactor) as simulations have shown that this composition is the one that corresponds to the biggest possible consumption of energy .

In a separate simulation, the feasibility of the unit was examined attributing to MVP the same price than ethylphenol.

Cost of starting material

The price of CNSL (85% cardanols) considered (750 £/ton), is 50 % higher than the actual price of technical CNSL (distilled CNSL).

Value of the products

MVP value was estimated as 14 250 £/ ton (price ex-factory).As MVP is not a commercial product, the value of 3-vinylphenol in this first approach was considered to be 50 % of the price of 3-hydroxybenzaldehyde (CIF Liverpool 28 500 £/ton, in 2001, imported into the UK from China). This is a very conservative assumption, as even if MVP from FVP is obtained as a solution, both chemicals could provide the same kind of products, and MVP has one carbon more than the aldehyde.Ethylphenol and 3-cresol were considered at 60 % of their current market value, i.e. respectively 4275 £/ ton and 720 £/ton ex-factory.

Energy cost

Thermochemical properties of cardanols and MVP were estimated using ChemDraw Ultra, while the ones of the others compounds found in the literature. The enthalpy of the reaction (scheme A4-1) in standard conditions is then 254 kJ/mol.

The basic heat balance shows that in the case of pyrolysis at 750 °C, the consumption of energy in the pyrolysis reactor is 2715 kWh/ ton cardanols processed, which at a cost of 0.09 £/kWh[4] gives 244 £/ton cardanols processed.

However, because the gases obtained in the reaction are burned, they provide not only the energy needed in the reaction, but also additional energy needed for the pumps and compressor.[5]

Cost of the plant

The cost of an erected plant in the West Coast of the US estimated by Selas (an American company specialized in the field) as US$ 2,650, 000 (This cost is roughly 5 times higher than the cost of the same plant estimated by standard chemical design procedure and

[4] Highest cost for industrial energy in the UK given by Manweb.

[5] Energy provided by the gases has been determined as a function of their composition, pyrolysis energy requirements have been estimated using Hess law applied to the chemical reaction describing the process and considering a thermal efficiency of the reactor of 50 % (remaining energy being lost, mainly through the chimney). This value was provided by Selas, and is in the same range than the one provided by the literature.

costing methods suggested by the literature).[6]The operating life of the unit, based in similar processes, is considered to be of 10 years with a major repair of the furnace tubes after 5 years, which gives a depreciation rate of 10 % annum. Capital costs of the plant have been estimated as corresponding to the depreciation rate plus 10 % (6 % above the current minimum lending rate).[7]

Others costs

Operating labour (9 persons @ 2000 £/month), supervision, laboratory and overhead costs have been estimated at 20, 30, and 100 % of the operating labour costs. Maintenance, insurance and local taxes at 5 %, 2 and 1 % of the fixed capital. Utilities refers to the cost of the fresh water to the cooling towers, and of chemicals to the water treatment.

Resume table

The resume table summarizes the value of the products versus a total estimated cost, in £ per ton of processed cardanols, in a FVP on copper in a 5000 tons/year installation.

TABLE A4- 1:ESTIMATED COSTS/EARNINGS OF A 5000 TONS/YEAR FVP PLANT

FVP @ 5000 tons/year	£/ton of processed cardanols
Value of the products	**4233**
Total estimated costs	**908**
Cardanols	750
Capital costs	25
Energy costs	-
Utilities	10
Maintenance	8
Operating labour	43
Supervision costs	9
Laboratory costs	13
Plant overheads	43
Local taxes, insurance	5
Gross earnings	**3325**

[6] i.e. Data from Coulson, 850 000 £ (1998) for a 5000 tons/year unit excluding the electrical generator erected in the UK, while Peters Timmermaus suggest US$ (1991), 1 300 000 and Walas US $ (1990) 1450000 for the same plant erected in the US.

[7] Procedure suggested by Vale Riestra