The synthesis of thiobisphenols from 3-alkylphenols derived from natural phenolic lipids†

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3-Alkylphenols derived from renewable natural resources have been used to synthesise thiobisphenols by reaction with sulfur dichloride. In contrast to previous work, we have found that 3-alkylphenols give isomeric products, the major symmetrical, the 4,4′-thiobis compound, the minor symmetrical, 2,2′-thiobisphenol, and some of the believed unsymmetrical isomer. The role of the solvent and catalyst have been studied in the reaction of 3-pentadecylphenol with sulfur dichloride. Evidence for the structures of the 2,2′ and 4,4′ isomers has been obtained from related reactions of 4-bromo-3-methylphenol, 2-bromo-5-methylphenol and their chloro analogues.

Keywords: anacardic acid, cardanol, 3-pentadecylphenol, 3-octylphenol, renewable resources, thiobisphenols, sulfur dichloride

We have studied the synthesis of thiobisphenols from phenolic lipid resources such as *Anacardium occidentale* (cashew) and *Anacardium giganteum* for technical examination of their role as additives in lubrication systems in comparison with related compounds derived from petrochemical intermediates. In this present work we describe the use of semi-synthetic C_{15} and C_8, 3-alkylphenols from a natural source and in other work we have synthesised a range of thiobisphenols to study the structure/property additive role of chain length and its position in the aryl ring in thiobisphenols

Anacardium occidentale occurs in a worldwide distribution of almost 10^6 tonnes [1–4] and contains principally C_{15} anacardic acid, Fig.1, (1, n = 15, m = 0,2,4,6) from which technical cashew nut shell liquid (CNSL), comprising mainly cardanol (2, n = 15, m = 0,2,4,6) is obtained by hot industrial decarboxylation of the natural raw cashew.nut

Anacardium giganteum[4,5] is a more limited source of the saturated C_{11} analogue (1, n =11, m = 0) and a source of 3-undecylphenol (2, n = 11, m = 0). 3-*n*-Octylphenol (2, n = 8, m = 0) is derived from the ozonisation[6] of cardanol (2).

This work arose because of the diminishing supply of fossil fuels, and hence that of 4-alkylphenols, such as 4-*t*-octyl and 4-*t*-nonyl phenols which are produced from isobutylene, propylene and benzene. In the reaction of 3-alkylphenols derived from natural sources, with sulfur dichloride, we have found several isomeric product as depicted in Scheme 1. Thus, cardanol (3-pentadecylphenol) (2, n = 15, m = 0) afforded a major proportion of the 4,4'-thiobisphenol, (6, n = 15) di-(4-hydroxy-2-pentadecylphenyl)-sulfide,

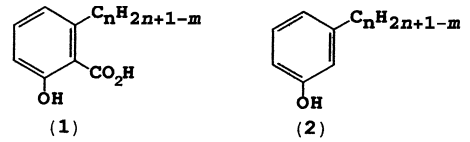


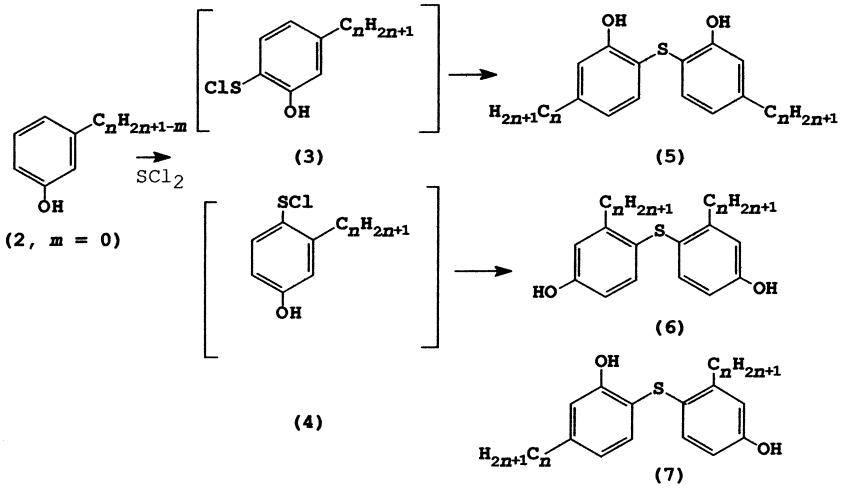
Fig. 1

a minor proportion of the 2,2'-thiobisphenol, (5, n = 15, m = 0), di-(2-hydroxy-4-pentadecylphenyl)-sulfide and some of the unsymmetrical product which we believe to be (7). The sulfenyl chlorides, (3) and (4) seem likely to be the intermediate electrophiles The isomeric products (5) and (6), were separated chromatographically by virtue of the hydrogen-bonding in the 2,2'-isomer compared with the 4,4' compound resulting in higher mobility by TLC, column chromatography or HPLC.

The ratio of isomer (6) to (5) was increased from 2:1 in benzene or chloroform to 4:1 in a polar solvent and to 5–6:1 in the same polar solvent containing an iron catalyst. 3-*n*-Octylphenol (2, n = 8, m = 0), reacted with sulfur dichloride to give chromatographically similar C_8 analogues although only the 4,4'-thiobisphenol was characterised.

Prior reports on the reaction of phenol[7] and *m*-cresol[8] (3-methylphenol) with sulfur dichloride describe a single para-substituted product. The reaction of 3-pentadecylphenol with sulfur monochloride[9] was reported to give only the ortho, 2,2'-thiobisphenol (5).

The improved yields of thiobisphenols in the present work, by the use of iron, and of aluminium chloride as catalysts



Scheme 1 Synthesis of thiobisphenols

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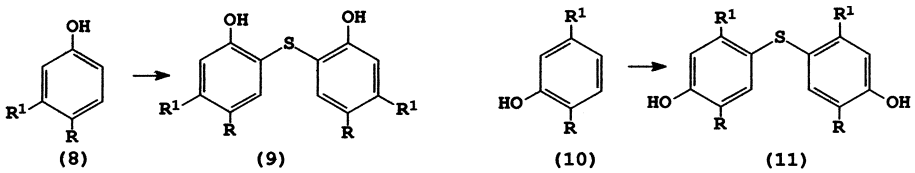
† Long Chain Phenols. Part 40: a



Scheme 2 Synthesis of bromo and chloro thiobisphenols

are considered attributable to the electrophiles, $[HOArS]^+$ $[FeCl_4]^-$.and $[HOArS]^+$ $[AlCl_4]^-$ respectively.

Independent structural proof for isomeric compounds (5) and (6) was sought (Scheme 2) by reaction of the isomeric bromocresols, 4-bromo-3-methylphenol (8, R^1= Me, R = Br) and 2-bromo-5-methylphenol (10, R^1 = Me, R = Br) with sulfur dichloride. In this series, (8) produced a 2,2'-thiobisphenol, (9) having a high R_f value (TLC) while the isomeric bromocresol (10) afforded a 4,4'-thiobisphenol (11) having a low R_f value. The chloro analogues were reacted with sulfur dichloride and afforded similar results.

The TLC results from both the bromo and chloro series provide evidence supporting the formulation of structures (5) and (6) given to the symmetrical isomers. The unsymmetrical 2,4'-thiobisphenols (7) are apparently formed in very small amount and such compounds through semi-hydrogen bonding could be predicted to have R_f values in TLC, between those of the isomers (5) and (6), reminiscent of the order of R_f values, *o*,*o*'-dihydroxy > *o*-hydroxy > *m*- or *p*-hydroxy groups found in the hydroxyanthraquinones[11] and in the hydroxybenzophenone series.[12]

Reference compounds (12) and (13), (Fig.2) were prepared from petrochemical intermediates 4-*t*-octylphenol and 4-*t*-nonylphenol.

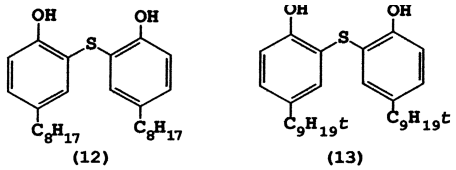


Fig. 2

Experimental

Materials: Technical cashew nutshell liquid (CNSL), was obtained by courtesy of 3M Research, St Paul, Minnesota, USA. Chemicals were obtained from Aldrich Chemical Co. Ltd. All solvents for reactions of phenols with sulfur dichloride were dried.

Sulfur dichloride was purified[13] by distillation from phosphorus trichloride and the process then repeated, with collection of the fraction, b.p. 58–61°C. The product was stored under nitrogen in brown glass containers. Reactions were carried out in a fume hood and it was dispensed from a pressure equalised dropping funnel.

Chromatography: Analytical TLC was carried out on silica gel G, type 60 on self-prepared plate with a layer 250μm and preparative TLC on layers 1mm. Bands were visualised by charring with sulfuric acid at 180°C or with rhodamine 6G and visualisation under UV light. Argentation TLC was effected on silica gel G containing 10% silver nitrate. Column chromatography was carried out on BDH silica gel particle size 0.13–0.25mm. and for flash chromatography, Merck kieselgel 60H and 60GF were used. HPLC was effected with columns containing Lichrosphere Si 100 and elution with 5% ethyl acetate in hexane.

Spectroscopy: Infrared spectra were recorded on a Perkin Elmer spectrometer. Proton NMR spectra were determined with a Varian T60 (60MHz) and CFT20 instruments with TMS as internal standard. Mass spectra were obtained on a modified AEI MS902 instrument and accurate mass determinations were made by the SERC mass spectrometry centre, University College of Wales, Swansea.

Separation of phenolic lipids

Cardanol: Unsaturated cardanol (2) was obtained from Technical CNSL by either the base addition method[14] or Mannich reaction method[15] and in each case the crude product was distilled *in vacuo*. Saturated cardanol was prepared by the atmospheric pressure catalytic hydrogenation of unsaturated cardanol in ethanol solution containing 10% palladium/carbon until absorption of hydrogen ceased; Argentation TLC then indicated a single band. It was also obtained, by analogy[16] with the preparation of anacardic acid, from chemical reduction of cardanol (2) (96g) with hydrazine hydrate (61.3g) and aeration and stirring in methylated spirit 200 cm^3 at 40°C during 7 days. Work-up by ethereal extraction, recovery and recrystallisation gave, pale cream crystals (65g) of saturated cardanol (2, m = 0), 3-pentadecylphenol, m.p. 49–50°C. 3-*n*-Octylphenol was prepared from cardanol [6] and also synthesised by the Wittig reaction of 3-hydroxybenzaldehyde and triphenylheptylphosphonium bromide followed by hydrogenation of the alkene product.[5]

Synthesis of thiobis-phenols from 3-pentadecylphenol

A variety of experiments was carried out with saturated cardanol (2mol) and sulfur dichloride (1mol) at 0°C with benzene, light petroleum, *n*-hexane, chloroform and acetonitrile and with aluminium chloride and iron powder.

4,4'-Thiobis-(3-pentadecylphenol), di-(4-hydroxy-2-pentadecylphenyl)-sulfide (6, n =15) and 2,2'-thiobis-(5-pentadecylphenol), di-(2-hydroxy-4-pentadecylphenyl)-sulfide (**5**, n = 15, m = 0).

3-Pentadecylphenol (10.0g, 0.033mol) in dry benzene (100cm^3) was stirred and cooled in an ice-bath. Sulfur dichloride (1.69g, 0.016mol) in dry benzene (20cm^3) was added dropwise under nitrogen over 1h and the mixture was then stirred for 6h (with TLC

Table 1 Reactions of 3-Pentadecylphenol and sulfur dichloride with different solvents and catalysts

Expt	No. g., mol)	Solvent (cm^3)	SCl_2 (g, mol, cm^3)	Catalyst (g,mol)	Products (4,4'),g , (%)	(2,2'),g , (%)
1	10.0, 0.033	PhH, 100	1.69, 0.016, 20	–	2.94, (27.9)	1.48, (14.1)
2	2.0, 0.0066	PhH, 40	0.37, 0.0036,15	$AlCl_3$ 0.097	0.66, (31.4)	0.17, (8.1)
3	2.0, 0.0066	PhH, 40	0.37, 0.0036,15	Fe, 0.02	1.02, (48.6)	0.36, (17.1)
4	2.22, 0.0073	$CHCl_3$ 50	0.41, 0.0042,15	$AlCl_3$, 0.054	0.39, (16.7)	0.08 (3.4)
5	2.0, 0.006	$CHCl_3$	0.37, 0.0036,15	$AlCl_3$, 0.097	0.25, (11.9)	0.12, (5.7)
6	2.0, 0.006	$CHCl_3$ 15	0.37, 0.0036,15	$AlCl_3$, 0.047	0.77 (36.8)	0.29 (13.8)
7	2.0, 0.006	$CHCl_3$ 40	0.37, 0.0036,15	Fe, 0.02	1.02, (48.6)	0.36 (17.2)
8	2.0, 0.006	$CHCl_3$ 35	0.37, 0.0036,15	Fe, 0.02	0.81 (38.6)	0.30 (14.3)
9	2.0, 0.006	$CHCl_3$ 40	0.37, 0.0036,15	Fe. 0.10	0.73, (34.6)	0.30 (14.3)
10	2.0, 0.006	$CHCl_3$	0.37, 0.0036,15	–	nil (reaction at -20°C)	
11	2.0 0.006	MeCN 20	0.37, 0.0036,15	–	0.58 (27.3)	0.15 (7.2)
12	2.0, 0.006	MeCN 20	0.37, 0.0036,15	Fe 0.02	0.48 (22.9)	0.09 (4.3)
13	2.0, 0.006	MeCN 20	0.37, 0.0036,15	$(Ph)_3PO$, 0.098	0.77 (36.7)	0.28 (13.3)
14	2.0, 0.006	MeCN 20	0.37, 0.0036,15	$(Ph)_3PO$, 0.098 + Fe (0.02)	0.89 (42.4) recovered cardanol,1.20g	0.30 (14.3)

monitoring, chloroform–ethyl acetate, 95:5). It was left for 16h to warm to ambient temperature. The mixture, diluted with light petroleum (40–60°C) was partially concentrated, washed with water ($2 \times 50cm^3$), dried (sodium sulfate) and separated by flash chromatography to give fractions 1–20, ($CHCl_3$-EtOAc, 98:2), fractions 21–26, ($CHCl_3$-EtOAc, 95:5), and fractions 27–70. Fractions 4–8 contained the high mobility component, R_f (0.69, $CHCl_3$–EtOAc, 95:5, 3-pentadecylphenol R_f 0.60), the 2,2'-isomer, 1.48g (14.1%), m.p. 53–55°C; *m/z*, M^+; Found: 638.5090. Required for $C_{42}H_{70}O_2S$, 638.5092; and fractions 46–62 gave the low mobility component, R_f (0.33), the 4,4'-isomer, 3.92g, crystallisation of which (light petroleum, 60–80°C) gave 2.94g (27.9%), m.p. 77–79°C; Found: C, 78.76; H, 10.95; S, 4.95. Required for $C_{42}H_{70}O_2S$, C, 78.93; H, 11.04; S, 5.02%.

In a polar solvent, the ratio of the yield of the 4,4' to the 2,2' isomer was increased (Table 1).

Thus, 3-pentadecylphenol (2.0g, 6.58×10^{-3}mol) in acetontrile ($20cm^3$) was cooled in an ice-bath. Sulfur dichloride (0.37g, 3.62×10^{-3}mol) in acetonitrile ($15cm^3$) was added dropwise to give, after work-up and chromatography as before, recovered 3-pentadecylphenol (0.86g), the 2,2'-thiobis isomer (0.15g, 7.15%) and the 4,4' isomer (0.58g, 27.3%, 48% on 3-pentadecylphenol used) in an isomer ratio, 4,4' to 2,2',of 3.8:1.

In acetonitrile and with identical quantities and conditions, except for inclusion of a catalyst, iron powder (0.02g, 10%), the ratio of isomers (6) to (5) was further enhanced. Work-up and flash chromatography gave the 2,2'-isomer (0.09g, 4.3%), unreacted 3-pentadecylphenol (1.14g), and the 4,4'-isomer (0.48g, 22.9%, 53% on 3-pentadecylphenol used), representing an isomer ratio, 4,4'/2,2' of 5.5:1.

Thiobisphenols from 3-n-octylpenol

Di-(4-hydroxy-2-octylphenyl)-sulfide (6, n = 8): 3-Octylphenol (3.33g, 0.0162mol) in chloroform ($50cm^3$) cooled in an ice-water bath was reacted with sulfur dichloride (0.0197g, 0.0089mol) in chloroform ($25cm^3$) by dropwise addition under nitrogen during 1h and the reaction was monitored by TLC.

The mixture was then allowed to warm to ambient temperature and worked up by prep TLC (chloroform-ethyl acetate, 95:5) and elution of bands with methanol to give the 4,4'-thiobisphenol, m.p., 55–57°C, R_f 0.23, 0.83g, (26%); Found, C, 75.76; H, 9.45. $C_{28}H_{42}O_2S$, requires, C, 75.97; H, 9.56%. However, other products, considered to be (a), the 2,2'-thiobisphenol, di-(2-hydroxy-4-octylphenyl)-sulfide, an oil, R_f 0.77, 0.51g, (14%), and (b), an oil, R_f 0.28, 0.27g, (8%) believed to be the non-hydrogen-bonded 4-hydroxy-2-octylsulfenyl chloride (**3**), were not fully characterised.

Di-(5-bromo-2-hydroxy-4-methylphenyl)-sulfide (9, R = Br, R^1= Me)): 4-Bromo-3-methylphenol (**8**) (6.0g, 0.032mol) in chloroform ($50cm^3$) cooled in an ice-water bath was stirred and treated dropwise under nitrogen with sulfur dichloride (1.65g, 0.016mol) in chloroform ($10cm^3$) over 1h. Further chloroform ($50cm^3$) was added after 20 min. and the reaction stirred for a further 3h (TLC monitoring). Upon warming to ambient temperature over 16h, a precipitate was filtered and washed with light petroleum to give 1.88g, m.p. 163°C, (29.1%), The filtrate and washings after concentration *in vacuo* gave an oil which crystallised (4.25g, 65.7%), and recrystallisation (light petroleum, 40–60°C) gave the 2,2'-thiobisphenol, di-(5-bromo-2-hydroxy-4-methylphenyl)-sulfide, R_f 0.64 (chloroform-ethyl acetate, 95:5), (4-bromo-3-methylphenol, R_f 0.49). m.p., 159°C; Found: C, 42.20; H, 3.04. $C_{14}H_{12}O_2SBr_2$, requires, C, 41.65; H, 2.99%.

Di-(5-bromo-4-hydroxy-2-methylphenyl)-sulfide (11, R = Br, R^1= Me): To 2-bromo-5-methylphenol (**10**) (4.49g, 0.024mol) in chloroform ($40cm^3$) cooled in an ice-water bath, sulfur dichloride (1,24g, 0.012mol) in chloroform ($10cm^3$) was added dropwise under nitrogen over 1h. The mixture was stirred for 3h and then warmed to ambient temperature over 16h. after which water ($50cm^3$) was added, the chloroform layer was separated, dried (sodium sulfate), filtered and concentrated to give an oil which solidified and was separated by prep TLC (chloroform–ethyl acetate, 95:5) to give unchanged 2-bromo-5-methylphenol, R_f 0.67, the 4,4'-thiobisphenol, di-(5-bromo-4-hydroxy-2-methylphenyl)-sulfide, R_f 0.34, (1.17g, 24.1%), which was crystallised (light petroleum), to yield pale yellow crystals, m.p. 144–145°C; Found: C, 41.15; H, 3.37. $C_{14}H_{12}O_2SBr_2$ requires, 41.65; H, 2.99%.

Di-((5-chloro-2-hydroxy-4-methylphenyl)-sulfide (**9**): 4-Chloro-3-methylphenol (28.52g, 0.2mol) in dry benzene ($70cm^3$) was cooled in an ice-water bath and treated dropwise with sulfur dichloride (10.3g, 0.1mol) over 1.5h under nitrogen (with TLC monitoring). The mixture was stirred for a further 3h and allowed to warm to ambient temperature, to give a light yellow solid which was filtered, washed with benzene and dried to yield (**9**), di-(5-chloro-2-hydroxy-4-methylphenyl)-sulfide, 22.4g (71.1%), m.p. 158–161°C, recrystallisation of which (benzene) gave the product, m.p., 175–177°C; (Found: C, 53.05; H, 3.65. $C_{14}H_{12}O_2SCl_2$ requires, C, 53.34; H, 3.84%); R_f 0.65 (chloroform-ethyl acetate, 95:5, 4-chloro-3-methylphenol, R_f 0.56).

Di-(5-chloro-4-hydroxy-2-methylphenyl)-sulfide (**11**): 2-Chloro-5-methylphenol (10.0g, 0.070mol) in chloroform ($50cm^3$) cooled in an ice-water bath was treated with sulfur dichloride (3.61g, 0.035mol) under nitrogen over 1.5h (TLC monitoring) and then allowed to warm to ambient temperature over 16h. The yellow solid was worked-up to give (**11**), di-(5-chloro-4-hydroxy-2-methylphenyl)-sulfide, 5.6g (51%), m.p. 167–170°C, R_f 0.30 (chloroform-ethyl acetate, 95:5, 2-chloro-5-methylphenol, R_f 0.67), and recrytallised; Found: C, 53.60; H, 3.48. $C_{14}H_{12}O_2SCl_2$ requires C, 53.34; H, 3.65%.

2,2'-Thiobis-4,4'-(1,1,3,3-tetramethylbutyl)phenol (**12**): 4-(1,1,3,3-Tetramethylbutyl)phenol (20.6g,0.10mol) suspended in *n*-hexane ($75cm^3$) and cooled in an ice-bath, was treated dropwise over 1.5h with sulfur dichloride (5.67g, 0.055mol) in hexane ($25cm^3$) under nitrogen. The mixture was stirred overnight and allowed to warm to ambient temperature. A white precipitate formed which gave the thiobisphenol (**12**) as white crystals, m.p. 132–133°C, (9.71g, 43.9%).(lit.[17], 132–134°C); *m/z*, M^+ 442; Found: 424.3095. Cald. for $C_2H_{42}O_2S$, 424.3095.

2,2'-Thiobis-4,4'-t-nonylphenol (**13**): Sulfur dichloride (2.575g, 0.025mol) in chloroform ($15cm^3$) was slowly added with stirring under nitrogen over 1h to 4-*t*-nonylphenol, which contains an isomeric mixture of side chains, (10.0g, 0.0455mol), in chloroform ($30cm^3$) cooled in an ice-bath. The mixture was allowed to warm to ambient temperature during 3h and concentrated *in vacuo* to afford the thiobisphenolic product (**13**), as an oil, (12.54g); R_f 0.78–98, streak, (chloroform-ethyl acetate, 95:5; *t*-nonylphenol, 0.35); *m/z*, M^+; Found: 470.3210. Cald. for $C_{30}H_{46}O_2$ S, 470.3210.:

In evaluations, as formulated 'overbased (magnesium salt derivatives)' additives in lubricating oils, the 4,4'-thiobisphenol (6, n = 15, m = 0) from 3-pentadecylphenol, showed a performance, superior to the 2,2' compound, when compared with commercial additives such as (**12**) and (**13**). For practical purposes, mixed products containing a major proportion of the 4,4' isomer were almost equally useful. The thiobisphenols also exhibited antifungal action.

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