Selective Preparation and Cyclization of 2-(2-Hydroxyphenyl)-2-(isopropylthio)ethanols. New Synthesis of 1-Benzofurans

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Reaction of phenols with 2-(isopropylthio)ethyl acetate activated by sulphuryl chloride afforded 2-[2-acetoxy-1-(isopropylthio)ethyl]phenols regioselectively, *via* [2,3]sigmatropic rearrangement of phenoxysulphonium ylides. The *ortho*-alkylated phenols thus obtained have been cyclized with conc. hydrochloric acid in 2-methoxyethanol to 1-benzofurans. 2-Methyl- and 2-phenyl-1-benzofurans have been prepared similarly.

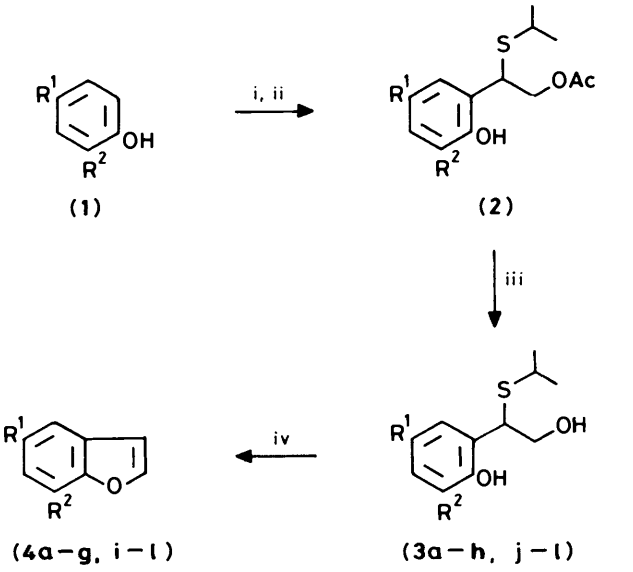
The cyclization of a suitably *ortho*-substituted phenol is the most often employed method for the synthesis of 1-benzofurans. The conventional approaches[1,2] to 1-benzofurans include the selective preparation and the cyclization of 2-(2-oxoalkyl)-phenols or their equivalent. We anticipated that another 1-benzofuran synthesis could be achieved by the cyclization of 2-(2-hydroxyalkyl)phenols possessing a relevant leaving group at the benzylic position. We reported previously a new efficient method of selective *ortho*-alkylation of phenols *via* [2,3]-sigmatropic rearrangement of phenoxysulphonium ylides employing dialkyl sulphide, sulphuryl chloride, and triethylamine.[3] Recently we explored the selective alkyl migration within alkyl isopropyl sulphides in this rearrangement and the extension of this method to the preparation of six-membered fused oxygen heterocycles such as coumarins, chromans, and chromenes.[4]

In this paper we report a new synthesis of 1-benzofurans, which includes the *ortho*-selective alkylation of phenols with 2-(isopropylthio)ethyl acetate activated by sulphuryl chloride, and the conversion of the products into 1-benzofurans. We also report the application of this methodology to the preparation of 2-methyl- and 2-phenyl-1-benzofurans.

First, we investigated the alkylation of *ortho*- and *para*-substituted phenols (**1**) with 2-(isopropylthio)ethyl acetate (Scheme 1). The addition of phenols (**1**) to 2-(isopropylthio)ethyl acetate activated by sulphuryl chloride and the subsequent treatment of the reaction mixture with triethylamine afforded acetates (**2**). Since the chromatographic mobility of these 2-alkylated phenols (**2**) turned out to be comparable to that of the starting phenols (**1**), the reaction products were isolated in the form of 2-[2-hydroxy-1-(isopropylthio)ethyl]phenols (**3**) after hydrolysis and purification by column chromatography in good yield. except in the case of the *p*-nitro derivative (**3g**). The results are summarized in Table 1.

We then investigated the conversion of compounds (**3**) into 1-benzofurans (**4**). Since intramolecular dehydration is involved in the formation of compounds (**4**) from (**3**), acidic reaction conditions would be desirable. In a preliminary examination on compound (**3b**), we found that treatment with a protic acid in alcoholic solvents at reflux yielded 5-phenyl-1-benzofuran (**4b**) in fair-to-moderate yields (Table 2). For this cyclization, conc. hydrochloric acid was the most effective among the acids investigated. Treatment of compound (**3b**) with toluene-*p*-sulphonic acid in non-polar solvents such as benzene or toluene failed to give the benzofuran (**4b**).

Next we investigated the influence of solvent on the behaviour of compounds (**3b**) and (**3h**) in aqueous alcoholic hydrochloric acid (Scheme 2). As shown in Table 3, product



Scheme 1. *Reagents:* i, $Me_2CHSCH_2CH_2OAc$-SO_2Cl_2; ii, Et_3N; iii, K_2CO_3 in aqueous MeOH; iv, conc. HCl in $MeOCH_2CH_2OH$

distribution was greatly affected by the reaction temperature, *i.e.* the boiling point of the solvent. 1-Benzofurans (**4b**) and (**4h**) were obtained in good yields in 2-methoxyethanol, while the yield of phenols (**6**) and (**7**) increased in low boiling alcohols. The formation of the substitution products (**6**) and (**7**) seems to be correlated to the reduced nucleophilicity of the phenolic hydroxy group due to electron-withdrawing substituents, and higher concentration of propane-2-thiol (b.p. 60 °C) in the reaction mixture at lower temperature.

Based on the above findings, a variety of 2-[2-hydroxy-1-(isopropylthio)ethyl]phenols (**3**) were converted into 1-benzofurans (**4**) in moderate-to-good yields with conc. hydrochloric

acid in 2-methoxyethanol under reflux. The results are shown in Table 4. The low yield of 5-nitro-1-benzofuran (**4g**) is obviously due to the decreased nucleophilicity of the phenolic hydroxy group of (**3g**) attributable to the nitro group.

It is apparent that the present methodology of 1-benzofuran synthesis from phenols *via* [2,3]sigmatropic rearrangement followed by cyclization can be applied to the preparation of 2-substituted 1-benzofurans. Thus, we investigated the synthesis and cyclization of 2-[2-hydroxy-1-(isopropylthio)propyl]-phenols and 2-[2-hydroxy-1-(isopropylthio)-2-phenylethyl]-phenols.

2-Isopropylthio-1-methylethyl acetate (**8**) was prepared from 1-chloropropan-2-ol in two steps. Reaction of a phenol and (**8**) mediated by [2,3]sigmatropic rearrangement afforded the *ortho*-substituted product (**10**) in good yield. The phenol (**10**) was treated with conc. hydrochloric acid in 2-methoxyethanol under reflux to give the corresponding benzofuran (**12**) in good yield (Scheme 3, Table 5). It is noteworthy that the treatment of compound (**10e**) with conc. hydrochloric acid in ethanol under reflux also yielded 5-methoxy-2-methyl-1-benzofuran (**12e**) in 54% yield. This readily occurring cyclization giving 2-methyl-1-benzofuran is in marked contrast to the reactivity of compounds (**3**) in aqueous alcoholic hydrochloric acid and seems to result from the secondary nature of the alcohol (**10**).

Table 1. Reaction of phenols (**1**) and 2-(isopropylthio)ethyl acetate activated by sulphuryl chloride

Phenol	R^1	R^2	Product	Yield (%)
(**1a**)	H	H	(**3a**)	66
(**1b**)[a]	Ph	H	(**3b**)	67
(**1c**)	Me	H	(**3c**)	74
(**1d**)[a]	OMe	H	(**3d**)	71
(**1e**)	Cl	H	(**3e**)	60
(**1f**)[b]	c-Hex	H	(**3f**)	58
(**1g**)[a]	NO_2	H	(**3g**)	27
(**1h**)[a]	CO_2Et	H	(**3h**)	61[c]
(**1j**)	H	Me	(**3j**)	61
(**1k**)	H	OMe	(**3k**)	65
(**1l**)	H	Cl	(**3l**)	40

[a] Dichloromethane–*N*,*N*-dimethylformamide (10:1) was used as solvent for *o*-alkylation of phenols. [b] Dichloromethane–*N*,*N*-dimethylformamide (20:1) was used as solvent for *o*-alkylation of (**1f**). [c] Ethanol was used as solvent for hydrolysis of (**2h**).

Table 2. Preparation of 5-phenyl-1-benzofuran (**4b**) in 2-methoxyethanol

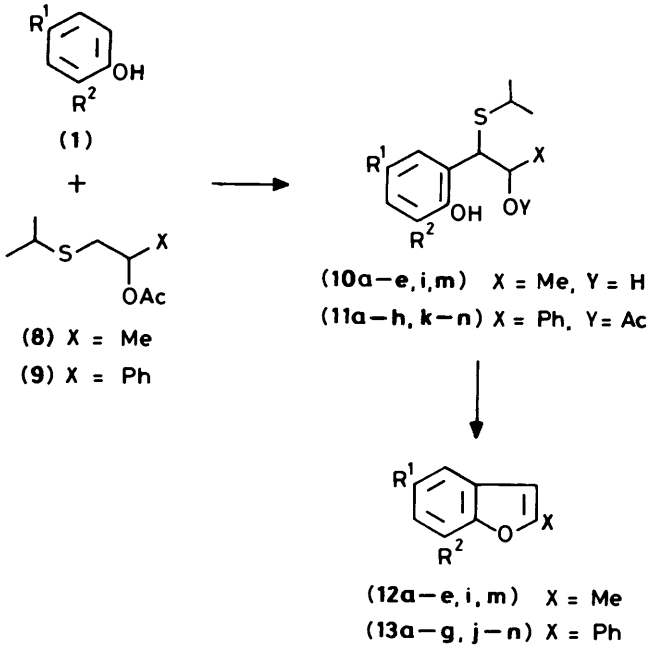
Protic acid	Yield (%)
Conc. HCl	58
14% $HClO_4$ aq.	19
Conc. HBr	34
10 mol% PTSA[a]	29

[a] PTSA = Toluene-*p*-sulphonic acid.

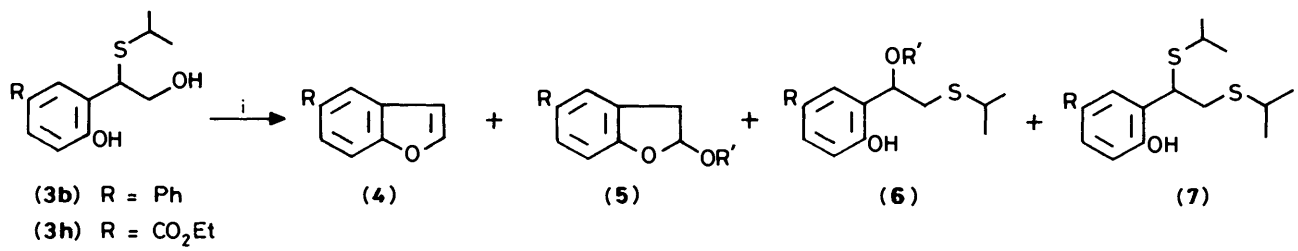
Table 3. Solvent effect of reaction of 2-[2-hydroxy-1-(isopropylthio)ethyl]phenols (**3**) with conc. hydrochloric acid

Starting material	R^1	Solvent	Yield (%) (4)	(5)	(6)	(7)
(**3b**)	Ph	MeOH	14	8		15
		PrOH	48			21
		$MeOCH_2CH_2OH$	58			
(**3h**)[a]	CO_2Et	MeOH		4	59	
		EtOH		25		24
		PrOH	5	20	24	14
		$MeOCH_2CH_2OH$	45			
		$EtOCH_2CH_2OH$	29			

[a] Ester exchange reaction of (**3h**) occurred under these conditions.



Scheme 3.



Scheme 2. *Reagents*: i, conc. HCl in R'OH

Table 4. Preparation of 1-benzofurans (**4**)

1-Benzofuran	R^1	R^2	Yield (%)
(**4a**)	H	H	61
(**4b**)	Ph	H	58
(**4c**)	Me	H	45
(**4d**)	OMe	H	59
(**4e**)	Cl	H	65
(**4f**)	c-Hex	H	50
(**4g**)	NO_2	H	10
(**4i**)[a]	$CO_2CH_2CH_2OMe$	H	45
(**4j**)	H	Me	42
(**4k**)	H	OMe	45
(**4l**)	H	Cl	40

[a] Ethyl 4-hydroxy-3-[2-hydroxy-1-(isopropylthio)]ethylbenzoate (**3h**) was used as starting material.

Table 5. Preparation of 2-[2-hydroxy-1-(isopropylthio)propyl]phenols (**10**) and 2-methyl-1-benzofurans (**12**)

Product	R^1	R^2	Yield (%)	1-Benzofuran	Yield (%)
(**10a**)	H	H	56	(**12a**)	61
(**10b**)	Me	H	81	(**12b**)	63
(**10c**)	Cl	H	50	(**12c**)	50
(**10d**)[a]	Ph	H	56	(**12d**)	58
(**10e**)[a]	OMe	H	84	(**12e**)	61
(**10i**)[b]	OBu	H	63	(**12i**)	51
(**10m**)	H	Me	80	(**12m**)	67

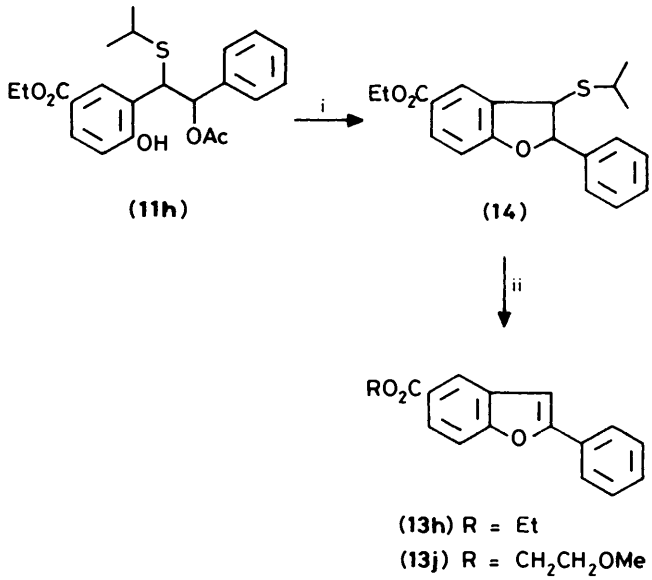
[a] Dichloromethane *N*,*N*-dimethylformamide (20:1) was used as solvent for *o*-alkylation of phenols. [b] Dichloromethane–*N*,*N*-dimethylformamide (10:1) was used as solvent for *o*-alkylation of the phenol.

Table 6. Preparation of 2-phenyl-1-benzofurans (**13**)

1-Benzofuran	R^1	R^2	Yield (%)	M.p. (°C) [lit.]
(**13a**)	H	H	50	123—125 (121)[5]
(**13b**)	Me	H	65	129.5—131 (131—132)[6]
(**13c**)	Cl	H	72	154—156 (156)[7]
(**13d**)[a]	Ph	H	35	166—168
(**13e**)[a]	OMe	H	55	128.5—130 (127)[7]
(**13f**)[a]	CHO	H	36	132—133.5
(**13g**)[a]	Ac	H	28	162—163.5
(**13j**)[a,b]	$CO_2CH_2CH_2OMe$	H	48	83.5—84.5
(**13k**)[c]	CH_2CO_2Et	H	56	86—88
(**13l**)	H	OMe	49	Oil
(**13m**)	H	Me	42	Oil
(**13n**)	Me	Me	53	60—62

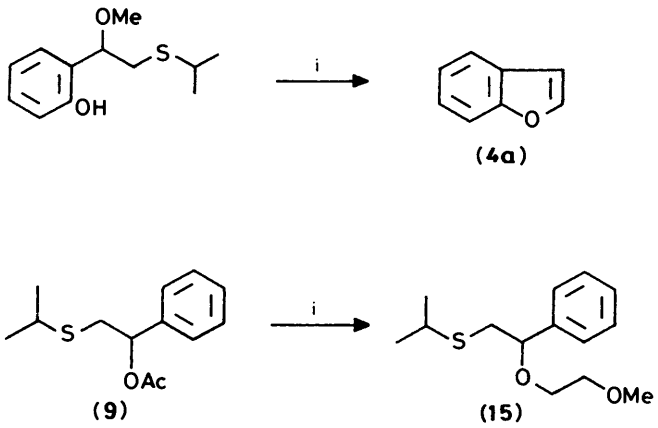
[a] Dichloromethane–*N*,*N*-dimethylformamide (10:1) was used as solvent for *o*-alkylation of phenols. [b] Ethyl 4-hydroxybenzoate (**1h**) was used as starting phenol. [c] Ethanol was used as solvent for cyclization of (**11k**).

Next, we investigated the preparation of 2-phenyl-1-benzofuran derivatives. 2-Isopropylthio-1-phenylethyl acetate (**9**) was prepared from phenacyl chloride in three steps, which involved reaction with sodium propane-2-thiolate (90% yield), sodium borohydride reduction (74% yield), and acetylation (84% yield). The alkylation of phenols with acetate (**9**) *via* [2,3]sigmatropic rearrangement was carried out as described earlier to give compounds (**11**) which, without isolation and hydrolysis, were directly treated with conc. hydrochloric acid in 2-methoxyethanol to afford 2-phenyl-1-benzofurans (**13**) in moderate-to-good yield as shown in Table 6 (Scheme 3). Within *para*-substituted phenols (**11b—h**) the yield of cyclization to 2-phenyl-1-benzofurans (**13**) decreased with an increase in the electron-withdrawing effect of the substituent in the acetate (**11**). Here we became interested in the behaviour of compounds (**11**) in ethanol at reflux in comparison with that of (**3**) and (**10**). When the phenol (**11a**) and ethyl [3-(2-acetoxy-1-isopropylthio-2-phenylethyl)-4-hydroxyphenyl]acetate (**11k**) were treated with conc. hydrochloric acid in ethanol at reflux for 3 h, 2-phenyl-1-benzofuran (**13a**) and ethyl (2-phenyl-1-benzofuran-5-yl)acetate (**13k**) were directly produced in 38 and 58% isolated overall yield, respectively. In contrast to these facts, to our great surprise, similar treatment of the benzoate (**11h**) afforded ethyl 2,3-dihydro-3-isopropylthio-2-phenyl-1-benzofuran-5-carboxylate (**14**) in 48% yield without any formation of ethyl 2-phenyl-1-benzofuran-5-carboxylate (**13h**). This 2,3-dihydro-1-benzofuran (**14**) did not undergo elimination of propane-2-thiol on heating in 2-methoxyethanol at reflux, but did afford 1-benzofurans (**13h** and **j**) in 67% combined yield when treated with conc. hydrochloric acid in 2-methoxyethanol under reflux (Scheme 4).



Scheme 4. *Reagents:* i, conc. HCl in EtOH; ii, conc. HCl in $MeOCH_2CH_2OH$

In order to gain insight into the mechanism of the present cyclization of 2-[2-hydroxy-1-(isopropylthio)ethyl]phenols, we performed some experiments on related compounds (Scheme 5). 2-(2-Hydroxyethyl)phenol did not give any cyclization product on heating with conc. hydrochloric acid in 2-methoxyethanol, while similar treatment of 2-[2-(isopropylthio)-1-methoxyethyl]-phenol did produce 1-benzofuran (**4a**) in 51% yield. 1-Phenylethyl acetate was recovered after being heated with conc. hydrochloric acid in 2-methoxyethanol, while 2-isopropylthio-1-phenylethyl acetate (**9**), on similar treatment, was converted into 2-isopropylthio-1-(2-methoxyethoxy)-1-phenylethane (**15**) in 59% yield. All these results suggest a great contribution of the isopropylthio group to the displacement reaction at the homobenzylic position. Therefore we can safely depict the reaction mechanism of the cyclization as in the Scheme 6. Protonation of a compound (**3**) followed by dehydration leads to the intermediary episulphonium salt (**16**), cyclization of which by



Scheme 5. *Reagents:* i, conc. HCl in $MeOCH_2CH_2OH$

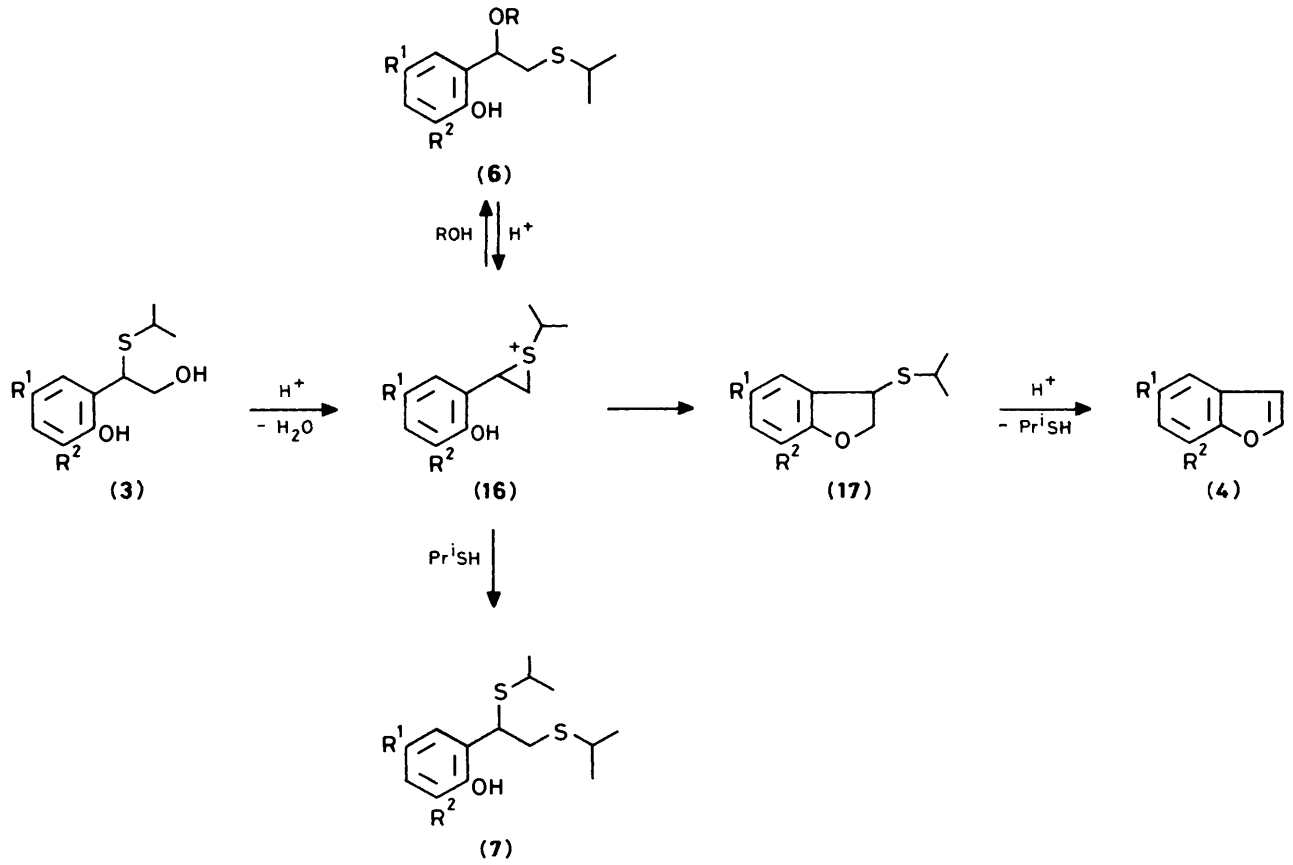
intramolecular nucleophilic attack of the phenolic hydroxy group affords the 2,3-dihydro-1-benzofuran (**17**), the immediate precursor of the corresponding 1-benzofuran (**4**). The formation of bimolecular substitution products (**6**) and (**7**) in some cases can be accounted for by the assumption of the episulphonium intermediate (**16**).

In conclusion, the introduction of a 2-hydroxy-1-(isopropylthio)ethyl moiety to the *ortho* position of phenols using [2,3]sigmatropic rearrangement and subsequent cyclization in the presence of a protic acid is an effective method for the preparation of 1-benzofuran derivatives.

Experimental

B.p.s and m.p.s (Shimadzu MM-2 hot-stage apparatus) are uncorrected. I.r. spectra were measured on a Hitachi 260-10 spectrometer. ^1H N.m.r. spectra were obtained with a JEOL JNM-C-60M or a JEOL FT-90-Q spectrometer with tetramethylsilane as internal standard. Column chromatography was normally effected with Wakogel C-200 (Wako Pure Chemical Industries). The known compounds were established on the basis of comparison of spectroscopic properties with those in the literature.

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]*phenols* (**3**).—*General procedure.* Sulphuryl chloride (3.2 ml, 40 mmol) was added dropwise to a mixture of 2-(isopropylthio)ethyl acetate (5.4 g, 33 mmol) and a phenol (**1**) (100 ml) in dry dichloromethane (300 ml) at −40 °C under nitrogen. After the reaction mixture had been stirred for 20 min at −40 °C, triethylamine (30 ml) was added. The reaction mixture was allowed to warm to room temperature, and was then poured into dil. hydrochloric acid. The organic layer was separated and the aqueous solution was extracted with dichloromethane (100 ml). The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), and then evaporated. Potassium carbonate (10 g, 70 mmol) was added to a solution of the resulting oil in methanol–water (7:1) (170 ml). The mixture was stirred for 20 h at room temperature, then acidified with dil. hydrochloric acid. The aqueous solution was poured into water, and then was extracted with chloroform (100 ml). The extract was washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The residue was chromatographed on a column (5—20% EtOAc–hexane) to give the desired *ortho*-alkylated phenol (**3**). The following phenols were thus prepared.



Scheme 6.

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]*phenol* (**3a**). M.p. 53—54 °C; $\nu_{max.}$(KBr) 3 400 and 1 050 cm^{-1}; δ($CDCl_3$) 1.20, 1.23 (6 H, each d, *J* 6 Hz), 2.80 (1 H, septet, *J* 6 Hz), 3.87 (2 H, d, *J* 6 Hz), 4.30 (1 H, t, *J* 6 Hz), and 6.6—7.5 (6 H, m) (Found: C, 62.0; H, 7.5. $C_{11}H_{16}O_2S$ requires C, 62.23; H, 7.60%).

3-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]*biphenyl*-4-*ol* (**3b**). $\nu_{max.}$(neat) 3 300 and 1 040 cm^{-1}; δ($CDCl_3$) 1.13, 1.20 (6 H, each d, *J* 6 Hz), 2.83 (1 H, septet, *J* 6 Hz), 3.90 (2 H, d, *J* 6 Hz), 4.30 (1 H, t, *J* 6 Hz), 5.4 (2 H, m), and 6.7—7.6 (8 H, m) (Found: C, 70.6; H, 6.8. $C_{17}H_{20}O_2S$ requires C, 70.80; H, 6.99%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]-p-*cresol* (**3c**). $\nu_{max.}$(neat) 3 350 and 1 050 cm^{-1}; δ($CDCl_3$) 1.17, 1.20 (6 H, each d, *J* 6 Hz), 2.20 (3 H, s), 2.82 (1 H, septet, *J* 6 Hz), 3.82 (2 H, d, *J* 6 Hz), 4.27 (1 H, t, *J* 6 Hz), 5.2 (2 H, m), and 6.4—7.2 (3 H, m) (Found: C, 63.6; H, 7.7. $C_{12}H_{18}O_2S$ requires C, 63.68; H, 8.02%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]-4-*methoxyphenol* (**3d**). $\nu_{max.}$(neat) 3 300, 1 200, and 1 040 cm^{-1}; δ($CDCl_3$) 1.20, 1.25 (6 H, each d, *J* 7 Hz), 2.81 (1 H, septet, *J* 7 Hz), 3.71 (3 H, s), 3.7—5.0 (5 H, m), and 6.6—7.0 (3 H, m) (Found: C, 59.7; H, 7.2. $C_{12}H_{18}O_3S$ requires C, 59.48; H, 7.49%).

4-*Chloro*-2-[2-*hydroxy*-1-(*isopropylthio*)*ethyl*]*phenol* (**3e**). M.p. 68—69.5 °C; $\nu_{max.}$(KBr) 3 150 and 1 060 cm^{-1}; δ($CDCl_3$) 1.22, 1.27 (6 H, each d, *J* 6 Hz), 2.83 (1 H, septet, *J* 6 Hz), 3.90 (2 H, d, *J* 6 Hz), 4.18 (1 H, t, *J* 6 Hz), and 6.3—7.1 (5 H, m) (Found: C, 61.4; H, 7.1. $C_{11}H_{15}ClO_2S$ requires C, 61.54; H, 7.04%).

4-*Cyclohexyl*-2-[2-*hydroxy*-1-(*isopropylthio*)*ethyl*]*phenol* (**3f**). $\nu_{max.}$(neat) 3 320, 2 930, 1 260, and 1 050 cm^{-1}; δ($CDCl_3$) 1.20 (3 H, d, *J* 7 Hz), 1.23 (3 H, d, *J* 7 Hz), 1.3—3.0 (11 H, m), 2.80 (1 H, septet, *J* 7 Hz), 3.89 (2 H, d, *J* 6 Hz), 4.23 (1 H, t, *J* 6 Hz), 6.70 (1 H, d, *J* 8 Hz), and 6.8—7.5 (4 H, m) (Found: C, 69.6; H, 8.75. $C_{17}H_{26}O_2S$ requires C, 69.35; H, 8.90%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]-4-*nitrophenol* (**3g**). M.p. 89—91 °C; $\nu_{max.}$(KBr) 3 500 and 1 040 cm^{-1}; δ[$(CD_3)_2SO$] 1.16, 1.18 (6 H, each d, *J* 6 Hz), 2.88 (1 H, septet, *J* 6 Hz), 3.4 (1 H, m), 3.7—3.9 (2 H, m), 4.39 (1 H, t, *J* 6 Hz), 5.0 (1 H, m), 7.00 (1 H, d, *J* 8 Hz), 8.04 (1 H, dd, *J* 4, 8 Hz), and 8.24 (1 H, d, *J* 4 Hz) (Found: C, 51.1; H, 5.9; N, 5.45. $C_{11}H_{15}NO_4S$ requires C, 51.35; H, 5.88; N, 5.44%).

Ethyl 4-*hydroxy*-2-[2-*hydroxy*-1-(*isopropylthio*)*ethyl*]-*benzoate* (**3h**). M.p. 127—129 °C; $\nu_{max.}$(KBr) 3 430, 1 680, 1 280, and 1 050 cm^{-1}; δ($CDCl_3$) 1.16, 1.18 (6 H, each d, *J* 6 Hz), 1.30 (3 H, t, *J* 8 Hz), 2.84 (1 H, septet, *J* 6 Hz), 3.3 (1 H, m), 3.6—3.8 (2 H, m), 4.28 (2 H, q, *J* 8 Hz), 4.38 (1 H, t, *J* 8 Hz), 4.9 (1 H, m), 6.90 (1 H, d, *J* 8 Hz), 7.70 (1 H, dd, *J* 2, 8 Hz), and 7.92 (1 H, d, *J* 2 Hz) (Found: C, 59.0; H, 6.95. $C_{14}H_{20}O_4S$ requires C, 59.13; H, 7.09%).

6-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]-o-*cresol* (**3j**). $\nu_{max.}$(neat) 3 300, 2 960, 1 470, and 1 050 cm^{-1}; δ($CDCl_3$) 1.20 (3 H, d, *J* 7 Hz), 1.23 (3 H, d, *J* 7 Hz), 2.23 (3 H, s), 2.80 (1 H, septet, *J* 7 Hz), 3.90 (2 H, d, *J* 6 Hz), 4.23 (1 H, t, *J* 6 Hz), and 6.6—7.4 (5 H, m) (Found: C, 63.7; H, 8.0. $C_{12}H_{18}O_2S$ requires C, 63.68; H, 8.02%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*ethyl*]-6-*methoxyphenol* (**3k**). $\nu_{max.}$(neat) 3 420, 2 970, 1 480, 1 275, and 1 080 cm^{-1}; δ($CDCl_3$) 1.22 (3 H, d, *J* 6 Hz), 1.27 (3 H, d, *J* 6 Hz), 2.91 (1 H, septet, *J* 6 Hz), 3.83 (3 H, s), 3.83 (2 H, d, *J* 6 Hz), 4.47 (1 H, t, *J* 6 Hz), and 6.7—7.1 (5 H, m) (Found: C, 59.8; H, 7.4. $C_{12}H_{18}O_3S$ requires C, 59.48; H, 7.49%).

2-*Chloro*-6-[2-*hydroxy*-1-(*isopropylthio*)*ethyl*]*phenol* (**3l**). M.p. 62—63 °C; $\nu_{max.}$(KBr) 3 350, 2 960, 1 450, 1 240, and 1 050 cm^{-1}; δ($CDCl_3$) 1.20 (3 H, d, *J* 7 Hz), 1.23 (3 H, d, *J* 7 Hz), 2.89 (1 H, septet, *J* 7 Hz), 3.87 (2 H, d, *J* 6 Hz), 4.40 (1 H, t, *J* 6 Hz), and 6.7—7.7 (5 H, m) (Found: C, 53.6; H, 6.1. $C_{11}H_{15}ClO_2S$ requires C, 53.54; H, 6.13%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]*phenols* (**10**).—These were prepared according to the general procedure. 2-(Isopropylthio)-1-methylethyl acetate (**8**) was used instead of 2-(isopropylthio)ethyl acetate. The following compounds were thus prepared.

2-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]*phenol* (**10a**). $\nu_{max.}$(neat) 3 350 and 1 080 cm^{-1}; δ($CDCl_3$) 1.1—1.3 (9 H, m), 2.69 (1 H, septet, *J* 6 Hz), 4.0—4.4 (2 H, m), 5.4 (2 H, m), and 6.7—7.3 (4 H, m) (Found: C, 63.7; H, 8.2. $C_{12}H_{18}O_2S$ requires C, 63.68; H, 8.02%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]-p-*cresol* (**10b**). $\nu_{max.}$(neat) 3 300 and 1 100 cm^{-1}; δ($CDCl_3$) 1.0—1.5 (9 H, m), 2.24 (3 H, s), 2.5—2.8 (1 H, m), 3.8—4.2 (2 H, m), and 6.7—7.1 (5 H, m) (Found: C, 64.85; H, 8.5. $C_{13}H_{20}O_2S$ requires C, 64.96; 8.39%).

4-*Chloro*-2-[2-*hydroxy*-1-(*isopropylthio*)*propyl*]*phenol* (**10c**). $\nu_{max.}$(neat) 3 300 and 1 050 cm^{-1}; δ($CDCl_3$) 1.1—1.4 (9 H, m), 2.72 (1 H, septet, *J* 7 Hz), 3.8—4.3 (2 H, m), and 6.7—7.3 (5 H, m) (Found: C, 55.5; H, 6.5. $C_{12}H_{17}ClO_2S$ requires C, 55.27; H, 6.57%).

3-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]*biphenyl*-4-*ol* (**10d**). $\nu_{max.}$(neat) 3 300 and 1 050 cm^{-1}; δ($CDCl_3$) 1.0—1.5 (9 H, m), 2.5—3.0 (1 H, m), 3.8—4.5 (2 H, m), 6.90 (1 H, d, *J* 8 Hz), and 7.2—7.8 (9 H, m) (Found: C, 71.6; H, 7.3. $C_{18}H_{22}O_2S$ requires C, 71.49; H, 7.33%).

2-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]-4-*methoxyphenol* (**10e**). $\nu_{max.}$(neat) 3 350 and 1 040 cm^{-1}; δ($CDCl_3$) 1.1—1.3 (9 H, m), 2.72 (1 H, septet, *J* 7 Hz), 3.74 (3 H, s), 3.8—4.3 (2 H, m), and 6.6—6.9 (5 H, m) (Found: C, 60.5; H, 8.0. $C_{13}H_{20}O_3S$ requires C, 60.91; H, 7.86%).

6-[2-*Hydroxy*-1-(*isopropylthio*)*propyl*]-o-*cresol* (**10m**). $\nu_{max.}$(neat) 3 300 and 1 100 cm^{-1}; δ($CDCl_3$) 1.0—1.5 (9 H, m), 2.24 (3 H, s), 2.5—2.8 (1 H, m), 3.8—4.2 (2 H, m), and 6.7—7.1 (5 H, m) (Found: C, 64.7; H, 8.15. $C_{13}H_{20}O_2S$ requires C, 64.96; H, 8.39%).

1-*Benzofurans* (**4**) *and* (**12**).—Conc. hydrochloric acid (10 ml) was added to a solution of the alkylated phenol (**3**) or (**10**) (18 mmol) in 2-methoxyethanol (80 ml). The solution was heated under reflux for 4 h and was poured into water. The aqueous solution was extracted with n-pentane (100 ml). The organic layers were washed successively with water and brine, dried ($MgSO_4$), and then concentrated. The resulting oil was chromatographed on a column (pentane) to give the 1-benzofuran (**4**) or (**12**). The following new compounds were prepared using the above procedure.

5-*Cyclohexyl*-1-*benzofuran* (**4f**). $\nu_{max.}$(neat) 2 930, 1 470, and 730 cm^{-1}; δ($CDCl_3$) 1.2—2.0 (10 H, m), 2.5—2.7 (1 H, m), 6.72 (1 H, d, *J* 2 Hz), 7.17 (1 H, dd, *J* 2, 8 Hz), 7.42 (1 H, d, *J* 8 Hz), 7.44 (1 H, d, *J* 2 Hz), and 7.60 (1 H, d, *J* 2 Hz) (Found: C, 83.7; H, 8.1. $C_{14}H_{16}O$ requires C, 83.96; H, 8.05%).

2-*Methoxyethyl* 1-*benzofuran*-5-*carboxylate* (**4i**). $\nu_{max.}$(neat) 2 900, 1 720, 1 290, and 770 cm^{-1}; δ($CDCl_3$) 3.37 (3 H, s), 3.65 (2 H, t, *J* 4 Hz), 4.47 (2 H, t, *J* 4 Hz), 6.67 (1 H, d, *J* 2 Hz), 7.37 (1 H, d, *J* 8 Hz), 7.53 (1 H, d, *J* 2 Hz), 7.93 (1 H, dd, *J* 2, 8 Hz), and 8.20 (1 H, d, *J* 2 Hz) (Found: C, 65.2; H, 5.45. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.49%).

2-*Methyl*-5-*phenyl*-1-*benzofuran* (**12d**). M.p. 83.5—84.5 °C; $\nu_{max.}$(KBr) 1 260 and 760 cm^{-1}; δ($CDCl_3$) 2.44 (3 H, d, *J* 1 Hz), 6.37 (1 H, s), and 7.2—7.3 (8 H, m) (Found: C, 86.2; H, 5.8. $C_{15}H_{12}O$ requires C, 86.51; H, 5.81%).

2-*Phenyl*-1-*benzofurans* (**13**).—*General procedure.* Sulphuryl chloride (3.2 ml, 40 mmol) was added dropwise to a mixture of 2-(isopropylthio)-1-phenylethyl acetate (**9**) (8.0 g, 33 mmol) and a phenol (**1**) (100 mmol) in dry dichloromethane (300 ml) at −40 °C under nitrogen. After triethylamine (30 ml) was added to the reaction mixture, the solution was allowed to warm up to room temperature. The solution was poured into dil. hydrochloric acid. The organic layer was separated and the aqueous solution was extracted with dichloromethane (100 ml).

The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The resulting mixture was treated with conc. hydrochloric acid (20 ml) in 2-methoxyethanol (150 ml) at reflux for 4 h. The solution was poured into water and the aqueous solution was extracted with chloroform (200 ml). The extract was washed successively with water and brine, dried ($MgSO_4$), and then concentrated. The resulting oil was chromatographed on a column (EtOAc–hexane) to give the desired 2-phenyl-1-benzofurans (**13**). Thus were prepared the following compounds.

2,5-*Diphenyl*-1-*benzofuran* (**13d**). M.p. 166—168 °C; $\nu_{max.}$(KBr) 1 455, 1 020, and 745 cm^{-1}; $\delta(CDCl_3)$ 7.06 (1 H, d, *J* 1 Hz) and 7.3—8.0 (13 H, m) (Found: C, 88.75; H, 5.2. $C_{20}H_{14}O$ requires C, 88.86; H, 5.22%).

2-*Phenyl*-1-*benzofuran*-5-*carbaldehyde* (**13f**). M.p. 132—133.5 °C; $\nu_{max.}$(KBr) 1 690 cm^{-1}; $\delta(CDCl_3)$ 7.12 (1 H, d, *J* 1 Hz), 7.3—8.2 (8 H, m), and 10.00 (1 H, s) (Found: C, 81.2; H, 4.45. $C_{15}H_{10}O_2$ requires C, 81.07; H, 4.54%).

5-*Acetyl*-2-*phenyl*-1-*benzofuran* (**13g**). M.p. 162—163.5 °C; $\nu_{max.}$(KBr) 1 670 cm^{-1}; $\delta(CDCl_3)$ 2.64 (3 H, s). 7.07 (1 H, s), 7.3—8.0 (7 H, m), and 8.23 (1 H, d, *J* 2 Hz) (Found: C, 81.4; H, 4.95. $C_{16}H_{12}O_2$ requires C, 81.34; H, 5.12%).

2-*Methoxyethyl* 2-*phenyl*-1-*benzofuran*-5-*carboxylate* (**13j**). M.p. 83.5—84.5 °C; $\nu_{max.}$(KBr) 1 695 and 755 cm^{-1}; $\delta(CDCl_3)$ 3.45 (3 H, s), 3.6—3.9 (2 H, m), 4.4—4.7 (2 H, m), 7.07 (1 H, s), and 7.1—8.4 (8 H, m) (Found: C, 72.85; H, 5.3. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44%).

Ethyl (2-*phenyl*-1-*benzofuran*-5-*yl*)*acetate* (**13k**). M.p. 86—88 °C; $\nu_{max.}$(KBr) 1 730, 1 160, and 770 cm^{-1}; $\delta(CDCl_3)$ 1.24 (3 H, t, *J* 6 Hz), 3.69 (2 H, s), 4.17 (2 H, q, *J* 6 Hz), 6.99 (1 H, s), 7.2—7.5 (6 H, m), and 7.86 (2 H, d, *J* 8 Hz) (Found: C, 77.3; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.12; H, 5.75%).

Ethyl 2,3-*Dihydro*-3-*isopropylthio*-2-*phenyl*-1-*benzofuran*-5-*carboxylate* (**14**).—According to the general procedure, ethyl *p*-hydroxybenzoate (**1h**) (11.1 g, 66 mmol) and the sulphide (**9**) (5.3 g, 22 mmol) were used. After work-up, the residual oil was dissolved with ethanol (50 ml). Conc. hydrochloric acid was added to the solution, which was refluxed for 4 h. After work-up, the residue was chromatographed on a column (20% EtOAc–hexane) to give compound (**14**) (3.7 g, 48%), $\nu_{max.}$(neat) 1 705, 1 280, 1 255, 1 155, and 765 cm^{-1}; $\delta(CDCl_3)$ 1.2—1.4 (9 H, m), 3.02 (1 H, septet, *J* 7 Hz), 4.34 (2 H, q, *J* 7 Hz), 4.46 (1 H, d, *J* 6 Hz), 5.60 (1 H, d, *J* 6 Hz), 6.90 (1 H, d, *J* 8 Hz), 7.35 (5 H, s), and 7.8—8.0 (2 H, m).

Conc. hydrochloric acid (3 ml) was added to a solution of the sulphide (**14**) (1.0 g, 2.9 mmol) in 2-methoxyethanol (30 ml). The solution was refluxed for 5 h, and then was poured into water. The aqueous mixture was extracted with chloroform (50 ml). The extract was washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The residue was chromatographed on a column (10% EtOAc–hexane) to give ester (**13j**) (0.18 g, 21%) and ester (**13h**) (0.36 g, 46%). *Ethyl ester* (**13h**); m.p. 102—104 °C; $\nu_{max.}$(KBr) 1 705, 1 175, and 1 025 cm^{-1}; $\delta(CDCl_3)$ 1.42 (3 H, t, *J* 7 Hz), 4.46 (2 H, q, *J* 7 Hz), 7.09 (1 H, s), and 7.3—8.4 (8 H, m) (Found: C, 76.5; H, 5.2. $C_{17}H_{14}O_3$ requires C, 76.68; H, 5.30%).

2-*Isopropylthio*-1-*methylethyl Acetate* (**8**).—Propane-2-thiol (41 g, 0.54 mol) was added to a solution of sodium hydroxide (23 g, 0.58 mol) in methanol (250 ml). After the mixture had been stirred for 30 min at 20 °C, 1-chloropropan-2-ol (50 g, 0.53 mol) was added dropwise to the mixture. The reaction mixture was refluxed for 4 h and then filtered. The filtrate was evaporated and the residue was dissolved in chloroform (500 ml). The solution was washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The resulting oil was distilled to give 1-(isopropylthio)propan-2-ol (64.9 g, 93%), b.p. 95—97 °C/31 mmHg; $\nu_{max.}$(neat) 3 400 and 1 070 cm^{-1}; $\delta(CDCl_3)$ 1.23 (3 H, d, *J* 6 Hz), 1.27 (6 H, d, *J* 6 Hz), 2.5—3.1 (3 H, m), 3.15 (1 H, s), and 3.82 (1 H, sextet, *J* 6 Hz).

Acetic anhydride (100 ml) was added dropwise to a solution of 1-(isopropylthio)propan-2-ol (52.3 g, 0.44 mol) and pyridine (100 ml) in dichloromethane (200 ml). The mixture was stirred for 20 h at ambient temperature and then poured into dil. hydrochloric acid. The organic layer was separated, washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The resulting oil was distilled to give the desired sulphide (**8**) (67.0 g, 79%), b.p. 101—103 °C/24 mmHg; $\nu_{max.}$(neat) 1 730 and 1 240 cm^{-1}; $\delta(CDCl_3)$ 1.27 (6 H, d, *J* 6 Hz), 1.30 (3 H, d, *J* 6 Hz), 2.03 (3 H, s), 2.5—3.3 (3 H, m), and 5.00 (1 H, sextet, *J* 6 Hz); *m/z* 176 (M^+), 133 (M^+ – Ac), and 116 (M^+ – HOAc).

2-*Isopropylthio*-1-*phenylethyl Acetate* (**9**).—Propane-2-thiol (32 ml, 0.35 mol) was added to a solution of sodium hydroxide (14.0 g, 0.35 mol) in methanol (300 ml) at 0 °C. After the solution had been stirred for 20 min at 0 °C, phenacyl chloride (48.5 g, 0.31 mol) was added, and the solution was stirred for 6 h at room temperature. The mixture was poured into water, and was neutralized with dil. hydrochloric acid. The aqueous solution was extracted with chloroform (500 ml). The extract was washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The residue was distilled to give 2-isopropylthio-1-phenylethanone (54.4 g, 90%), b.p. 130—131.5 °C/5 mmHg; $\nu_{max.}$(neat) 2 960, 1 675, and 1 275 cm^{-1}; $\delta(CDCl_3)$ 1.14 (6 H, d, *J* 7 Hz), 2.83 (1 H, septet, *J* 7 Hz), 3.60 (2 H, s), and 7.2—8.0 (5 H, m).

Sodium borohydride (54.3 g, 0.28 mol) was added to a solution of 2-isopropylthio-1-phenylethanone (54.3, g, 0.28 mol) in methanol (500 ml) at 0 °C. The mixture was stirred for 6 h at room temperature and was then poured into water, and was neutralized with dil. hydrochloric acid. The aqueous solution was extracted with chloroform (500 ml), and the extract was washed successively with water and brine, dried ($MgSO_4$), and evaporated. The residue was distilled to give 2-isopropylthio-1-phenylethanol (40.4 g, 74%), b.p. 141—142 °C/7 mmHg; $\nu_{max.}$(neat) 3 425 and 2 965 cm^{-1}; $\delta(CDCl_3)$ 1.29 (6 H, d, *J* 7 Hz), 2.5—3.1 (3 H, m), 3.22 (1 H, br s), 4.54 (1 H, m), and 7.15 (5 H, s).

Acetic anhydride (40 ml, 0.42 mol) was added to a solution of 2-isopropylthio-1-phenylethanol (40.4 g, 0.21 mol) and pyridine (33 ml, 0.41 mol) in dichloromethane (30 ml). The mixture was stirred for 20 h at room temperature and was then poured into dil. hydrochloric acid. The organic layer was separated, washed successively with water and brine, dried ($MgSO_4$), and then evaporated. The resulting oil was distilled to give the desired sulphide (**9**) (41.4 g, 84%), b.p. 148—150 °C/7 mmHg; $\nu_{max.}$(neat) 2 960, 1 740, and 1 240 cm^{-1}; $\delta(CDCl_3)$ 1.21 (6 H, d, *J* 7 Hz), 1.98 (3 H, s), 2.6—3.2 (3 H, m), 5.74 (1 H, t, *J* 7 Hz), and 7.21 (5 H, s) (Found: C, 65.2; H, 7.6. $C_{13}H_{18}O_2S$ requires C, 65.51; H, 7.63%).

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