Intramolecular Cyclization using Methyl(bismethylthio)sulphonium Salts. Part 1. 2,3-Dihydrobenzofurans

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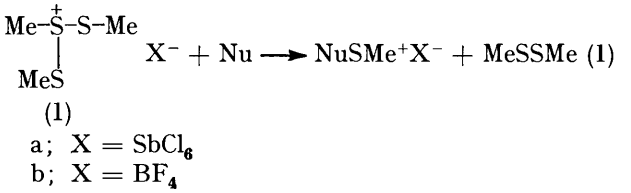
Methyl(bismethylthio)sulphonium hexachloroantimonate (1a) reacts under mild conditions with 2-allylphenol (3a) to give 2-(methylthiomethyl)-2,3-dihydrobenzofuran (4a). Methylthiolation at position 5 in the heterocycle may also occur. With 4-substituted 2-allylphenols (3b—d) (substituents: methyl, chloro, nitro) only the corresponding 5-substituted 2-(methylthiomethyl)-2,3-dihydrobenzofurans (4b—d) are obtained.

SOME years ago [1] we introduced methyl(bismethylthio)-sulphonium hexachloroantimonate (1a) or tetrafluoroborate (1b) as methylthiolating agents for several nucleophiles [equation (1)]. With these reagents we



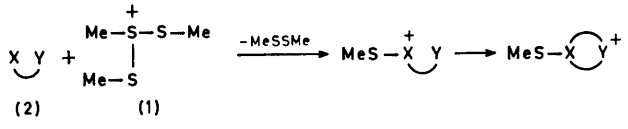
$$Me\text{–}\overset{+}{S}\text{–}S\text{–}Me \quad (MeS) \quad X^- + Nu \longrightarrow NuSMe^+X^- + MeSSMe \quad (1)$$

(1)
a; X = $SbCl_6$
b; X = BF_4

could prepare stable thiirenium [2-4] and thiiranium [5] ions and methylthio-substituted sulphonium ions [6] by reaction with alkynes, alkenes, and sulphides respectively. Thiirenium and thiiranium salts react with nucleophiles to yield ring-opening products which are methylthio-substituted alkenes or alkanes.[4,7-10]

Peculiarities of sulphonium salts (1) are the anion's poor nucleophilicity and the release of dimethyl disulphide, which is also a very weak nucleophile.

The methylthiolating ability and the above cited properties make the sulphonium ion (1) a suitable reagent for internal cyclization reactions in substrates of type (2) which possess two functionalities X and Y. They may be electrophilically attached by (1) and may subsequently give nucleophilic ring closure (Scheme 1).



(2) (1)

SCHEME 1

Moreover the reaction of (1) with compounds (2) introduces in the cyclized product a methylthio-functionality which may undergo further conversion.†

In order to verify the reliability of the reaction outlined in Scheme 1, we investigated the reaction of (1a) with 2-allylphenols (3); in fact the phenols (3) meet the requirements for the feasibility of the reactions in Scheme 1: the ethylene functionality should allow the transfer of the MeS^+ moiety from (1) to (3) and the OH group is in a suitable position for intramolecular ring closure. Other electrophilic reagents have been proposed to promote internal cyclization of 2-allylphenols.[11-17]

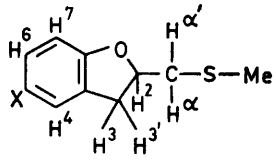
† For similar reactions the term cyclofunctionalization has been proposed.[11]

RESULTS

Reaction of Methyl(bismethylthio)sulphonium Hexachloroantimonate (1a) *with 2-Allylphenol* (3a).—The reaction, carried out in dichloromethane at room temperature, gives an 88 : 12 mixture of the cyclization products (4a) and (5) (Scheme 2), which were separated by column chromatography. The structure of the products was established on the basis of elemental analyses, n.m.r. spectra, and in some cases chemical conversion. Analysis of the non-aromatic part of the ^1H n.m.r. spectrum of 2-(methylthiomethyl)-2,3-dihydrobenzofuran (4a) allowed the correct determination of the magnetic parameters (Table 1). These parameters, together with the ^{13}C spectrum (Table 2), agree with the proposed structure.

TABLE 1

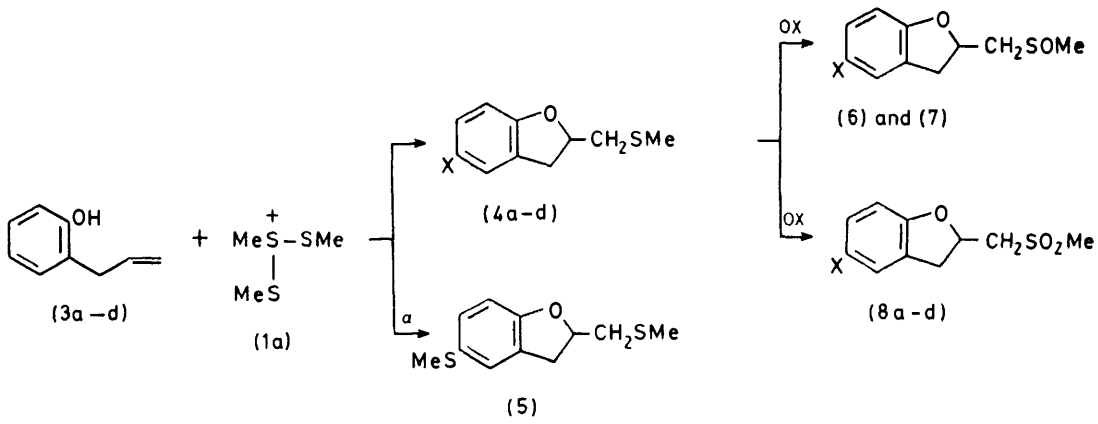
^1H N.m.r. parameters (from iterative analysis of selected magnetic systems) for compounds (4a) and (5) in $CDCl_3$. Coupling constants are approximated to the nearest 0.05



(4a) X = H		(5) X = MeS	
δ_α	2.89	δ_4	7.18
$\delta_{\alpha'}$	2.78	δ_6	7.11
δ_2	4.96	δ_7	6.71
δ_3	3.36	J_{34} = $J_{3'4}$	1.05
$\delta_{3'}$	3.06	J_{36} = $J_{3'6}$	0.8
$J_{\alpha\alpha'}$	13.45	J_{37} = $J_{3'7}$	−0.35 [a]
$J_{\alpha 2}$	5.45	J_{47}	0.45
$J_{\alpha' 2}$	7.1	J_{46}	2.05
$J_{\alpha 3}$ = $J_{\alpha' 3}$ = $J_{\alpha 3'}$ = $J_{\alpha' 3'}$	0.2 [a]	J_{67}	8.2
J_{23}	8.5		
$J_{23'}$	7.4		
$J_{33'}$	15.6		

[a] Gives correct broadening for unresolved lines.

Reductive desulphurization of (4a) with Raney nickel gives 2-methyl-2,3-dihydrobenzofuran (9) and 2-propylphenol (10) [equation (2)]. The carbon–oxygen bond cleavage that leads to (10) may occur either in (4a) or in (9). Attempts to obtain a cleaner desulphurization of (4a) by reduction of the sulphonium tetrafluoroborate derivative



(3a), (4a), (6), (7), (8a) X = H

(3b), (4b), (8b) X = Me

(3c), (4c), (8c) X = Cl

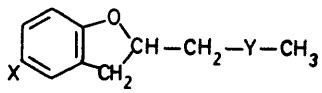
(3d), (4d), (8d) X = NO_2

a For X = H only.

SCHEME 2

TABLE 2

^1H and ^{13}C N.m.r. data for 2,3-dihydrobenzofuran derivatives in $CDCl_3$



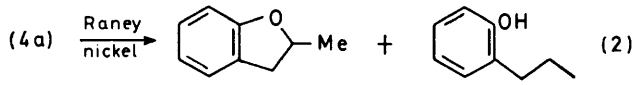
^1H Compound	X	Y	Aromatic	CH [a]	CH_2Ph [a]	CH_2Y [a]	CH_3Y [a]	Y [a]	X [b]
(4a)	H	S	7.26—6.68	4.96	3.16	2.83	2.20		
(4b)	CH_3	S	6.95—6.50	4.90	3.10	2.78	2.17		2.25
(4c)	Cl	S	7.20—6.46	4.92	3.13	2.78	2.15		
(4d)	NO_2	S	8.40—6.70	5.20	3.31	2.90	2.23		
(5)	CH_3S	S	7.21—6.55	4.91	3.13	2.78	2.16		2.38
(6)	H	SO	7.26—6.73	5.33	3.33	3.15	2.73		
(7)	H	SO	7.33—6.76	5.31	3.33	3.10	2.68		
(8a)	H	SO_2	7.33—6.73	5.33	3.8—2.8 [c]		3.00		
(8b)	CH_3	SO_2	7.16—6.50	5.20	3.7—2.7 [c]		3.05		2.26
(8c)	Cl	SO_2	7.26—6.58	5.26	3.8—2.8 [c]		3.03		
(8d)	NO_2	SO_2	8.10—6.80	5.40	3.9—2.9 [c]		3.06		
(11)	H	$\overset{+}{S}CH_3$	7.30—6.86	5.37	3.86	3.39	3.16		

^{13}C Compound	X	Y	Aromatic	CH	CH_2Ph	CH_2Y	CH_3Y
(4a)	H	S	128.1, 125.0, 120.6, 109.5 [d] 159.4, 126.3 [e]	82.1	35.0	39.3	16.3
(6)	H	SO	128.4, 125.2, 121.2, 109.8 [d] 158.9, 125.6 [e]	76.2	35.3	58.6	39.1
(7)	H	SO	128.5, 125.2, 121.2, 109.9 [d] 158.7, 125.6 [e]	76.4	35.6	61.3	39.9
(8a)	H	SO_2	128.5, 125.2, 121.4, 109.8 [d] 158.3, 125.3 [e]	76.9	35.2	59.9	42.8

[a] Multiplet centres. [b] Singlets. [c] Overlapping multiplets. [d] Unsubstituted carbon atoms. [e] Substituted carbon atoms.

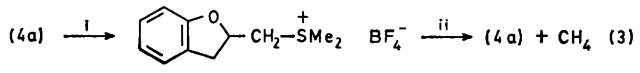
(11) with lithium aluminium hydride failed and only (4a) was recovered [equation (3)].

The dihydrobenzofuranoic structure of 2-methylthiomethyl-5-methylthio-2,3-dihydrobenzofuran (5) is deduced from the non-aromatic section of the ^{1}H n.m.r. spectrum,



(9) (10)

strictly similar to that of (4a). The integrated intensity for aromatic protons (3 H) indicates methylthiolation of the aromatic system. The position of the methylthio-substituent was determined through the analysis of the n.m.r. pattern for aromatic protons (Table 1): methylthiolation at position 5 is suggested by the values of the aromatic and benzylic coupling constants and by the values of proton



(11)

Reagents: i, $MeO^+ BF_4^-$; ii, $LiAlH_4$

shifts.[18] The position of the substituent also agrees with the orientation expected for electrophilic substitution in substrates of this type.

When (1a) and (3a) in a 2 : 1 molar ratio were allowed to react in dichloromethane at 41 °C for 3 h, only (5) was obtained, in a 78% yield.

Some attempts to find the best conditions for the exclusive formation of (4a) were carried out by changing temperature (between −50 and 25 °C) and reaction time (*cf.* Table 3):

TABLE 3

Reaction between 2-allyphenols (3a—d) and methyl(bismethylthio)sulphonium hexachloroantimonate (1a) in dichloromethane

Wt (g) in 50—100 ml CH_2Cl_2 (mmol)		Conditions		Yield (%)	
(3a—d)	(1a)	T (°C)	t	(4a—d)	(5)
(3a): 1.54 (11.5)	5.5 (11.6)	r.t.	15 m	59	8
		−50 [a]	2 h	37	
		−50 [a]	2 h		
		and then			28
		r.t.	10 h		
		−17	13 h	48	
		0	15 m	34	
		0	2 h	36	
		0	13 h	48.5	2
(3a): 1.0 (7.5)	7.3 (15.3)	reflux	3 h		78
(3b): 2.0 (13.5)	6.5 (13.7)	−50 [a]	2 h	62	
(3c): 1.0 (5.9)	2.9 (6.1)	and then		74	
(3d): 1.3 (6.0)	2.9 (6.1)	r.t.	15 h	74	

[a] Acetonitrile–CO_2 slurry.

when the reaction was run at −17 °C for 12 h, (4a) was exclusively obtained in a 48% yield.

Dihydrobenzofuran (4a) was oxidized with 3-chloroperbenzoic acid to the corresponding sulphone and sulphoxides (Scheme 2). Two equivalents of the oxidizing agent gave the sulphone (8a) in almost quantitative yield. Elemental analysis and n.m.r. data (Table 2) are consistent with the proposed structure. Oxidation of (4a) with 1 mol equiv. of 3-chloroperbenzoic acid afforded an almost equimolar mixture of diastereoisomeric sulphoxides (6) and (7), which were separated by low pressure column chromatography and characterized by melting points and ^{1}H and ^{13}C n.m.r. spectra (Table 2). No attempt was made to assign absolute configurations.

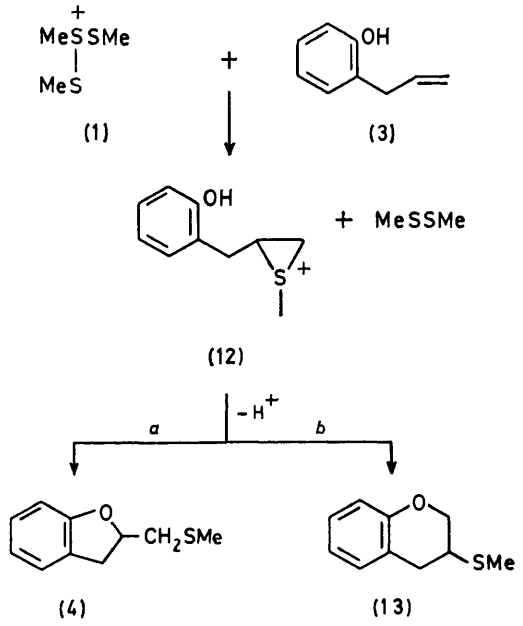
Reactions of Methyl(bismethylthio)sulphonium Hexachloroantimonate (1a) *with 4-Substituted 2-Allylphenols* (3b—d).—The 4-substituted 2-allylphenols (3b—d) were prepared from the corresponding 4-substituted phenylallyl ethers by thermal Claisen rearrangement.[19]

The reactions of allylphenols (3b—d) with sulphonium salt (1a) in dichloromethane at −50 °C yielded 5-substituted 2,3-dihydrobenzofuran derivatives (4b—d) only (Scheme 2). No evidence was obtained for products deriving from aromatic methylthiolation. The ^{1}H n.m.r. spectra (Table 2) clearly indicate the dihydrobenzofuranoic structure of the cyclized products (4b—d). They were in turn oxidized with 3-chloroperbenzoic acid to the corresponding sulphones (8b—d). In all cases correct elemental analyses and ^{1}H n.m.r. data consistent with the proposed structures have been obtained.

DISCUSSION

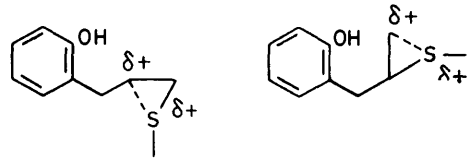
The reaction of the sulphonium salt (1a) with the 2-allylphenols (3) probably occurs with initial attack of the methylthiolating agent at the double bond of the allylic residue with formation of thiiranium ions (12). These ions may in principle undergo ring opening through intramolecular nucleophilic attack of the phenolic oxygen atom either at the internal carbon (Markownikov attack, path *a* in Scheme 3) to give (4) or at the terminal carbon (*anti*-Markownikov attack, path *b*) affording the dihydrobenzopyran derivatives (13). As a matter of fact the addition of sulphenic derivatives, particularly chlorides, to ethylenic double bonds occurs with formation of Markownikov and *anti*-Markownikov adducts.[9,20]

The exclusive formation of Markownikov products may be ascribed to the low nucleophilicity of phenolic oxygen,



SCHEME 3

which cannot open the thiiranium ring unless the attack is preceded by some weakening of one of the carbon–sulphur bonds. In other words the thiiranium ion ring opening should have S_N1 character and follow the Markownikov rule. Under this hypothesis a transition state similar to (14), which leads to dihydrobenzofuran



(14)

(15)

derivatives, is to be preferred to (15), which gives the dihydrobenzopyran heterocycle.

The electrophilic substitution that leads to (5) is prevented at low temperature. Under our reaction conditions only the position *para* to oxygen seems to undergo aromatic substitution: no substitution products were obtained from the 4-substituted phenols (3b—d), nor were bismethylthiolated products isolated from the unsubstituted phenol (3a).

The behaviour of the sulphonium ion (1) towards the 2-allylphenols (3) differs from that of iodonium nitrate: with the latter cyclization occurs only after aromatic halogenation at positions *ortho* or *para* to the hydroxy-group.[15]

Our results indicate that methyl(bismethylthio)sulphonium salts (1) are efficient reagents for the synthesis of 2,3-dihydrobenzofuranoic systems from 2-allylphenols *via* intramolecular ring closure. Whereas this cyclization is also possible with other reagents,[11-17] the nature of the sulphonium salts (1) may open new synthetic routes for several classes of cyclic compounds from precursors that fit into the general Scheme 1. Studies in this area are in progress.

EXPERIMENTAL

2-Allylphenol (3a), 3-chloroperbenzoic acid, and trimethyloxonium tetrafluoroborate were commercial products. Methyl(bismethylthio)sulphonium hexachloroantimonate (1a) [1] and 4-substituted 2-allylphenols (3b—d) [19] were prepared by literature methods.

^1H and ^{13}C N.m.r. spectra were recorded on a Bruker WP-60 instrument. Computer analyses of the spectra were accomplished with the Bruker ITRCAL program.

Reaction of Methyl(bismethylthio)sulphonium Hexachloroantimonate (1a) *with 2-Allylphenols* (3).—To the sulphonium salt (1a) in anhydrous dichloromethane the phenol (3) in the same solvent was added dropwise under stirring at the reported temperature. The reaction mixture was poured into water saturated with sodium carbonate and the inorganic insoluble material was filtered off. The organic layer was separated and the aqueous phase extracted three times with dichloromethane. The collected organic phases were washed with water to neutrality and dried ($CaCl_2$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel [eluant 1% (v/v) ether–light petroleum]. Reaction conditions and yields in cyclization products (4a—d) and cyclization–substitution product (5) are given in Table 3. Purification procedures are as follows: 2-(*methylthiomethyl*)-2,3-*dihydrobenzofuran* (4a), vacuum distillation (0.05 mmHg; b.p. 101—102 °C; 5-*methyl*-2-(*methylthiomethyl*)-2,3-*dihydrobenzofuran* (4b), vacuum distillation (0.05 mmHg, b.p. 88—90 °C); 5-*chloro*-2-(*methylthiomethyl*)-2,3-*dihydrobenzofuran* (4c), vacuum distillation (0.08 mmHg; b.p. 116—117 °C); 2-(*methylthiomethyl*)-5-*nitro*-2,3-*dihydrobenzofuran* (4d), chromatographed on silica gel [eluant 33% (v/v) ether–light petroleum] and recrystallized from methanol, m.p. 46—47 °C; 5-*methylthio*-2-(*methylthiomethyl*)-2,3-*dihydrobenzofuran* (5), bulb-to-bulb vacuum distillation (0.8 mmHg, oil-bath at 150 °C). Elemental analyses: (4a) (Found: C, 66.35; H, 6.5. $C_{10}H_{12}OS$ requires C, 66.6; H, 6.7%); (4b) (Found: C, 67.9; H, 6.9. $C_{11}H_{14}OS$ requires C, 68.0; H, 7.25%); (4c) (Found: C, 56.2; H, 4.95. $C_{10}H_{11}ClOS$ requires C, 56.2; H, 5.2%); (4d) (Found: C, 53.1; H, 5.0; N, 6.0; S, 13.9. $C_{10}H_{11}NO_3S$ requires C, 53.3; H, 4.9; N, 6.2; S, 14.25%); (5) (Found: C, 58.9; H, 6.25. $C_{11}H_{14}OS_2$ requires C, 58.4; H, 6.2%).

Oxidation of 2,3-*Dihydrobenzofurans* (4) *to Sulphones* (8).—To an ice-cooled solution of (4) in dichloromethane a 20% excess of 3-chloroperbenzoic acid in the same solvent was added dropwise with stirring. The solution was kept for 2 days at room temperature. 3-Chlorobenzoic acid precipitated partially and was filtered off. The filtrate was washed with sodium carbonate in water to neutrality and dried ($CaCl_2$), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluant ether) and the white crystals (75—95%) were recrystallized. M.p.s are as follows: 2-(*methylsulphonylmethyl*)-2,3-*dihydrobenzofuran* (8a), 114—115 °C (from methanol); 2-(*methylsulphonylmethyl*)-5-*methylthio*-2,3-*dihydrobenzofuran* (8b), 110—112 °C (from ether); 2-(*methylsulphonylmethyl*)-5-*chloro*-2,3-*dihydrobenzofuran* (8c), 131—132 °C (from tetrachloromethane); 2-(*methylsulphonylmethyl*)-5-*nitro*-2,3-*dihydrobenzofuran* (8d), 196—198 °C (from acetone). Elemental analyses: (8a) (Found: C, 56.5; H, 5.85; S, 15.0. $C_{10}H_{12}O_3S$ requires C, 56.6; H, 5.7; S, 15.1%); (8b) (Found: C, 57.5; H, 6.45; S, 13.9. $C_{11}H_{14}O_3S$ requires C, 58.4; H, 6.25; S, 14.15%); (8c) (Found: C, 48.55; H, 4.3; Cl, 14.15; S, 12.65. $C_{10}H_{11}ClO_3S$ requires C, 48.7; H, 4.55; Cl, 14.35; S, 13.0%); (8d) (Found: C, 46.6; H, 4.4; N, 5.35; S, 12.4. $C_{10}H_{11}NO_5S$ requires C, 46.7; H, 4.3; N, 5.45; S, 12.45%); $\nu_{max.}$ SO_2 stretchings: (8a) 1 300 and 1 195; (8b) 1 310 and 1 120; (8c) 1 295 and 1 130; (8d) 1 320 (br) and 1 110 cm^{-1}.

Oxidation of 2-(*Methylthiomethyl*)-2,3-*dihydrobenzofuran* (4a) *to the Sulphoxides* (6) *and* (7).—3-Chloroperbenzoic acid (1.7 g, 9.9 mmol) was added at 0 °C to a stirred solution of (4a) (1.6 g, 9 mmol) in dichloromethane (80 ml). The reaction was kept for 18 h at room temperature. The same procedure as described for the synthesis of sulphones afforded almost equimolar amounts of the diastereoisomeric sulphoxides (6) and (7), which were separated by low pressure chromatography (230 mesh silica gel, eluant ether) and recrystallized from n-hexane. 2-*Methylsulphonylmethyl*-2,3-*dihydrobenzofuran* (6) had m.p. 101—103 °C; the *diastereoisomer* (7) had m.p. 53—54 °C. Elemental analyses: (6) (Found: C, 61.2; H, 6.2; S, 16.45%); (7) (Found: C, 58.4; H, 6.2; S, 16.2. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.15; S, 16.3%).

Reductive Desulphurization of 2-(*Methylthiomethyl*)-2,3-*dihydrobenzofuran* (4a) *with Raney Nickel*.[21]—The thioether

(4a) (0.86 g, 4.8 mmol) in absolute ethanol (50 ml) was slowly added at room temperature to a stirred suspension in the same solvent (9 ml) of Raney nickel. The latter was filtered off after 4 h and washed with dichloromethane. Solvents were removed at reduced pressure. Chromatography of the residue on silica gel [eluant 6% (v/v) ether–light petroleum] gave 2-*methyl*-2,3-*dihydrobenzofuran* (9) (0.09 g, 15%) and 2-(1-*propyl*)*phenol* (10) (0.18 g, 30%) which were identified through comparison with authentic samples.[22]

Reaction of 2-(*Methylthiomethyl*)-2,3-*dihydrobenzofuran* (4a) *with Trimethyloxonium Tetrafluoroborate.*—Trimethyloxonium tetrafluoroborate (0.8 g, 5.5 mmol) was added at room temperature to (4a) (1 g, 5.5 mmol) in dichloromethane (50 ml). The solution was stirred for 18 h and the solvent removed at low pressure. *Dimethyl*[2-(2,3-*dihydrobenzofuranyl*)]*methylsulphonium tetrafluoroborate* (11) (1.55 g, quantitative) was obtained as a pale pink oil. The oil was treated with n-pentane, the latter was decanted, and the residue was kept under vacuum. ^{1}H N.m.r. parameters of (11) are reported in Table 2.

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