

Terpenoid Ether Formation in Superacids

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A number of terpenoid bicyclic ethers have been prepared by cyclisation of suitable precursors in fluorosulphuric acid–sulphur dioxide. The products are formed under a mixture of thermodynamic and kinetic control, and five-, and six-, and seven-membered-ring ethers are obtained. Both primary and secondary alcohols have been cyclised by attack of the hydroxy group on carbocation centres generated by protonation of alkenes or ionisation of tertiary alcohols; tertiary alcohols ionise too readily to provide an ethereal oxygen atom. Reaction of the unsaturated secondary alcohol dihydrocarveol (**2**) with antimony pentafluoride in sulphur dioxide gives the ether by a reaction which may not involve a carbocation, and hence may be suitable for ether formation from substrates which rearrange readily in acids.

One of the earliest uses of fluorosulphuric acid as a reagent was in the cyclisation of ψ -ionone to a mixture of α -ionone and β -ionone.¹ This and similar carbocyclisations result from suppression of both elimination reactions and reactions with external nucleophiles, favouring capture of the carbocation by an internal double bond.² Alternatively, a hydroxy group can act as the internal nucleophile, giving rise to ethers; the work of Banthorpe, Boullier, and Fordham on geraniol³ and on citronellol⁴ provides examples of cyclisation reactions of this type. To date, formation of bicyclic ethers from monocyclic terpenes has been neglected, even though they are difficult to synthesise in good yield, and are best known for a few naturally occurring examples such as 1,8-cineole and 1,4-cineole.

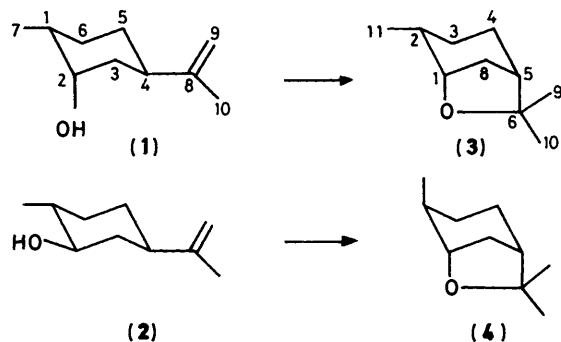
The starting point for this investigation was the report⁵ that the 1,6-dihydrocarveols (**1**) and (**2**) can be cyclised in aqueous sulphuric acid to the 2,6,6-trimethyl-7-oxabicyclo[3.2.1]octanes (**3**) and (**4**) though these were not isolated. We reduced dihydro-

the oxonium ions derived from (**3**) and (**4**), these being formed within the time required to run the spectrum (approximately 1 h). Details of the spectra are given in the Table. On quenching the reaction mixture in a potassium carbonate–methanol slurry at -78°C , a red oil was obtained which was distilled to give a mixture of equal amounts of two products in an overall yield of 50%.

The two stereoisomers were separated by preparative gas liquid chromatography and their spectra analysed. Where the 2-methyl is equatorial (**3**) the ^1H n.m.r. spectrum displays a quartet at δ 4.03 for the 1-H. The quartet arises because of axial–equatorial coupling of 1-H with 2-H and 8a-H. Where the 2-methyl is axial (**4**) 1-H couples only with 8a-H and appears as a doublet δ 3.94 in the ^1H spectrum. The 2-methyl is affected more by the lanthanide shift reagent when equatorial as would be expected; oxygen is the site of binding of the lanthanide ion and the 2-methyl is closest to this when in the equatorial position.

Formation of (**4**) from (**2**) requires only a ring flip to put the isopropenyl and hydroxy groups axial, after which the carbocation centre formed by protonation of the double bond is attacked by the nucleophilic oxygen to yield (**4**). Formation of (**3**) from (**1**) is a more complex reaction; the side chain can become axial only by protonation, migration of the carbocation from C-7 to C-4, rotation of the isopropenyl group, and return of the carbocation to C-7. In superacids, the long life of the carbocation makes such a sequence reasonable.

We attempted to convert the mixture of (**1**) and (**2**) described earlier into the 1-isopropyl-4-methylcyclohexenyl cation by addition of SbF_5 in SO_2ClF at -78°C , since this reagent should dehydrate the alcohol without protonating the double bond.⁶ Surprisingly, the solution revealed the oxonium ion derived from (**4**). Since antimony pentafluoride is a strong Lewis acid, it probably first accepts an oxygen lone pair of electrons; interaction with the double bond then gives rise to ether. Since the reaction probably does not involve formation of a carbocation, it is a potentially useful method of forming ethers



carvone with LiAlH_4 to give a 1 : 1 mixture of the dihydrocarveols. This was difficult to separate, so the mixture, dissolved in SO_2 , was added to an excess of FSO_3H in SO_2 at -78°C . The ^{13}C n.m.r. spectrum of the solution was consistent with a mixture of

Table. ^{13}C N.m.r. chemical shifts from Me_4Si

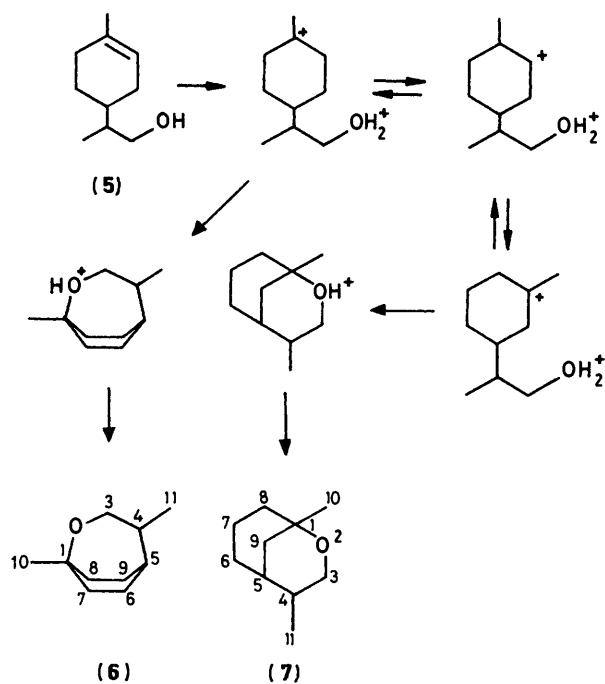
Substrate	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
(3)	$\text{FSO}_3\text{H}-\text{SO}_2$	97	38	25	32	43	110	—	36	28*	21*	19
(4)	$\text{FSO}_3\text{H}-\text{SO}_2$	98	29	24	23	42	109	—	27	27*	22*	17
(6)	CDCl_3	82	—	70	37	33	24	41	38	22	31	15
(7)	CDCl_3	70	—	66	34	33	32	33	39	18	29	18
(14)	$\text{FSO}_3\text{H}-\text{SO}_2$	250	141	211	51	22	42	35	33	21	21	—
(15)	$\text{FSO}_3\text{H}-\text{SO}_2$	104	30*	28*	99	28*	30*	—	26	22	22	34

* Assignments could be interchanged.

when the substrate is expected to rearrange readily. Clearly, the reaction of (1) to form (3) requires formation of a carbocation in order to permit the isomerisation necessary for cyclisation, so that (3) is not formed. The reaction yields polymer rather than the cyclohexenyl carbocation.

Both ethers have tetrahydrofuran rings, and are stable in fluorosulphuric acid at -78°C ; large rings may be expected to be less stable, so we tried to make a seven-membered-ring ether by cyclisation of *p*-menth-1-en-9-ol (5). The substrate was extracted from solutions in CS_2 into $\text{FSO}_3\text{H}-\text{SO}_2$, and at -50°C showed the presence of two ethers, revealed by ^{13}C n.m.r. peaks at δ 104 and 101 p.p.m. (both singlets) and at δ 82 and 76 p.p.m. (both triplets), together with some unchanged alcohol. The mixture was quenched to yield an oil containing two ethers which were purified by preparative g.l.c., and identified as 1,4-dimethyl-2-oxabicyclo[3.2.2]nonane (6) and 1,4-dimethyl-2-oxabicyclo[3.3.1]nonane (7). The ^{13}C n.m.r. spectra of the ethers are given in the Table.

A suggested reaction mechanism for their formation is given in the Scheme. Formation of (6) from (5) is straightforward, but



Scheme.

formation of (7) involves a methyl shift. The driving force in this reaction is presumably contraction of the seven-membered ring to six-membered, but it is not clear why it involves a methyl shift rather than cyclisation to a secondary carbocation, nor why the reaction does not involve a further shift to form a five-membered-ring ether.

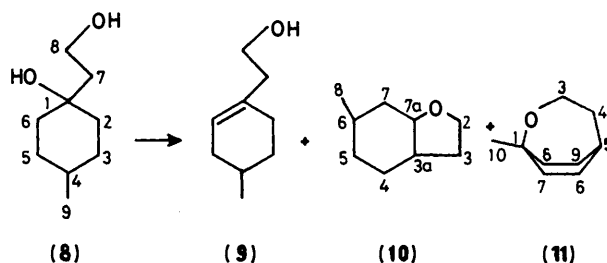
The ^1H n.m.r. spectrum of 1,4-dimethyl-2-oxabicyclo[3.3.1]nonane (7) shows the two ether protons at δ 3.63 (dd, 11.5 and 6.6 Hz), and 3.22 (t, J 11.5 Hz). The two methyl groups have peaks at δ 1.03 (s) and 0.8 (d, 5.8 Hz). The deshielded ether proton is equatorial. Two possible conformations fit this result, the chair-chair conformation, and the chair-boat, with the ether function forming part of the boat.

In each conformation, the two methyl groups are equatorial and hence 1,3-interaction is reduced. Also, the methyl at C-4 bisects the C-3, 3a-H, 3e-H angle, and thus deducing which of the two protons is deshielded by virtue of 1,2-*trans*-diaxial methyl interaction is difficult. However, in the chair-chair conformation, 3a-H is deshielded by the C-5-C-6 and C-1-C-8

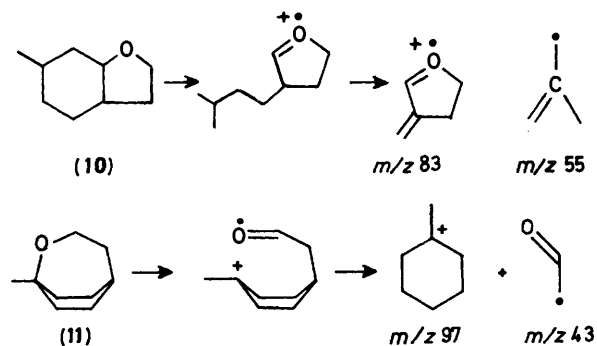
bonds, and thus should be at lower field than it is. Therefore the chair-boat conformation is more likely.

The less volatile component of the quench of menth-1-en-9-ol (5), 1,4-dimethyl-2-oxabicyclo[3.2.2]nonane (6), possesses a multiplet at δ 3.86 for the two ether protons. No small couplings are observed which rules out a structure in which 4-H bisects the C-3, 3a-H, 3e-H angle. Instead, a conformation is favoured in which the 3a-H proton is *trans* to the 4-H proton.

Since formation of (7) was unexpected, we wished to generate the carbocation at a different point in the substrate to see how far our reactions are kinetic or thermodynamically controlled. We therefore prepared the closely related substrate (8), and dissolved it in $\text{FSO}_3\text{H}-\text{SO}_2$ at -70°C . Reaction did not occur until the temperature was raised to -30°C . On quenching the solution a mixture of two ethers and an unsaturated alcohol was obtained.



Since ether yields were low, the products were identified by g.c.-m.s. Studies of a number of bicyclic ethers⁷ showed that those with a substituent on the carbon atom next to the oxygen underwent α -cleavage, while ethers which did not have such a substituent underwent *ipso*-cleavage.

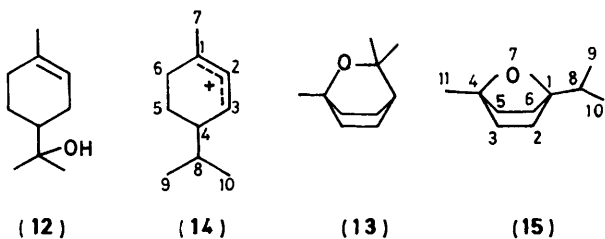


The mass spectra of (10) and (11) fitted these patterns. We conclude that (10) is 6-methylperhydrobenzofuran, and that (11) is 1-methyl-2-oxabicyclo[3.2.2]nonane.

Clearly, when (8) reacts with superacids the carbocation centre tends to remain at C-1. Some migration to C-2 yields the perhydrobenzofuran, and a small amount of further migration yields another bicyclic ether. Comparison with the products of cyclisation of (5) indicates that our ethers are formed to some extent under kinetic control. Since rearrangements of the ions are usually fast, capture of the ion by intramolecular hydroxy must proceed fairly slowly and selectively, favouring formation of the five-membered-ring ethers.

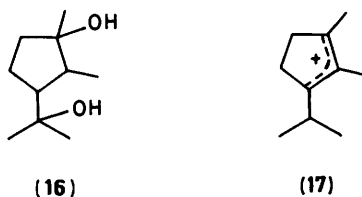
Since we have been able to prepare both the 2-oxabicyclo[3.2.2]nonanes (6) and (11) in superacids, we attempted to cyclise α -terpineol (12) to 1,8-cineole (1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane) (13). The reaction failed giving only the cycloalkenyl cation (14).

However, when (13) is dissolved in FSO_3-SO_2 at -70°C , the ^{13}C n.m.r. spectrum shows the presence of the ion (14), plus another substance whose spectrum is consistent with that of 1,4-



cineole (1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane) (15), which probably arises from cleavage of (13), followed by cyclisation of the rearranged hydroxy carbocation. We have been unable to confirm the identification by independent synthesis.

In a further attempt to cyclise a tertiary alcohol, we prepared¹⁰ iridanediol (16) which could give a bridged tetrahydrofuran; only the ion (17) was obtained.



We conclude that terpenoid ethers can be formed in superacids from either primary or secondary alcohols interacting with a carbocation centre. Products from kinetic and thermodynamic control of the reaction are obtained. The yields are good in favourable circumstances, and permit the preparation of ethers which are difficult of access by conventional routes.

Experimental

¹H N.m.r. spectra were recorded on a Perkin-Elmer R34 (220 MHz) spectrometer using CDCl₃ as solvent and SiMe₄ as internal standard. Decoupling experiments were carried out on a Bruker WM250 (250 MHz) spectrometer operating in the F.T. mode. ¹³C N.m.r. spectra were recorded on a Varian XL 100 (25.2 MHz) spectrometer with CDCl₃ as solvent and SiMe₄ as internal standard for neutral solutions, and sulphur dioxide or sulphuryl chloride fluoride as solvent for superacidic solution with an external deuterium lock of [²H₆]acetone or [²H₄]methanol and external standard of SiMe₄ enclosed within a 5 mm n.m.r. tube. I.r. spectra were recorded on a Perkin-Elmer 1320 i.r. spectrometer using either liquid films or Nujol mulls. Mass spectra were recorded on an A.E.I. MS 12 spectrometer. Accurate mass and g.l.c.-mass spectral analyses were recorded on a VG 7070E mass spectrometer.

Reaction mixtures were analysed by Perkin-Elmer F17 and Dani 3800 gas liquid chromatographs with flame ionisation detectors using N₂ as carrier gas. The F17 employed a 5 ft stainless steel column of 2 mm i.d. with 10% OV351 on Celite as support material. The 3800 employed a 25 m capillary column of 0.3 mm i.d., coated with OV351.

Preparative separations were carried out on a Perkin-Elmer F21 instrument using a 10 ft glass column of 3 mm i.d. containing Celite 60–80 mesh as support, and 20% Aeoplex 100 as coating.

Dihydrocarveols (4-Isopropenyl-1-methylcyclohexan-2-ol).—Dihydrocarvone (4-isopropenyl-1-methylcyclohexan-2-one) was reduced in the usual way with LiAlH₄. Integration of the n.m.r. spectrum showed the product to be 53% axial alcohol and 47% equatorial alcohol; δ (220 MHz; CDCl₃, Me₄Si) 0.93 and 0.98 (3 H, both d, MeCH), 1.69 (3 H, s, Me-vinyl), 2.25 (1 H, t, CH-vinyl), 1.16 (0.53 H, m, CHOH-eq), 3.87 (0.47 H, br s,

CHOH-ax), 4.67 (2 H, s, =CH₂); ν_{max.} 3 320br, 3 060, 2 900, 1 640, 1 450, and 885 cm⁻¹.

Quench of Dihydrocarveols.—The mixture of dihydrocarveols (10 g) was treated with FSO₃H–SO₂ and quenched using the standard method described later. Distillation of the product at 62–64 °C at 20 Torr gave a colourless oil (5 g) which was shown by g.l.c. to be a mixture of two products in approximately equal amounts. The two components were separated by preparative g.l.c.

2α,6,6-Trimethyl-7-oxabicyclo[3.2.1]octane (4). *m/z* 154; δ (220 MHz; CDCl₃, Me₄Si) 0.82 (3 H, d, *J* 6 Hz, Me-*exo*), 1.17 (3 H, s, Me-*gem*), 1.33 (3 H, s, Me-*gem*), 1.3–1.6 (5 H, br m 3-, 4-, and 5-H), 1.7 (1 H, m, HCH-ax-CO), 1.8 (1 H, m, HCH-eq-CO), 2.34 (1 H, m, MeCH), and 3.94 (1 H, d, *J* 7 Hz, OCH); the ¹³C n.m.r. spectrum is given in the Table; ν_{max.} 2 900, 1 460, 1 130, and 995 cm⁻¹.

2β,6,6-Trimethyl-7-oxabicyclo[3.2.1]octane (3). *m/z* 154; δ (220 MHz; CDCl₃, Me₄Si) 0.87 (3 H, d, *J* 8 Hz, Me-*endo*), 1.17 (3 H, s, Me-*gem*), 1.38 (3 H, s, Me-*gem*), 1.6–2.1 (8 H, set of broad multiplets, 3-, 4-, 5-, and 8-H), and 4.03 (1 H, q, *J* 4 Hz, –O–CH); the ¹³C n.m.r. spectrum is given in the Table; ν_{max.} 2 900, 1 460, 1 130, and 995 cm⁻¹.

p-Menth-1-en-9-ol [2-(4-Methylcyclohex-3-en-1-yl)propan-1-ol] (5).—In a 500 ml flask were placed diglyme (80 ml), 2-methylbut-2-ene (23.1 g, 0.33 mol), and sodium borohydride (4.7 g, 0.125 mol). The flask was ice-cooled and boron trifluoride diethyl etherate (23.5 g, 0.16 mol) was slowly added over 0.5 h to give a semi-solid mixture containing 0.165 mol disiamylborane which was left at 0 °C for 15 h. Limonene (20.4 g, 0.15 mol) was then added and the mixture stirred for 3 h before addition of NaOH (3M; 50 ml) followed by H₂O₂ (30%; 50 ml). The mixture was then extracted with ether, and concentrated *in vacuo*. Distillation gave the alcohol (15 g), b.p. 120 °C at 15 Torr (lit.,⁸ 115–116 °C at 10 Torr); *m/z* 154; δ (200 MHz; CDCl₃, Me₄Si) 0.85 (3 H, d, Me), 1.6 (3 H, s, Me), 1.2–2.0 (8 H, m, CH and CH₂), 3.65 (1 H, q, CH¹OH), 3.87 (1 H, q, CH²OH), and 5.35 (1 H, br s, =CH); ν_{max.} 3 300, 2 900, 1 430, 1 050, and 800 cm⁻¹.

Quench of *p*-Menth-1-en-9-ol [2-(4-Methylcyclohex-3-en-1-yl)propan-1-ol] (5).—This was quenched from FSO₃H solution, as described below. G.l.c. showed the presence of two ethers in the remaining oil (21% and 33.5% of oil). These were separated by preparative g.l.c. to give the separate ethers identified as 1,4-dimethyl-2-oxabicyclo[3.2.2]nonane (6) (33.5%) and 1,4-dimethyl-2-oxabicyclo[3.3.1]nonane (7) (21%). Compound (6) had *m/z* 154 (*M*⁺, 7%), 139 (3), 111 (100), 81 (10), 69 (12), and 43 (50); ν_{max.} 2 950, 1 450, 1 350, 1 080, 1 050, and 1 010 cm⁻¹. Compound (7) had *m/z* 154 (*M*⁺, 16%), 139 (4), 125 (12), 111 (100), 97 (12), 83 (10), 69 (18), 55 (20), and 43 (41); ν_{max.} 2 950, 1 440, 1 070, and 1 050 cm⁻¹. The ¹³C n.m.r. spectra of (6) and (7) are given in the Table; the ¹H n.m.r. spectra have already been discussed.

Ethyl (1-Hydroxy-4-methylcyclohexyl)acetate. This preparation was carried out by a Reformatsky-type reaction.⁹ A portion (50 ml) of a mixture of cyclohexanone (17.7 g, 0.15 mol), benzene (120 ml), toluene (100 ml), and ethyl bromoacetate (26.5 g, 0.158 mol) was added to zinc powder (10.3 g, 0.157 mol) in a 500 ml flask. The contents were heated to 100 °C whereupon a vigorous reaction set in. The rest of the mixture was added at a rate sufficient to maintain reflux. After addition, the solution was refluxed for a further 2 h. After cooling, the solution was acidified with dilute H₂SO₄ and the organic layer was separated, dried, and concentrated. Work-up gave an oil which was distilled to give the ester (17.8 g, 56%), b.p. 86–90 °C at 0.8 Torr; *m/z* 200; δ (220 MHz; CDCl₃, Me₄Si) 0.85 (3 H, d, Me), 1.22 (3 H, t, Me), 1.3–1.7 (9 H, CH₂ ring and CH), 2.38 [2

H, s, $\text{CH}_2\text{CO}_2\text{Et}$ (*cis*), 2.52 [0.5 H, s, $\text{CH}_2\text{CO}_2\text{Et}$ (*trans*)], 3.38 (1 H, s, OH), and 4.15 (2 H, q, CH_2Me); ν_{max} . 3 500, 2 900, 2 840, 1 700, 1 360, 1 300, 1 180, 1 020, 1 000, and 920 cm^{-1} .

1-(2-Hydroxyethyl)-4-methylcyclohexanol (**8**). Ethyl (1-hydroxy-4-methylcyclohexyl)acetate (10 g, 0.05 mol) was reduced by LiAlH_4 (2.5 g, 0.066 mol) in the usual manner. Work-up gave an oil (7.5 g) which solidified on standing and was recrystallised from hexane, m.p. 60–65 °C (Found: C, 68.2; H, 11.5. $\text{C}_9\text{H}_{18}\text{O}_2$ requires C, 68.3; H, 11.4%); m/z 158; δ (220 MHz; CDCl_3 , Me_4Si) 0.9 (3 H, d, Me), 1.67 (2 H, t, CH_2COH), 1.27 (4 H, m, CH_2), 1.5 (2 H, m, CH_2), 1.75 (2 H, m, CH_2), 3.25 (2 H, br s, OH), 3.85 (2 H, t, CH_2OH), and 1.5–1.8 (1 H, br m, CH); ν_{max} . 3 350, 2 900, 2 840, 1 450, 1 050, 1 020, and 880 cm^{-1} .

Quench of 1-(2-Hydroxyethyl)-4-methylcyclohexanol.—G.l.c. of the quenched oil (3.5 g) showed the presence of two ethers (20% of the mixture). These were identified as 6-methylperhydrobenzofuran (**10**) (8% of mixture) and 1-methyl-2-oxabicyclo[3.2.2]nonane (**11**) (12% of mixture). Compound (**10**) had m/z 140 (M^+ , 10%), 122 (8), 97 (8), 95 (10), 94 (9), 93 (8), 84 (8), 83 (10), 81 (8), 70 (12), 69 (15), 68 (9), 67 (8), 55 (25), and 41 (23). Compound (**11**) had m/z 140 (M^+ , 7%), 125 (1), 98 (7), 97 (100), 55 (11), 43 (26), and 41 (11).

Iridanediol [3-(2-Hydroxypropan-2-yl)-1,2-dimethylcyclopentan-1-ol] (**16**).—Mercuric acetate (63.8 g, 0.2 mol) was dissolved in distilled water (150 ml) in a 1 l flask. Acetic acid (75%; 200 ml) was rapidly run in and after stirring for 15 min, linalool (15.4 g, 0.1 mol) was added and stirred for 1 h. Addition of NaOH (3M; 200 ml) was followed by NaBH_4 (3.8 g, 0.1 mol) in NaOH (3M; 100 ml). After stirring for 12 h the organic phase was separated and the aqueous phase extracted with ether. The organic extracts were combined, dried, and concentrated. Distillation of the remaining oil gave the title compound (**16**) (7 g), b.p. 97 °C at 1 Torr (lit.,¹⁰ 110 °C at 5 Torr); ν_{max} . 3 400, 2 950, 1 380, 1 160, and 930 cm^{-1} .

Generation and Study of Carbocations.—Sulphur dioxide (1 ml) was condensed in a 10 ml round-bottomed flask and FSO_3H (2 ml) added. The solution was cooled to –78 °C and the substrate (250–500 mg) in SO_2 (1 ml) at –78 °C was added dropwise with stirring. This was placed in a 12 mm bore n.m.r. tube cooled in cardice–acetone. An external lock of

$[^2\text{H}_6]$ acetone or $[^2\text{H}_4]$ methanol in a sealed 5 mm tube held in place by two guides was added, and the 12 mm tube stoppered, wiped, and placed in the Varian X-L 100 spectrometer. The tube was cooled in a stream of nitrogen passed through a cooling coil immersed in liquid nitrogen. The temperature of the probe was controlled using a heating coil in the nitrogen stream. The tube was spun at 14 r.p.s. A sweep width of 10 000 Hz was used in conjunction with an acquisition time of 0.4 s.

For substrates which polymerised rapidly, the substrate was dissolved in 2 ml carbon disulphide before cooling to –70 °C and adding to the acid– SO_2 solution.

Quenching of Acid–Substrate Solutions.—Solutions were prepared as before but on a larger scale [substrate (3 g) to FSO_3H (10 ml)]. After stirring for 2 h at the required temperature, the solution was transferred to a cooled, jacketed dropping funnel and added slowly to a rapidly stirred, cooled slurry of potassium carbonate (20 g) in methanol (200 ml). If CS_2 was used as co-solvent this could be withheld from the slurry as it separated out as the upper layer on standing in the dropping funnel. After the addition of water the slurry was carefully warmed to room temperature. Further potassium carbonate was added to ensure basicity before ether extraction. After drying, the solvent was removed either under reduced pressure or by fractional distillation if a volatile product was expected.

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