Citronellal Cyclisation in Superacids

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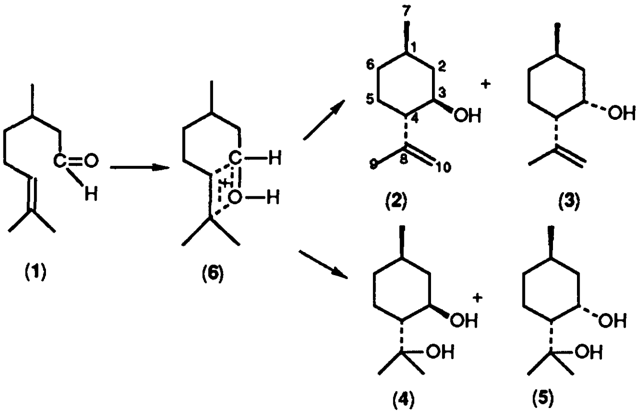
The cyclisation of citronellal in superacids parallels closely the reaction in 'normal' acids, yielding isopulegol and neoisopulegol. Each alcohol then undergoes protonation at the double bond; neoisopulegol loses water to give 2-(4-methylcyclohex-1-en-1-yl)prop-2-yl cation, but in isopulegol this process is stereochemically unfavourable, and competes with a 1,5-hydride shift to yield the 1-methyl-4-isopropyl cyclohexenyl cation. Hydroxycitronellal yields only the 2-(4-methylcyclohex-1-en-1-yl)prop-2-yl cation by an unknown route.

The cyclisation of citronellal (**1**) (3,7-dimethyloct-6-enal) by aqueous sulphuric acid[1] yields isopulegol (**2**) (*p*-menth-8-en-3-ol) together with neoisopulegol (**3**), menthoglycol (**4**), and neomenthoglycol (**5**). A kinetic study[2] is consistent with the hypothesis that the reaction is an intramolecular Prins reaction[3] in which the transition state is probably similar to (**6**).



The reaction is of commercial importance in the synthesis of menthol.[4] It has been found to be catalysed by a number of acidic and heterogeneous catalysts,[5] all of which yield mixtures of isopulegol and neoisopulegol in varying proportions. Catalysis of the reaction by a homogeneous rhodium catalyst[6] yields 75% of neoisopulegol; catalysis by $SbCl_5$ yields 57% of this isomer.[5] In all other cases, isopulegol is the main product.

We have found[7] that many reactions of difunctional molecules follow different pathways in superacids (fluorosulphuric acid or fluorosulphuric acid/antimony pentafluoride mixtures) from reactions of the same material in dilute acids. We therefore studied the reactions of citronellal and related compounds in FSO_3H/SO_2.

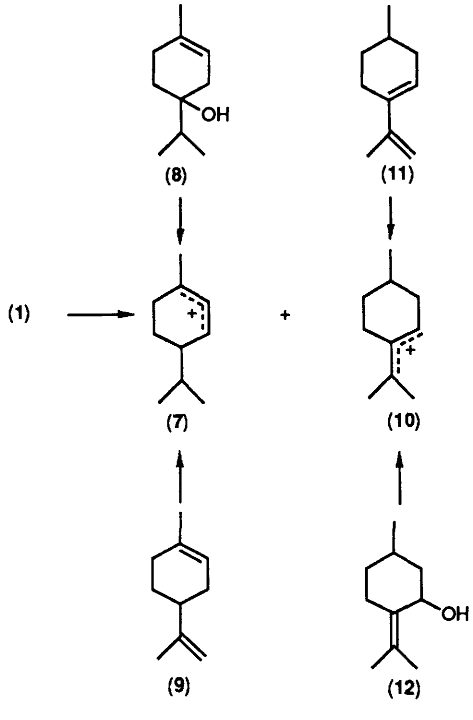
Results and Discussion

Citronellal (**1**) in SO_2 was added to a solution of FSO_3H/SO_2 at −78 °C. The molar ratio of acid to substrate was 7:1. The ^{13}C NMR spectrum of the solution, recorded at −80 °C, showed the presence of two alkenyl cations, described in the Table, with little evidence of polymerisation. The minor ion occurred to 25%, and was shown to be the 1-methyl-4-isopropylcyclohexenyl cation (**7**). As confirmation, this ion was also obtained from 4-terpineol (**8**) and from limonene (**9**) under similar conditions.

Table. ^{13}C NMR chemical shifts (in ppm relative to $SiMe_4$) in FSO_3H/SO_2 at −80 °C.

Ion	(7)	(10)
(1)	211	27
(2)	141	45
(3)	251	202
(4)	42	152
(5)	22	29
(6)	36	26
(7)	33	21
(8)	23	248
(9)	21	32
(10)	21	34

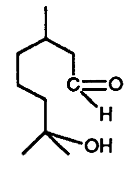
The major ion was shown to be the 2-(4-methylcyclohex-1-en-1-yl)prop-2-yl cation (**10**). Its structure was confirmed by preparing it from *p*-mentha-3,8-diene (**11**) and from pulegol (**12**) under similar conditions.



When the solution of the ions in FSO_3H/SO_2 was warmed to −40 °C, the endocyclic ion (**7**) disappeared, leaving only the exocyclic ion (**10**). On re-cooling the solution to −80 °C the ion (**7**) was not regenerated; the ions are clearly not in equilibrium.

Formation of two ions was unexpected; a possible explanation is direct reaction of citronellal competing with reaction *via* isopulegol (**2**). In order to test this, isopulegol was treated with FSO_3H/SO_2 at −78 °C. It yielded a mixture of the two ions, (**7**) and (**10**) in approximately equal proportions.

Hydroxycitronellal (**13**; 7-hydroxy-3,7-dimethyloctanal) was treated under similar conditions, and only ion (**10**) was obtained.



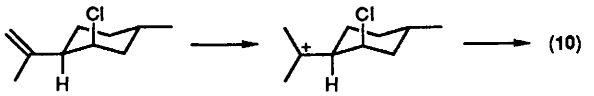
(**13**)

The problem of the routes from (**1**) and (**2**) to (**7**) and (**10**) was further studied by repeating each of the three previous experiments using the deuteriated reagent, FSO_3D/SO_2. In all three cases we obtained the same ion or ions as previously in similar amounts, however, all the ions were deuteriated. When formed from citronellal, ion (**10**) is found to be deuteriated at the dimethyl group, C-9 and C-10, to *ca.* 50%. Ion (**7**) incorporated considerably more deuterium; C-9 and C-10 were fully deuteriated, C-6 was almost fully deuteriated and C-7 only slightly less so. The methyl groups at C-4 and C-8 are partially deuteriated. Isopulegol and hydroxycitronellal give ions with a similar pattern of deuteriation.

Since the ions are formed in similar quantities with the use of FSO_3H and FSO_3D, the mechanism of formation must not involve competing reactions following from reversible protonation on the carbonyl group and irreversible protonation on the double bond. We considered first the reaction of isopulegol, since it is known that in superacids a cyclopropane ring, which is less reactive than a double bond,[7] reacts at a higher rate than a secondary hydroxyl group,[8] which yields an hydroxy carbocation.[9]

To check the view that the first step of the reaction is the protonation of the double bond, we treated isopulegol with SbF_5 in SO_2ClF, a reagent known to form carbocations from alcohols but which is unable to protonate at a double bond. This reaction differed from that described earlier as it yields only polymer.

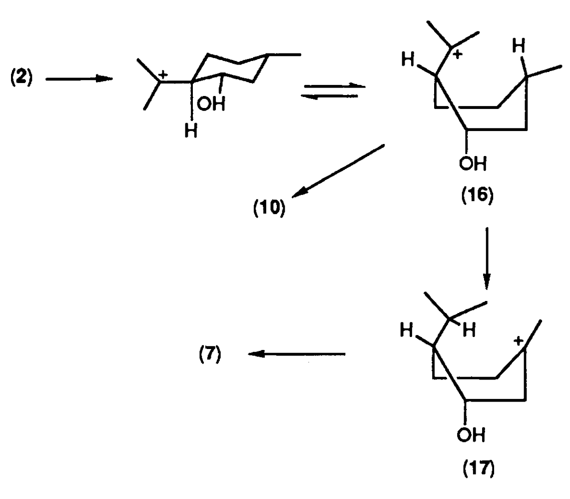
After protonation of the isopulegol double bond, the next step is probably loss of water, and this is probably dependent upon the orientation of the hydroxyl group. Pure neoisopulegol is difficult to obtain, but we converted isopulegol into neoisopulegyl chloride (**14**) stereospecifically. This also reacted with SbF_5 in SO_2ClF to give polymer, but with FSO_3H in SO_2 gave only the exocyclic ion, (**10**).



(**14**) (**15**)

Ion (**15**) can readily lose HCl to give (**10**). If, however, we consider isopulegyl derivatives, where the substituent on C-3 is equatorial, the ion must flip into a boat form (**16**) in order that elimination may take place. When this happens, we have competition between elimination to yield the ion (**10**), and a 1,5-hydride shift to the ion (**17**), from which water is eliminated to yield (**7**).

Ions (**16**) and (**17**) can both exchange deuterium with solvent, and (**16**) has a long lifetime, which leads to the extensive labelling of (**7**) reported here. It is thus proposed, that neoisopulegol leads exclusively to (**10**) while isopulegol leads to equal amounts of (**10**) and (**7**).



The mixture of ions obtained from citronellal suggests that cyclisation of this substance with FSO_3H/SO_2 results initially in the formation of a mixture of equal parts of isopulegol and neoisopulegol, which ionise as outlined above. The ratio of iso- to neoiso-pulegol is sensitive to cyclisation conditions,[5] but since the product is not stable under the present reaction conditions we cannot check this hypothesis.

Although hydroxycitronellal (**13**) yields (**10**) in FSO_3H/SO_2 at −78 °C, the reaction mechanism must be different. The reaction gives a single ion, so must not, therefore, proceed *via* citronellal or isopulegol. The work of Olah[10] on the reaction of unsaturated aldehydes in FSO_3H/SO_2 shows that cyclisation is a favourable reaction when a 5-membered ring is formed.

Cyclisaton of the ion from (**13**) would yield an 8-membered ring ion which is not observed. Any mechanisms proposed for this reaction must be totally speculative.

The reaction of citronellal (**1**) with FSO_3H/SO_2 is thus very similar to its reaction with dilute acid. Ionisation of the product mixture involves the unusual 1,5-hydride shift from (**16**) to (**17**) when elimination of water is stereochemically unfavoured. The hydroxy group cannot be converted to an ether group by reaction with the carbocation, since 4-membered ring ethers are unstable under superacid conditions.[11]

Experimental

^1H NMR spectra were recorded on a Perkin-Elmer R34 (220 MHz) spectrometer using $CDCl_3$ as solvent and $SiMe_4$ as internal standard, on a Varian XL 100 (25.2 MHz) spectrometer with $CDCl_3$ and $SiMe_4$ as internal standard for neutral solutions and sulphur dioxide or sulphuryl chloride fluoride as solvent for superacid solution with an external deuterium lock of [$^2H_6$]acetone or [$^2H_4$]methanol and $SiMe_4$ as external standard enclosed within an NMR tube (5 mm). IR spectra were recorded on a Perkin-Elmer 1320 spectrometer using either liquid films or Nujol mulls. GLC analyses were carried out on a Perkin-Elmer F17 gas–liquid chromatograph, using a stainless steel column (1.5 m) (i.d. 2 mm) with 10% OV 351 on Celite (60–80 mesh) as support material.

Citronellal, Hydroxycitronellal, Limonene, 4-*Terpineol, iso-Pulegol, and Pulegol.*—Were all commercial samples, whose purity was checked by GLC and enhanced by distillation under reduced pressure if required.

Neoisopulegyl Chloride.—Triphenylphosphine (24 g) in tetrahydrofuran (THF) (50 cm^3) was added to *N*-chlorosuccinimide (13 g) in THF (200 cm^3) cooled in an ice–salt bath. Isopulegol (12.5 g) in THF (50 cm^3) was slowly added to the cooled slurry, then stirred for 4 h. The solvent was removed under vacuum and the product extracted with pentane, the solution dried, and the pentane removed. Distillation of the resulting oil gave neoisopulegyl chloride (12 g, 85%) b.p. 54 °C at 0.3 Torr; *m/z* 174 and 172; δ 0.85 (3 H, d, *J* 7 Hz, CH_3), 1.4 (1 H, t, *J* 13 Hz, $CHPr^i$), 1.74 (3 H, s, CH_3-vinyl), 1.6–2.2 (7 H, br m ring CH_3), 4.5 (1 H, br s CHCl), and 4.7 and 4.85 (2 H, both s, $=CH_2$); $\nu_{max}(cm^{-1})$ 3 080, 2 910, 1 640, 1 445, 890, and 685.

Generation and Study of Carbocations.—Sulphur dioxide (1 cm^3) was condensed in a round-bottomed flask (10 cm^3) and FSO_3H (2 cm^3) was added. The solution was cooled to -78 °C and the substrate (250–500 mg) in SO_3 (1 cm^3) at -78 °C was added dropwise with stirring. This was placed in an NMR tube (i.d. 12 mm), and cooled in Cardice–acetone. An external lock of $[^2H_6]$acetone or $[^2H_4]$methanol in a sealed 5 mm tube held in place by two guides was added, and the 12 mm tube was stoppered with Parafilm, 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 *ca.* 14 rps. A sweep width of 10 000 Hz was used in conjunction with an acquisition time of 0.4 s.

For substrates which polymerise rapidly, the substrate was dissolved in carbon disulphide (2 cm^3) prior to cooling it to -70 °C and the addition to the FSO_3H/SO_2 solution.

Study of Carbocations in Deuteriated Acid.—The solutions were prepared in the same way as above, except that FSO_3H was replaced by FSO_3D. The ^{13}C NMR spectrum showed some peaks to be reduced in intensity, due to the attachment of deuterium to a carbon atom. The approximate extent of deuteriation was determined by comparison of peak sizes.

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Paper 0/00639D
Received 12*th February* 1990
Accepted 22*nd March* 1990