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THE SYNTHESIS OF SOME 2,10-EPOXYPINANES

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Abstract—Several 2,3,10-oxygenated pinanes have been prepared and their stereochemistry determined.

IN THE course of other studies we required the epoxides of *cis*- and *trans*-pinocarveol. As a consequence we studied the stereochemistry of the epoxidation of *cis*- and *trans*-pinocarveol, and of earlier reported oxidation reactions of α-pinene, and β-pinene.

Oxidation of β-pinene with potassium permanganate ($KMnO_4$) has been reported to yield a diol,[1] m.p. 75°. In contrast hydroxylation with osmium tetroxide, also a *cis*-hydroxylating agent, gave a material m.p. 51° which was supposed[2] to be a mixture of two *cis*-diols, presumably the 2α,10- and 2β,10-diols. However, in our hands both reagent systems lead to the formation of a single diol (**1**) m.p. 83–85° to which we assign the 2α,10-diol structure. This assignment is made on the basis of the preferred attack by the *cis*-hydroxylating reagents on the less hindered α-face of the 2,10-double bond, on the side remote from the geminal β-methyl groups, and on the following chemical evidence. Reaction of the diol (**1**) with *p*-toluene sulphonyl chloride in pyridine gave the 2α-hydroxy-10-tosylate (**2**), the structure of which was confirmed by its NMR spectrum which exhibited signals at 3·83 ppm (2H singlet; C_{10} protons), 1·17 and 0·77 ppm (3H each; C_8 and C_9 methyl groups) and 2·44 ppm (4H; *p*-Me group and 2α-OH); treatment of the sample with D_2O reduced the integral of the 2·44 ppm signal to 3 protons (*p*-Me group) thus confirming the assumed superposition of signals. Reduction of the tosylate (**2**) with LAH gave 10β-pinane-2α-ol (**3**) identical with the material produced by LAH reduction of 2α,10-epoxypinane (**4**) reported earlier.[3]

10α-Pinane-2β-ol (**5**), produced by methyl Grignard attack on the α-face of the carbonyl group of nopinone[4] (**6**), has now been prepared by an alternative route. Reaction of nopinone (**6**) with trimethyl sulphonium iodide-DMSO-NaH[5] proceeded by attack again on the α-face of the molecule to give 2β,10-epoxypinane (**7**) in 89% yield. Reduction of this epoxide (**7**) with LAH gave 10α-pinane-2β-ol (**5**).

Oxidation of α-pinene with aqueous $KMnO_4$ has been reported[6] to give a diol of unknown configuration. It was later reported[7] that oxidation with $KMnO_4$ in 90% aqueous acetone gave a ketol (**8**) with a 2α-hydroxyl group. Reduction of the ketol (**8**) with aluminium isopropoxide gave[7] isopinene-glycol (**9**), m.p. 35–40° (m.p. 55·5–56° analytical sample). Later the structure assigned to isopinene-glycol was corrected[8] to **10**. Similarly, the stereochemistry of the product of reaction[7] of ketol **8** with LAH was subsequently changed[8] from that of neoisopinene-glycol

(**11**) to **12**. These reassignments of stereochemistry are inconsistent with the relative rates[7] of cleavage of the C_3-epimeric diols **9** or **10** and **11** or **12** with lead tetraacetate; isopinene-glycol (**9**), m.p. 55·5–60° reacts more rapidly with lead tetraacetate than neoisopinene-glycol (**11**), m.p. 160°, a result more readily interpreted in terms of the former having the *cis*-diol formulation.

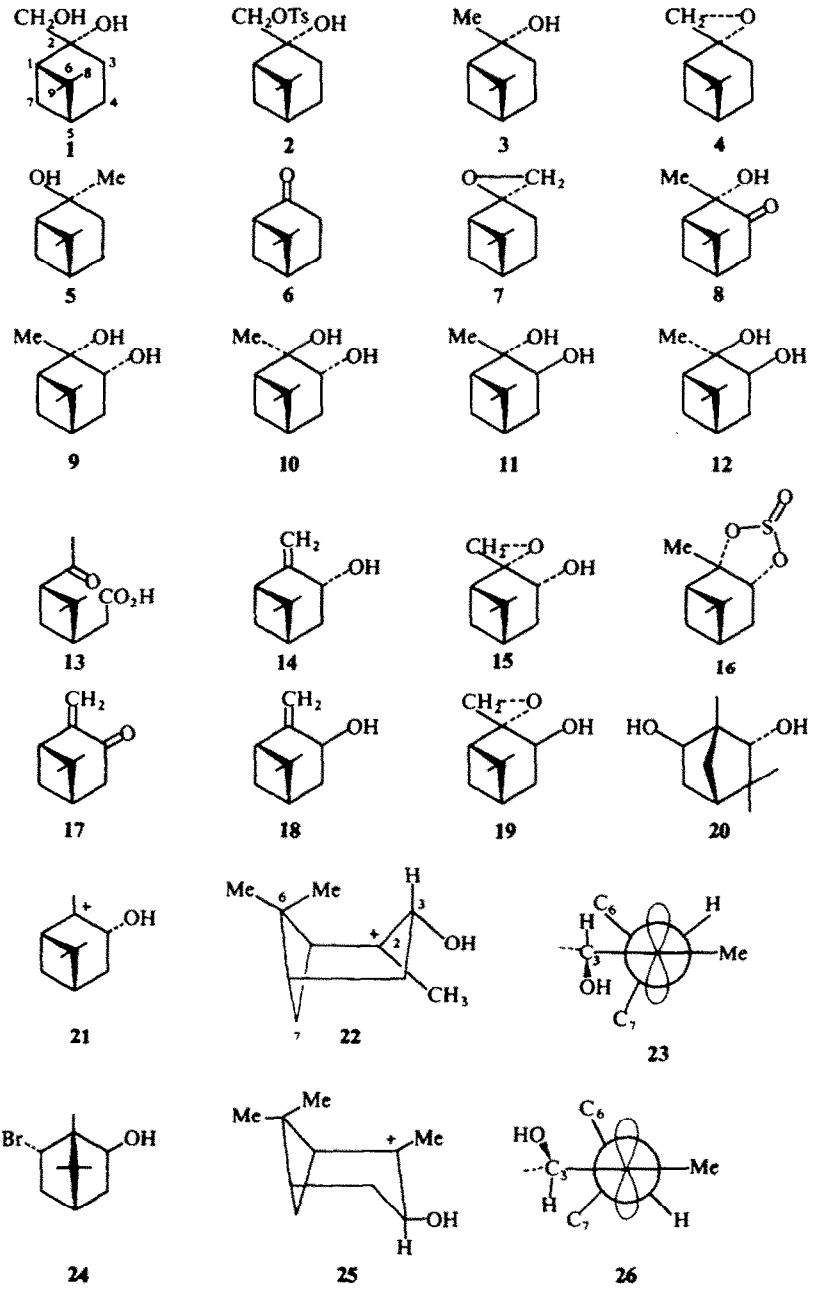
In our hands, oxidation of α-pinene with neutral $KMnO_4$ gave in addition to recovered starting material, pinonic acid (**13**), ketol **8** and 10β-pinane-2α,3α-diol (**9**). Reduction of the ketol **8** with aluminium isopropoxide gave the *cis*-diol (**9**), while reduction with LAH gave a second diol (**11**) presumably epimeric at C-3. These reactions of ketol **8** repeat those quoted earlier[7] by Schmidt. The stereochemical assignments made immediately above were confirmed as follows. Perbenzoic acid oxidation of *trans*-pinocarveol (**14**) gave 2α,10-epoxy-10β-pinane-3α-ol (**15**) which on reduction with LAH gave a diol identical with that obtained from the neutral $KMnO_4$ oxidation. As it is known that neutral $KMnO_4$ *cis*-hydroxylated olefins and that the diol **9** must contain a 3α-hydroxyl group as it may arise from *trans*-pinocarveol, then the 2-hydroxyl group must also have the α-configuration. The *cis*-character of the 2,3-diol (**9**) was confirmed by the formation of a crystalline cyclic sulphite (**16**) on reaction with thionyl chloride. The identity of the diol (**9**) samples produced *via* α-pinene-$KMnO_4$ oxidation, and epoxidation of *trans*-pinocarveol, necessitates the assignment of 2α,10-epoxy-10β-pinane-3α-ol (**15**) as the product of epoxidation of *trans*-pinocarveol. This result is in accord with the anticipated attack by a peracid on the less-hindered α-face of the double bond.

Pinocarvone (**17**) required as the precursor of *cis*-pinocarveol (**18**) and normally prepared by selenium dioxide oxidation of β-pinene,[9] is more conveniently obtained by MnO_2 oxidation (87% yield) of the readily available *trans*-pinocarveol (**14**).

Perbenzoic acid treatment of *cis*-pinocarveol (**18**) in ether solution gave the epoxide (**19**). The α-orientation of the epoxide ring system was confirmed by LAH reduction of the epoxide (**19**) to the known 2α,3β-diol (**11**).

Schmidt recently reported[8] the reaction of isopinene-glycol (analytical sample m.p. 56°) with dilute sulphuric acid to yield the fenchane-diol (**20**). In view of the demonstration above that isopinene-glycol has the 2α,3α-diol structure (**9**) it becomes necessary to discuss the mechanism of this rearrangement. Clearly the *cis* relationship of the departing 2α-hydroxyl group and the migrating methylene group excludes the possibility of a concerted process. We suggest that the rearrangement, carried out by Schmidt *et al.*[8] on the compound (**9**) whose stereochemistry is established above, proceeds by a mechanism which involves the discrete carbonium ion (**21**). The reaction of *trans*-pinocarveol (**14**) with hydrogen bromide[10] is also now thought to proceed *via* the identical carbonium ion intermediate. The specificity for $—C^7H_2$ migration as opposed to $—C^6(CH_3)_2$ migration is considered to arise as a result of the preferred conformation (**22**) of the common carbonium ion, in which the α-lobe of the carbonium ion orbital is directed inwards and readily accessible to approach by C_7 (see **23**). In contrast C_6 lies close to the plane of the carbonium ion, a poor situation for migration.

An analogous discussion allows the rationalization of the formation of the rearranged compound (**24**) on treatment[10] of *cis*-pinocarveol (**18**) with hydrogen bromide. Here the discrete carbonium ion will adopt the conformation **25**, Newman projection **26**, in which the $—C^6(CH_3)_2$ migration would clearly be preferred.



EXPERIMENTAL

Rotations ($CHCl_3$ solns at room temp): IR spectra (CS_2 solns used unless otherwise stated, on a Perkin–Elmer 221 spectrometer); alumina used for chromatography (P. Spence, Grade H); NMR spectra (determined on a Varian A-60 in CCl_4 with $CHCl_3$ and TMS as internal standards).

Pinane-2α,10-diol (1). A soln of $KMnO_4$ (100 g) and $MgSO_4$ (75 g) in water (2 l.) was carefully added to a stirred soln of β-pinene (100 g) in EtOH (1·5 l.). The temp was kept below 5° by immersion in an

ice–salt bath. After 2 hr the mixture was filtered through a celite filter-aid filter and the residue washed with CH_2Cl_2 (1 l.). The reaction product was extracted *via* CH_2Cl_2 and after removal of solvents was absorbed onto deactivated alumina (250 g). Elution with 20% ether in pentane and crystallization from pentane ether gave pinane-2α,10-diol (8·4 g), m.p. 83·5° (lit. cit., 75°).

Oxidation of β-pinene with osmic acid.[2] To a soln of β-pinene (8·3 g), osmic acid (0·04 g) and ether (100 ml) was added a soln of H_2O_2 (3·5 M, 100 ml) in anhyd ether. After an induction period of 6 hr a violent reaction occurred. The reaction mixture was washed with $FeSO_4$aq and the organic phase dried over Na_2SO_4. After removal of solvents the residue was absorbed onto deactivated alumina (50 g). Elution with pentane gave nopinone (1·8 g). Further elution with 20% ether in pentane gave pinane-2α,10-diol (1·48 g), m.p. 82°.

10-*Tosyl-pinane-2α-ol* (**2**). A soln of pinane-2α,10-diol (2 g), *p*-toluenesulphonyl chloride (2·5 g) in pyridine (2·5 ml) was heated at 60° for 2 hr. The reaction mixture was poured into ice-water and the product extracted *via* ether to give a gum (2·7 g), the NMR spectrum consistent with 10-tosyl-pinane-2α-ol.

Reduction of 10-*tosyl-pinane-2α-ol.* To a soln of 10-tosyl-pinane-2α-ol (1 g), in ether (50 ml) was added LAH (1 g) and the mixture heated under reflux for 2 hr. Isolation *via* ether and sublimation of the product gave 10β-pinane-2α-ol **3** (0·37 g), m.p. 76°.

Pinane-2α,3α-diol (**9**). A soln of $KMnO_4$ (100 g) and $MgSO_4$ (75 g) in water (2 l.) was carefully added to a stirred solution of α-pinene ($[\alpha]_D^{20}$ +4°) in EtOH (1·5 l.). The temp was kept below 5° by immersion in an ice–salt bath. After 2 hr the mixture was filtered through a celite filter-aid filter and the residue washed with CH_2Cl_2 (1 l.). The reaction product was extracted from the aqueous layer with CH_2Cl_2. Evaporation and fractional distillation at 5 mm with a Nester–Faust spinning band distillation column gave α-pinene b.p. 29° (13·4 g), pinonic acid b.p. 113–115° (**13**) m.p. 105° (23·4 g) (lit. cit. 103°), mother liquor from crystallization contained **8**, and pinane-2α,3α-diol, b.p. 125–126° m.p. 38–40° (14 g). (Lit. cites[7] m.p. 55·5–56° for material from α-pinene $[\alpha]_D$ +38·5°).

Cyclic sulphite of pinane-2α,3α-diol. To a soln of pinane-2α,3α-diol in pyridine (10 ml) ether (500 ml) was added $SOCl_2$ (5 ml) and the soln kept at 0° for 15 min. Isolation by means of ether and crystallization from pentane gave the *cyclic sulphite* (**16**) of pinane-2α,3α-diol (8·7 g), m.p. 60–64°, ν_{max} 1210 cm^{-1}. (Nujol mull). (Found: C, 55·2; H, 7·4; S, 14·5. $C_{10}H_{16}O_3S$ requires: C, 55·5; H, 7·5; S, 14·8%.)

2α,10-*Epoxypinane-3α-ol* (**15**). *trans*-**14** (20 g) was added to an ice-cold soln of perbenzoic acid (72 g) in ether (1 l.). The soln was allowed to warm to 7° and kept at that temp for 3 days. The reaction mixture was washed with dilute alkali. Evaporation and distillation at 1 mm gave 2α,10-*epoxypinane-3α-ol* (14 g), b.p. 70–72° m.p. 15°, $[\alpha]_D^{20}$ +44° (*c*, 0·90). (Found: C, 71·6; H, 9·5; $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·6%.)

Reduction of 2α,10-*epoxypinane-3α-ol.* To a soln of 2α,10-epoxypinane-3α-ol (0·75 g) in ether (75 ml) was added LAH (0·5 g) and the soln heated under reflux for 4 hr. Isolation in the usual manner gave a gum, shown by NMR to be pinane-2α,3α-diol.

2β,10-*Epoxypinane* (**7**). Sodium hydride (24 g of 50% dispersion in oil) was washed with pentane to remove paraffin oil, and then added to dry DMSO (250 ml) at 65–70°. The mixture was stirred vigorously under N_2. To this mixture THF (100 ml) was added and the mixture cooled to −10°. Keeping the temp below 0°, tri-methylsulphonium iodide (125 g) was added, followed by nopinone (35·5 g). The soln was stirred for 2 hr at 10°. Water (500 ml) was added and the epoxide extracted with pentane (1 l.). Evaporation of the solvent and distillation of the resulting product gave 2β,10-*epoxypinane* (32·9 g, m.p. 18·5°, $[\alpha]_D^{20}$ +38° (*c*, 1·1)). (Found: C, 78·9; H, 10·4; $C_{10}H_{16}O$ requires: C, 78·9; H, 10·6%.)

Reduction of 2β,10-*epoxypinane.* To a soln of 2β,10-epoxypinane (2 g) in ether (75 ml) was added LAH (2 g) and the resulting mixture heated under reflux for 2 hr. Isolation *via* ether and sublimation of the product gave **5** (1·4 g), m.p. 58°.

Pinocarvone (**17**). *trans*-Pinocarveol (35 g) was stirred into 350 g of MnO_2 in pentane (1·5 l.) for 24 hr. The MnO_2 was filtered off and the pentane evaporated to give pinocarvone (31 g) $[\alpha]_D^{20}$ +60° (*c*, 1·0), identical by NMR and IR with a sample made by the method of Stallcup and Hawkins.[9]

2α,10-*Epoxypinane-3β-ol* (**19**). *cis*-Pinocarveol (7·3 g) was added to a soln of perbenzoic acid (24 g) in ether (250 ml) and kept at room temp for 3 days. The reaction mixture was washed with dilute alkali. Evaporation and distillation gave 2α, 10-*epoxypinane-3β-ol* (3·3 g), m.p. 6° $[\alpha]_D^{20}$ −30°. (Found: C, 71·5; H, 9·4. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·6%.)

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