The Chemistry of Terpenes. Part XIX.[1] Reaction of (+)-3α,4α-Epoxycarane with Halogen Acids and Acetic Acid

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The reaction of (+)-3α,4α-epoxycarane (2) with ethereal hydrogen chloride affords a mixture of (−)-3β-chlorocaran-4α-ol (1a; X = Cl) and (+)-4β-chlorocaran-3α-ol (4). The acetate of the former can be converted into (+)-4α-acetoxycaran-3α-ol (6a) by heating with 1,4-diazabicyclo[2.2.2]octane in dimethylformamide. Treatment of the epoxide (2) with hydrogen bromide in acetic acid yields *p*-cymene, (−)-3β-bromocaran-4α-ol (1a; X = Br), (−)-2β-bromo-*p*-menth-8-en-1α-ol (3b), and (−)-2β,8-dibromo-*p*-menthan-1α-ol (8). The reaction of (2) with hot acetic acid leads to (−)-4α-acetoxycaran-3β-ol (1c), (+)-8-acetoxy-*p*-mentha-1,5-diene (10a), and (−)-car-3(10)-en-4α-ol (11).

In connection with our studies of carane chemistry, we required a source of 3-halogenocaran-4-ols of the type (1a; R = H, X = Cl or Br). (+)-3α,4α-Epoxycarane (2) had been reported [2] to react with ethereal hydrogen chloride to yield the chlorohydrin (1a; X = Cl), together with a solid unsaturated chlorohydrin, later shown [3] to be the menthene (3a). It was also found [3] that when the reaction was carried out at low temperature the isomeric chlorohydrin (4) was produced.

Using the epoxide (2) which had been conveniently prepared from (+)-car-3-ene (5) by the method of Payne,[4] we repeated this reaction and obtained a mixture of the chlorohydrins (1a; X = Cl) (43%) and (4) (57%). The structures of these compounds follow from their n.m.r. spectra (see Experimental section), and from their ready base-catalysed reconversion into the epoxide (2). Models suggest that formation of the 'abnormal' chlorohydrin (4) in substantial yield results from the more sterically favourable β-face attack of chloride ion at C-4 than at C-3 of an intermediate species derived from (2). The methyl-substituted cyclopropane system inhibits attack of chloride ion at C-3.

Acetylation of (1a; X = Cl) afforded the ester (1b). Heating this under reflux in dimethylformamide solution with 1,4-diazabicyclo[2.2.2]octane (DABCO), followed by aqueous work-up, yielded the *cis*-hydroxy-acetate (6a). Heating in dimethylformamide alone was ineffectual. The structure of (6a) was confirmed by its hydrolysis to the *cis*-diol (6b), itself prepared by the oxidation of (+)-car-3-ene (5) with alkaline permanganate. The transformation of (1b) into (6a) may be rationalised as shown in Scheme 1. Formation of the cyclic intermediate is greatly facilitated by the *trans*-diaxial arrangement of the participating groups. The latter is a consequence of the conformation adopted by the carane ring system of (1b). Treatment of *trans*-1-acetoxy-2-chlorocyclohexane (7) with DABCO under identical conditions leads to no significant reaction. In this instance, the substituents largely adopt the *trans*-diequatorial relationship.[5]

Attention was next turned to the reaction of (+)-3α,4α-epoxycarane (2) with hydrogen bromide in acetic acid. While this work was nearing completion, similar results were reported [6] by another group for the reaction of (2) with ethereal hydrogen bromide. Four major products were obtained by us. These were *p*-cymene, the bromohydrin (1a; X = Br), the rearranged bromohydrin (3b), and the product (8) arising from the latter

[1] Part XVIII, W. Cocker, H. St. J. Lauder, and P. V. R. Shannon, *J.C.S. Perkin I*, 1975, 332.

[2] B. A. Arbuzov, Z. G. Isaeva, and G. Sh. Bikbulatova, *Doklady Akad. Nauk S.S.S.R.*, 1970, **195**, 599 (*Chem. Abs.*, 1971, **74**, 88, 147q).

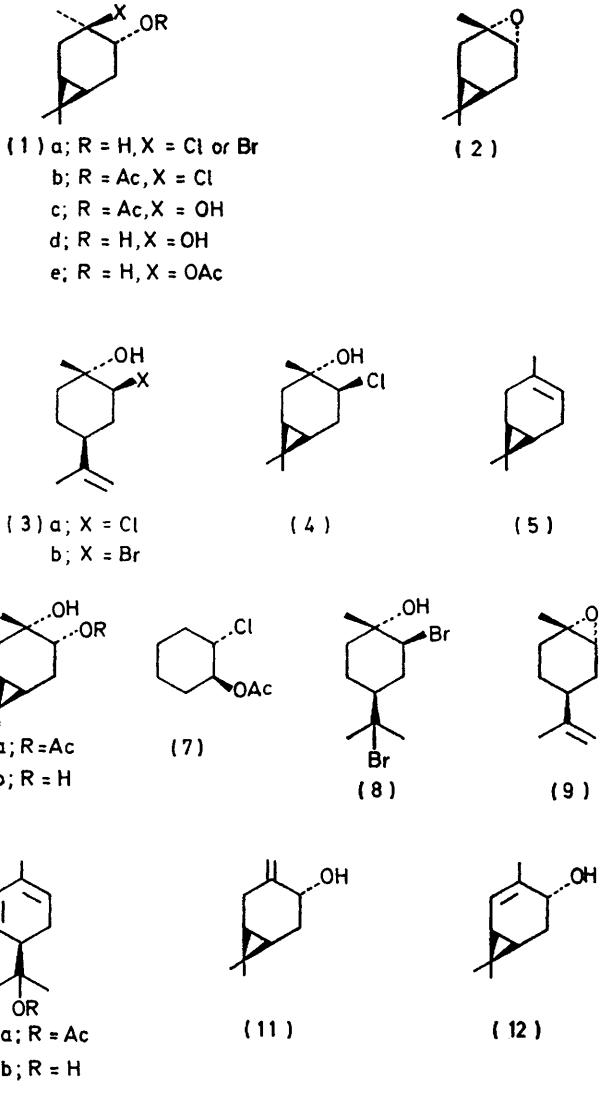
[3] B. A. Arbuzov, Z. G. Isaeva, G. Sh. Bikbulatova, and N. I. Semakhina, *Doklady Akad. Nauk S.S.S.R.*, 1972, **207**, 853 (*Chem. Abs.*, 1973, **78**, 159,887b).

[4] G. B. Payne, P. H. Denning, and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 659.

[5] H. R. Buys, H. J. A. De Vries, H. J. Hageman, and C. Altona, *Rec. Trav. chim.*, 1970, **89**, 245.

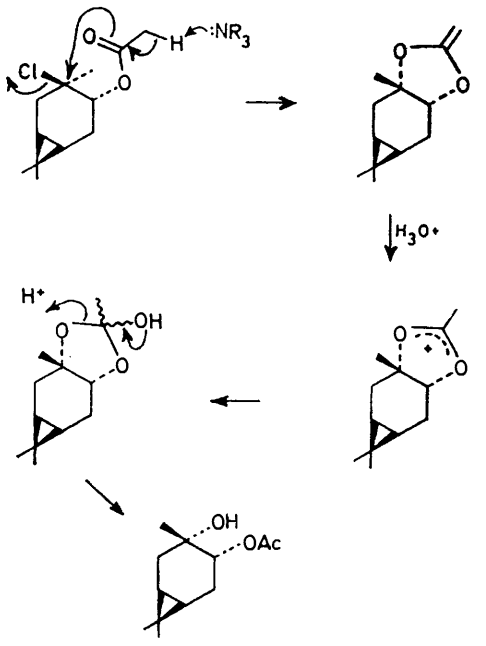
[6] B. A. Arbuzov, Z. G. Isaeva, and E. C. Kazakova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 2554 (*Chem. Abs.*, 1974, **80**, 83,277w).

by addition of hydrogen bromide. Of these compounds, (1a; X = Br) and (3b) have been reported by the Russian group.[6]



The structure of (1a; X = Br) follows from its n.m.r. spectrum and reconversion into the oxide (2); that of (3b) as a result of its base-catalysed transformation into the limonene oxide (9); and that of (8) by its formation from (3b) and hydrogen bromide in acetic acid.

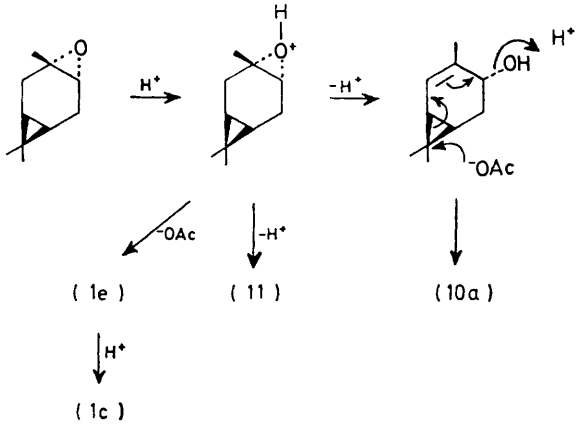
We have also investigated the reaction of the epoxide (2) with acetic acid and, for convenience, report our results here. When the oxide (2) was heated with acetic acid, an exothermic reaction commenced at *ca.* 95° and reflux became self sustaining. When this had subsided, three products were isolated. These were the hydroxy-acetate (1c),[7] (+)-8-acetoxy-*p*-mentha-1,5-diene (10a), and (−)-car-3(10)-en-4α-ol (11). The first of these was prepared from the diol (1d), into which it can be converted by hydrolysis. Its precursor seemed likely to be the isomeric compound (1e), which was a major product of the reaction of the oxide (2) with cold, buffered acetic acid (*cf.* ref. 6 where it was assumed to



SCHEME 1

be formed). Heating (1e) in acetic acid gave (1c) as, to a lesser extent, did chromatography on silica gel.

The structure of (10a) was deduced from its n.m.r. spectrum (see Experimental section), and by its hydrolysis to the corresponding alcohol (10b), which was identical with an authentic specimen.[8] The acetate (10a) has previously been reported[9] as a product of the reaction of (+)-3α,4α-epoxycarane (2) with acetic



SCHEME 2

anhydride. Its formation may be rationalised by invoking the intermediacy of the carenol (12) (Scheme 2).

The allylic alcohol (11), which was identified from its

[7] P. J. Kropp, *J. Amer. Chem. Soc.*, 1966, **88**, 4926.
[8] W. Cocker and D. A. Baines, unpublished work.
[9] B. A. Arbuzov, Z. G. Isaeva, and I. P. Povodyreva, *Doklady Akad. Nauk S.S.S.R.*, 1964, **159**, 827 (*Chem. Abs.*, 1965, **62**, 7801g).

spectral and other data (see Experimental section), arises from (2) in a predictable way.

EXPERIMENTAL

The general experimental conditions were those described earlier.[1] Unless otherwise stated, n.m.r. spectra were obtained at 60 MHz for solutions in carbon tetrachloride, i.r. spectra for Nujol mulls (N) or neat liquids (L),† and optical rotations for ethanolic solutions on a Perkin-Elmer 141 automatic polarimeter.

Epoxidation of (+)-*Car*-3-*ene* (5) *with Hydrogen Peroxide–Acetonitrile.*—(+)-Car-3-ene (5) (136 g, 1 mol), $[\alpha]_D^{20}$ +16° (*c* 0·5), in methanol (1000 ml) and acetonitrile (65 g, 1·5 mol) was heated to 60°, and hydrogen peroxide (30%; 120 ml) was added dropwise with stirring during 2 h. Sodium hydroxide solution (1M) was added concurrently to keep the pH at 9·5—10. After a further 3 h at 60°, the methanol was largely removed by distillation, nearly all the residual carene being carried over as an azeotrope. The residue was diluted with water (1000 ml) and extracted with ether (3 × 250 ml), and the combined extract was washed, dried, and distilled giving (+)-3α,4α-epoxycarane (2) (65 g), b.p. 42—43° at 0·5 mmHg,[10] and a residue (8 g).

Reaction of (+)-3α,4α-*Epoxycarane* (2) *with Ethereal Hydrogen Chloride.*—A stirred solution of the epoxide (2) (20 g) in ether (500 ml) was treated at 0° with hydrogen chloride until the latter was in slight excess. After 0·5 h at 0—5°, the solution was washed with brine containing 5% sodium carbonate, dried, and evaporated giving an oil (24 g). Chromatography over silica gel afforded the chlorohydrins (1a; X = Cl) (10 g) and (4) (13·5 g) in this order of elution. (−)-3β-Chlorocaran-4α-ol [3,*] (1a; X = Cl) had b.p. 63—65° at 0·6 mmHg, $[\alpha]_D^{20}$ −1° (*c* 0·7), $\nu_{max.}$ (L) 3430 and 1072 cm^{-1}, τ 9·30 (2H, m, cyclopropyl), 9·02 (6H, s, Me_2C), 8·49 (3H, s, 3-Me), 7·44br (1H, s, exch. D_2O, OH), and 6·57 (1H, q, *J* 10·5 and 8·0 Hz, 4-H) (Found: C, 63·9; H, 9·3. Calc. for $C_{10}H_{17}ClO$: C, 63·7; H, 9·0%). (+)-4β-Chlorocaran-3α-ol [3,*] (4) had b.p. 73—74° at 0·7 mmHg, $[\alpha]_D^{20}$ +12·5° (*c* 0·8), $\nu_{max.}$ (L) 3410 and 1077 cm^{-1}, τ 9·30 (2H, m, cyclopropyl), 8·96 (6H, s, Me_2C), 8·77 (3H, s, 3-Me), 7·46 (1H, s, exch. D_2O, OH), and 6·17 (1H, t, *J* 7·0 Hz, 4-H) (Found: C, 63·4; H, 9·1. Calc. for $C_{10}H_{17}ClO$: C, 63·7; H, 9·0%).

Acetylation of the Chlorohydrin (1a; X = Cl).—A solution of the chlorohydrin (1 g) in pyridine (10 ml) and acetic anhydride (1 ml) after 12 h afforded a product (1·1 g) which on distillation gave (−)-4α-*acetoxy*-3β-*chlorocarane* (1b) * as an oil, b.p. 76—78° at 0·6 mmHg, $[\alpha]_D^{20}$ −3·4° (*c* 0·8), $\nu_{max.}$ (L) 1740 and 1239 cm^{-1}, τ 9·26 (2H, m, cyclopropyl), 9·02 and 8·93 (6H, 2s, Me_2C), 8·44 (3H, s, 3-Me), 8·01 (3H, s, COMe), and 5·35 (1H, q, *J* 10·0 and 8·0 Hz, 4-H) (Found: C, 62·6; H, 8·2. $C_{12}H_{19}ClO_2$ requires C, 62·5; H, 8·2%).

Reaction of the Chloro-acetate (1b) *with DABCO.*—A mixture of the chloro-acetate (5 g), DABCO (2·5 g), and dimethylformamide (25 ml) was refluxed for 4 h, cooled, poured into dilute sulphuric acid (5%), and extracted with ether giving a pale yellow oil (4 g). Chromatography over silica gel followed by distillation afforded (+)-4α-acetoxycaran-3α-ol [7,*] (6a) (3·6 g) as an oil, b.p. 82—84° at 0·4 mmHg, $[\alpha]_D^{20}$ +28·5° (*c* 0·8), $\nu_{max.}$ (L) 3540, 1735, and 1249 cm^{-1}, τ 9·26 (2H, m, cyclopropyl), 8·97br (s) and 8·94br (s) (9H, Me_2C and 3-Me), 8·26 (1H, s, exch. D_2O, OH), 7·96 (3H, s, COMe), and 5·55 (1H, q, *J* 10·0 and 8·5 Hz, 4-H) (Found: C, 67·6; H, 9·2. Calc. for $C_{12}H_{20}O_3$: C, 67·9; H, 9·4%).

Hydrolysis of the Hydroxy-acetate (6a).—The ester (1 g) was heated at 50° for 0·5 h with potassium hydroxide (1 g) in methanol (10 ml) and water (2 ml) giving (+)-carane-3α,4α-diol * (6b) (0·6 g), m.p. 70—71° (from light petroleum) (lit.,[11] 69—70°), $[\alpha]_D^{20}$ +12·6° (*c* 0·5), τ 9·13 and 9·03 (6H, 2s, Me_2C), 8·88 (3H, s, 3-Me), 6·95 (1H, q, *J* 10·0 and 8·0 Hz, 4-H), and 6·98 (2H, s, exch. D_2O, 2 OH).

Permanganate Oxidation of (+)-*Car*-3-*ene* (5).—A stirred solution of the olefin (3 g) in t-butyl alcohol (50 ml) and water (20 ml) was slowly treated at 0° with a solution of potassium permanganate (4·6 g) and sodium hydroxide (0·8 g) in water (80 ml). After 10 min at 0°, the alcohol was removed below 40° under reduced pressure and the residue was saturated with sodium chloride and extracted with ethyl acetate (3 × 100 ml), giving the crude diol as a gum (2·3 g) which was chromatographed on silica gel (ether). The solid product (2·1 g) was crystallised from light petroleum giving the diol (6b), m.p. and mixed m.p. 70—71°. Treatment of the diol (1 g) with acetic anhydride (1 ml) in pyridine (10 ml) regenerated the acetate (6a) (1·2 g).

Reaction of trans-1-*Acetoxy*-2-*chlorohexane* (7) *with DABCO.*—A solution of sodium hypochlorite (300 ml; 14%) was added over 20 min to a stirred ice-cold mixture of cyclohexene (32 g), acetic acid (300 ml), and water (50 ml). After a further 10 min, the usual work-up afforded the product (7) contaminated (i.r.) with chlorohydrin. The mixture was set aside for 6 h with acetic anhydride (10 ml) in pyridine (50 ml), giving *trans*-1-acetoxy-2-chlorocyclohexane (7) * as an oil (57·4 g), b.p. 47—48° at 0·1 mmHg.

The chloro-acetate (7) (3·5 g) was refluxed for 12 h with DABCO (2·5 g) in dimethylformamide (60 ml). Work-up gave (i.r.) only unchanged chloroacetate (7) (3·2 g).

Reaction of (+)-3α,4α-*Epoxycarane* (2) *with Hydrogen Bromide in Acetic Acid.*—An ice-cold solution of the epoxide (2) (25 g) in acetic acid (20 ml) was stirred and treated over 20 min with a solution of hydrogen bromide in acetic acid (31 ml; 45%), giving an oil (36·2 g). Chromatography on silica gave *p*-cymene (5·3 g), (−)-3β-bromocaran-4α-ol (1a; X = Br) (12·1 g), (−)-2β-bromo-*p*-menth-8-en-1α-ol (3b) (8 g), and (−)-2β,8-dibromo-*p*-menthan-1α-ol (8) (4 g) in this order of elution.

(−)-3β-Bromocaran-4α-ol * (1a; X = Br) [6] was an oil, b.p. 66—68° at 0·35 mmHg, $[\alpha]_D^{20}$ −1° (*c* 1·0), $\nu_{max.}$ (L) 3410 and 1072 cm^{-1}, τ 9·25 (2H, m, cyclopropyl), 8·98 and 8·96 (6H, 2s, Me_2C), 8·23 (3H, s, 3-Me), 7·64 (1H, s, exch. D_2O, OH), and 6·31 (1H, q, *J* 10·0 and 8·0 Hz, 4-H) (Found: C, 51·8; H, 7·3. Calc. for $C_{10}H_{17}BrO$: C, 51·5; H, 7·3%).

(−)-2β-Bromo-*p*-menth-8-en-1α-ol (3b),[6,*] obtained as an oily solid, was purified by distillation; b.p. 76—78° at 0·3 mmHg, m.p. 73—74° (lit.,[6] 75—76°), $[\alpha]_D^{20}$ −11·4° (*c* 0·5), $\nu_{max.}$ (L) 3300, 1642, 1137, and 898 cm^{-1}, τ 8·66 (3H, s, 1-Me), 8·25br (3H, s, MeC=C), 8·15 (1H, s, exch. D_2O, OH), 5·84 (1H, m, 2-H), and 5·22br (2H, s, $C=CH_2$) (Found: C, 51·7; H, 7·3. Calc. for $C_{10}H_{17}BrO$: C, 51·5; H, 7·3%).

(−)-2β,8-*Dibromo*-p-*menthan*-1α-*ol* * (8) crystallised from light petroleum as needles, m.p. 88—89°, $[\alpha]_D^{20}$ −4·7°

† I.r. data for compounds marked with an asterisk are available as Supplementary Publication No. SUP 21346 (12 pp.). For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index issue.

[10] W. D. P. Burns, M. S. Carson, W. Cocker, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1968, 3073.

[11] J. L. Simonsen, *J. Chem. Soc.*, 1920, **117**, 570.

(*c* 0·8), $\nu_{max.}$ (N) 3270 and 1137 cm^{-1}, τ 8·68 (3H, s, 1-Me), 8·19 (6H, s, Me_2C), and 7·74 (1H, s, exch. D_2O, OH) (Found: C, 38·4; H, 5·8. $C_{10}H_{18}Br_2O$ requires: C, 38·2; H, 5·7%).

Conversion of (−)-2β-*Bromo*-p-*menth*-8-*en*-1α-*ol* (3b) *into* trans-1,2-*Epoxylimonene* (9).—The bromohydrin (3b) (100 mg) was shaken for 5 min with a cold solution of potassium hydroxide (100 mg) in methanol (2 ml) and water (1 ml) giving a yellow oil. Its i.r. spectrum was almost identical with that of a 50 : 50 mixture of the *cis*- and *trans*-isomers prepared by the *m*-chloroperbenzoic acid oxidation of (+)-limonene,[12] but the presence of a sharp, medium-strength band [12] at 948 cm^{-1} confirmed its identity as the *trans*-isomer (9).

Preparation of (−)-2β,8-*Dibromo*-p-*menthan*-1α-*ol* (8) *from the Bromohydrin* (3b).—Compound (3b) (180 mg) in acetic acid (2 ml) was added at room temperature to a solution of hydrogen bromide in acetic acid (0·2 ml; 45%). After 10 min, the usual work-up gave an oily solid (210 mg) which consisted largely (i.r.) of the dibromide (8). Chromatography gave the dibromo-compound (180 mg), identical with the specimen obtained earlier.

Reaction of (+)-3α,4α-*Epoxycarane* (2) *with Acetic Acid.*—The epoxide (2) (10 g) in acetic acid (25 ml) was gently heated to 95°; an exothermic reaction then set in. When this had subsided, the mixture was poured on to ice, neutralised with potassium carbonate, and extracted with ether, giving a yellow oil (12·5 g) containing (g.l.c.) three main components, a little residual starting material, and a smaller quantity of *p*-cymene. Column chromatography over silica gel afforded the first of these (30%) as an oil which was identified as (+)-8-acetoxy-*p*-mentha-1,5-diene * (10a), $[\alpha]_D^{21}$ +174° (*c* 0·1), $\nu_{max.}$ (L) 1737 and 1260 cm^{-1}, τ 8·60 (6H, s, Me_2C), 8·30br (3H, s, MeC=C), 8·19 (3H, s, COMe), and 4·59 and 4·31 (3H, 2m, HC=).

Next eluted was (−)-car-3(10)-en-4α-ol (11),* m.p. 55—56°, $[\alpha]_D^{20}$ −84° (*c* 0·5) {lit.,[13] m.p. 56—57°, $[\alpha]_D$ −118·7° ($CHCl_3$)}, $\nu_{max.}$ (L) 3450, 1048, and 899 cm^{-1}, τ 9·13 and 8·99 (6H, 2s, Me_2C), 6·03 (1H, t, *J* 4·0 Hz, 4-H), and 5·30 (2H, m, $C=CH_2$).

Finally (−)-4α-acetoxycaran-3β-ol * (1c) was eluted; m.p. 72—73° (from pentane), $[\alpha]_D^{20}$ −12° (*c* 0·4) (lit.,[7] m.p. 73—73·5°, $[\alpha]_D$ −13°), $\nu_{max.}$ (L) 3480, 1725, and 1260 cm^{-1}, τ 9·32 (2H, m, cyclopropyl), 9·01 and 8·96 (6H, 2s, Me_2C), 8·82 (3H, s, 3-Me), 7·99 (3H, s, COMe), 7·10br (1H, exch. D_2O, OH), and 5·53 (1H, q, *J* 10·0 and 8·0 Hz, 4-H).

Hydrolysis of the Acetate (10a).—A solution of this compound (0·5 g) in methanol (10 ml) and water (3 ml) containing potassium hydroxide (0·5 g) was refluxed for 6 h, giving (+)-*p*-mentha-1,5-dien-8-ol * (10b) (0·3 g), $[\alpha]_D^{20}$ +182° (*c* 0·1), $\nu_{max.}$ (L) 3370, 1173, and 1137 cm^{-1}, identical with an authentic specimen obtained by oxidation of (+)-car-3-ene with selenium dioxide in pyridine.[8]

Preparation of the Hydroxy-acetate (1c).[7]—The diol (1d) (1·5 g), treated in pyridine (10 ml) with acetic anhydride (1 ml) in the usual way, gave a product (1·7 g) identical (i.r. and n.m.r.) with the hydroxy-acetate (1c).

Reaction of (+)-3α,4α-*Epoxycarane* (2) *with Buffered Acetic Acid.*—A solution of the epoxide (2) (2 g) in acetic acid (20 ml) containing anhydrous sodium acetate (3 g) was set aside at room temperature for 72 h. The product (2·2 g) contained (g.l.c.) starting material (35%) and compounds (10a) (4%), (11) (1%), and (1e) (60%) [which was similar to, but not identical in retention time with the hydroxy-acetate (1c)]. Chromatography on silica gel yielded (−)-3β-*acetoxycaran*-4α-*ol* * (1e) as an oil, $[\alpha]_D^{20}$ −2°, $\nu_{max.}$ (L) 3450, 1730, and 1257 cm^{-1}, τ 9·33 (2H, m, cyclopropyl), 9·00 (6H, s, Me_2C), 8·57 (3H, s, 3-Me), 8·05 (3H, s, COMe), 7·41br (1H, exch. D_2O, OH), and 6·35 (1H, q, *J* 9·5 and 7·5 Hz, 4-H) (Found: C, 67·5; H, 9·6. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·5%). Further elution of the column provided a little (1c).

Conversion of (1e) *into* (1c). The hydroxy-acetate (1e) (1 g) was refluxed in acetic acid (10 ml) for 0·5 h and gave (1c) (0·9 g) (i.r. and g.l.c.).

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