

## REACTIONS OF EPOXIDES—XX\*

### THE PREPARATION AND SOME REACTIONS OF EPOXIDES OF 3-, 6-, AND 7-METHYLENECHOLESTANE DERIVATIVES

B. N. BLACKETT, J. M. COXON, M. P. HARTSHORN, B. L. J. JACKSON  
and C. N. MUIR

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

(Received in the UK 12 October 1968; accepted for publication 25 October 1968)

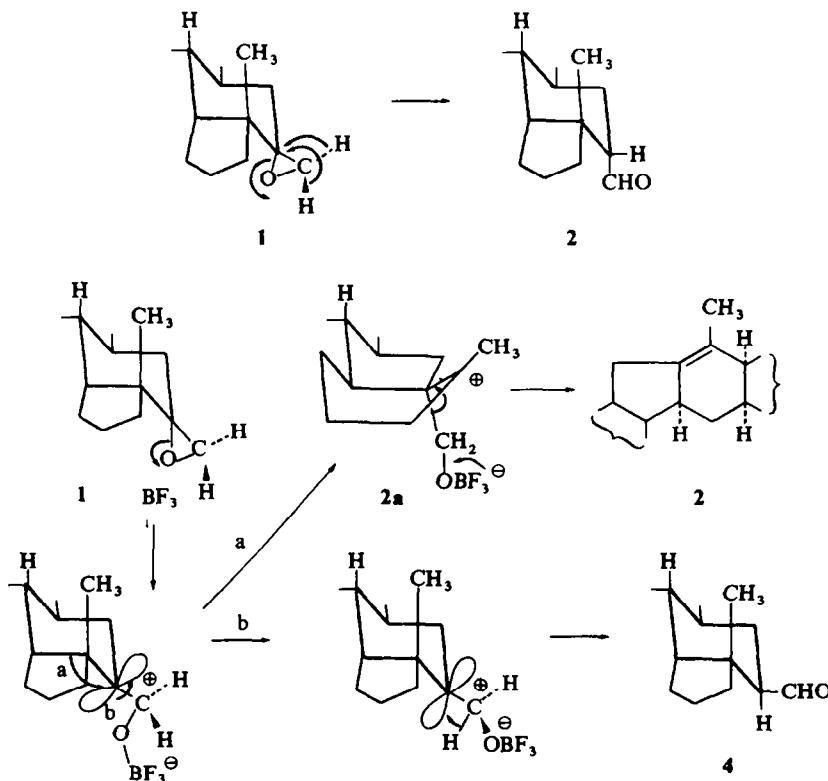
**Abstract**—The  $\text{BF}_3$ -catalysed rearrangements of exocyclic methylene epoxides at C-3, C-6, C-7 and C-12 give mixtures of epimeric aldehydes. These results are explained on the basis of the involvement of discrete carbonium ion intermediates in the rearrangement processes.

THE boron trifluoride catalysed rearrangement of the  $12\alpha,12'$ -epoxide (1) of 12-methylenetigogenin has been shown<sup>1</sup> to give, in addition to the  $\Delta^{13(17\alpha)}$ -olefin (2; 19%), a mixture of the epimeric 12-aldehydes [12 $\alpha$ - (3), 53%; 12 $\beta$ - (4), 13%]. Furthermore, while the 12 $\alpha$ -aldehyde (3) epimerized at C-12 during chromatography on alumina, this aldehyde (3) was not affected when treated under the reaction conditions,  $\text{BF}_3$  etherate in benzene. As the product of concerted hydride migration in the  $12\alpha,12'$ -epoxide (1) would be the 12 $\alpha$ -aldehyde (3; Fig. 1), the isolation of the 12 $\beta$ -aldehyde (4) pointed to the intermediacy of a discrete C-12 carbonium ion (Fig. 1) which would also give rise to the rearranged olefin (2). In the formation of the olefin (2) there is no clear evidence for the configuration at C-13 in structure (2a).

In order to test the generality of the intermediacy of a discrete carbonium ion in the boron trifluoride catalysed rearrangement of epoxides derived from exocyclic methylene-steroids, we examined the rearrangement of the epimeric epoxides derived from the 3-, 6- and 7-methylene-cholestane systems, in addition to a more detailed examination of the rearrangements of the epoxides of 12-methylenetigogenin.

The required epoxides were obtained by conventional routes. Epoxidation of 3-methylenecholestane (5) gave a mixture (ca. 4:1), separable by chromatography, of the 3 $\alpha,3'$ -epoxide (6) and the 3 $\beta,3'$ -epoxide (7). The stereochemistry of the epoxides was established by their reduction by LAH to the known 3-methylcholest-3-ols.<sup>2</sup> Epoxidation of 3 $\beta$ -acetoxy-6-methylenecholestane (8), prepared by reaction of the 6-ketone with a Wittig reagent, gave only the 6 $\alpha,6'$ -epoxide (9). None of the isomeric 6 $\beta,6'$ -epoxide (10) could be detected. The 6 $\beta,6'$ -epoxide (10) was formed, free from the 6 $\alpha,6'$ -epoxide (9), by reaction of 6-ketocholest-3 $\beta$ -ol with dimethylsulphonium methylide.<sup>3</sup> Reduction of the 6 $\beta,6'$ -epoxide (10) with LAH followed by acetylation with acetic anhydride-pyridine gave the known<sup>4</sup> 6 $\alpha$ -methyl-6 $\beta$ -hydroxy compound (11). Similar reaction of the 6 $\alpha,6'$ -epoxide (9) gave the 6 $\beta$ -methyl-6 $\alpha$ -hydroxy compound (12). The assignment of configuration at C-6 of these compounds was supported by

\* Part XIX J. M. Coxon, R. P. Garland, M. P. Hartshorn and G. A. Lane, *Chem. Commun.* in press.



NMR spectra. For the  $6\beta$ -orientation of the oxygen function in both the 6,6'-epoxide (10) and the 6-methyl-6-alcohol (11) the C-19 Me resonance is shifted downfield by comparison with the spectra for  $6\alpha$ -oxygenated compounds. This is in accord with the expected<sup>5</sup> effect on the C-19 Me resonance of a *syn*-axial or near *syn*-axial oxygen function at C-6. The marked stereospecificity of the reactions of  $5\alpha$ -6-ketones with dimethylsulphonium methylide and Grignard reagents and the epoxidation of 6-methylenecholestane derivatives with peracids is explicable in terms of the marked steric hindrance by the 19-Me group to approach of a reagent on the  $\beta$ -face of the carbonyl or olefinic group.

Epoxidation of  $3\beta$ -acetoxy-7-methylenecholestane (13) with monoperoxyphthalic acid gave a separable mixture (ca. 3:2) of the  $7\beta,7'$ - (14) and  $7\alpha,7'$ - (15) epoxides. Reduction of the  $7\beta,7'$ -epoxide (14) with LAH followed by acetylation with acetic anhydride-pyridine gave the  $7\alpha$ -methyl- $7\beta$ -alcohol (16), which on treatment with thionyl chloride-pyridine at  $-20^\circ$  gave only the 7-methylene compound (13). Elimination towards the exocyclic C atom would be expected for the  $7\beta$ -hydroxy-(equatorial) compound (16). In contrast the  $7\beta$ -methyl- $7\alpha$ -alcohol (17) derived from the  $7\alpha,7'$ -epoxide (15) by reduction with LAH followed by acetylation of the 3-OH group reacted with thionyl chloride-pyridine at  $-20^\circ$  to give a mixture (ca. 1:1; NMR) of the 7-methylene compound (13) and the 7-methyl- $\Delta^6$ -compound (18). The absence of significant amounts of the 7-methyl- $\Delta^7$ -compound (19) from the products may be

attributed to the steric hindrance to approach of pyridine to the  $8\beta$ -proton—the less hindered  $6\beta$ -proton and  $7'$ -Me protons which may also be orientated *anti*-coplanar with the axial  $7\alpha$ -chlorosulphite group are consequently removed by pyridine in the E2 elimination.

The relative yields of the epoxides ( $\alpha : \beta = 2 : 3$ ) formed on reaction of the 7-methylene compound (13) are in accord with predictions based on an examination of a Dreiding model. The greater sensitivity to steric effects of the ketone—methyl Grignard reaction as compared with the exocyclic methylene group—peracid reaction noted earlier,<sup>1</sup> lead to the formation in the  $3\beta$ -acetoxycholestan-7-one-methyl Grignard reaction of predominantly the  $7\beta$ -methyl- $7\alpha$ -alcohol (17;  $7\alpha$ -Me :  $7\beta$ -Me = 1 : 3).

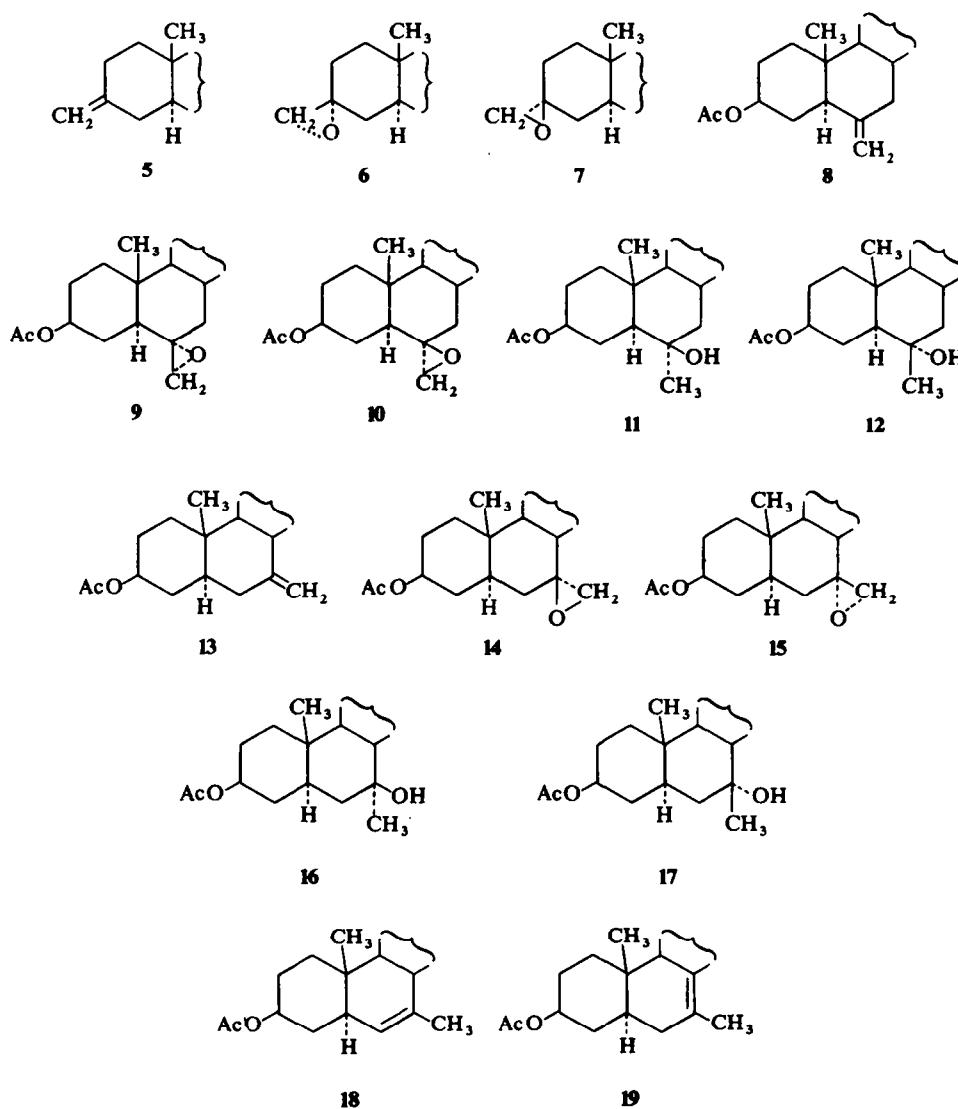
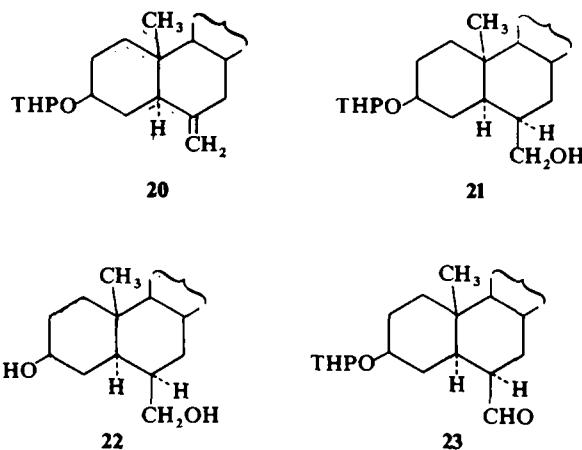


FIG. 1.



### **BF<sub>3</sub> Catalysed rearrangements**

Each of the epoxides derived from 3-, 6- and 7-methylenecolestane derivatives were shown (TLC) on rearrangement with boron trifluoride etherate in benzene to give mixtures of the corresponding aldehydes and a trace of a major component. No separation of these materials could be achieved by chromatography. The ratio of epimeric aldehydes formed from a single epoxide was determined by integration of the NMR spectrum of the mixture in the aldehydic proton region (ca. 9.1–10.0 ppm). These data are present in Table 1 and are discussed below.

TABLE 1.

Compound	Product of concerted rearrangement	% axial CHO	% equatorial CHO
3 $\alpha$ ,3'-Epoxide	3 $\alpha$ -(axial)CHO	26	74
3 $\beta$ ,3'-Epoxide	3 $\beta$ -(equatorial)CHO	20	80
6 $\alpha$ ,6'-Epoxide	6 $\alpha$ -(equatorial)CHO	52	48
6 $\beta$ ,6'-Epoxide	6 $\beta$ -(axial)CHO	67	33
7 $\alpha$ ,7'-Epoxide	7 $\alpha$ -(axial)CHO	95	5
7 $\beta$ ,7'-Epoxide	7 $\beta$ -(equatorial)CHO	67	33
12 $\alpha$ ,12'-Epoxide	12 $\alpha$ -(axial)CHO	72	28
12 $\beta$ ,12'-Epoxide	12 $\beta$ -(equatorial)CHO	60	40

Clearly the validity of the data presented in Table 1 depends upon the correct assignment of NMR signals due to the aldehyde functions to the axial and equatorial epimers. The assignments of signals are given in Table 2. For each pair of aldehydes, the signal due to the axial CHO proton appears downfield from the signal due to the equatorial CHO group.<sup>1,6</sup>

These assignments have been confirmed chemically for the 6- and 12-aldehydes. Both the axial and the equatorial 12-aldehydes were isolated<sup>1</sup> from the rearrangement of the 12 $\alpha$ , 12'-epoxide. Chromatography on alumina induced the conversion of the thermodynamically less stable axial aldehyde into the equatorial epimer.

TABLE 2.

Compound	Configuration of CHO	NMR Signal (ppm)
3 $\alpha$ -CHO	axial	9.72 ( $W_{h,2} = 1.6$ cs)
3 $\beta$ -CHO	equatorial	9.60 and 9.62 ( $J = 1.7$ cs)
6 $\alpha$ -CHO	equatorial	9.30 and 9.37 ( $J = 4.2$ cs)
6 $\beta$ -CHO	axial	9.83 ( $W_{h,2} = 1.8$ cs)
7 $\alpha$ -CHO	axial	9.94 and 9.97 ( $J = 2$ cs)
7 $\beta$ -CHO	equatorial	9.50 and 9.57 ( $J = 4$ cs)
12 $\alpha$ -CHO	axial	9.88 and 9.93 ( $J = 2.7$ cs)
12 $\beta$ -CHO	equatorial	9.68 and 9.70 ( $J = 1.5$ cs)

While no separation of the 6 $\alpha$ - and 6 $\beta$ -aldehydes was possible, the assignment of the CHO signals in the NMR spectrum of the mixed aldehydes followed from the NMR spectrum of the 6 $\beta$ -aldehyde prepared stereospecifically from 3 $\beta$ -hydroxy-6-methylenecolestane. The tetrahydropyranyl ether (20) on hydroboration at low temperatures gave two 6'-hydroxy-tetrahydropyranyl ethers (21) separable by chromatography, but with identical NMR spectra. Since hydrolysis of each gave the same compound (22) the hydroxy-tetrahydropyranyl ethers must be diastereoisomers arising from the asymmetry of the tetrahydropyranyl ether moiety. The stereochemistry at C-6 of the hydroxy-tetrahydropyranyl ether (21) was assigned on the basis of the preferred attack by diborane on the  $\alpha$ -face of the 6,6'-methylene group. Since reactions of Grignard reagents and dimethylsulphonium methylide with 6-ketones, and peracids with 6,6'-methylene systems all occur exclusively from the  $\alpha$ -face of the molecule, the stereochemical assignment of the low-temperature diborane addition would appear secure. Oxidation of either hydroxy-tetrahydropyranyl ether with manganese dioxide in acetonitrile<sup>7</sup> gave a crude sample of the 6 $\beta$ -formyl compound (23). The NMR spectrum of this material showed signals at  $\delta$  9.85 ppm;  $W_{h,2} = 1.8$  c/s (CHO) and  $\delta$  0.79 ppm (19-Me) in accord with the assignments made above for the axial-6-aldehyde. The epimeric aldehyde (6 $\alpha$ -CHO) gave an NMR spectrum with signals at  $\delta$  = 9.30, 9.37 ppm;  $J = 4.2$  c/s (CHO) and  $\delta$  = 0.88 ppm (19-Me). The 6 $\beta$ -aldehyde was not epimerized on treatment with  $BF_3$  under normal epoxide-rearrangement conditions.

The NMR spectrum of the 6 $\beta$ -aldehyde provides further confirmation of the C-6 configuration. The small degree of coupling between the aldehyde proton and the 6 $\alpha$ -proton, as evidenced by the appearance of the aldehyde proton signal, would suggest a dihedral angle close to 90°. This conformation would have been predicted for the 6 $\beta$ -aldehyde in order to minimize non-bonded interaction between the 19-Me group and the axial formyl group. The location of the 19-Me NMR signal at relatively high field ( $\delta$  = 0.79 ppm) is consistent with it being shielded by the proximate aldehyde CO group.

The notable feature of the results of the  $BF_3$ -catalysed rearrangement of the exocyclic epoxides (Table 1) was the formation of mixtures of epimeric aldehydes. Further, similar axial:equatorial aldehyde ratios were obtained for a given pair of epimeric epoxides, with consistent, but minor, deviations from a common aldehyde

product ratio in favour of that aldehyde in each case which could be formed in a concerted reaction (3 in Fig. 1).

These data suggest that for an exocyclic epoxide the  $\text{BF}_3$ -catalysed rearrangement proceeds by a mechanism involving complete carbonium ion formation (Fig. 2). The similar aldehyde product ratios for a pair of epimeric epoxides would arise as a

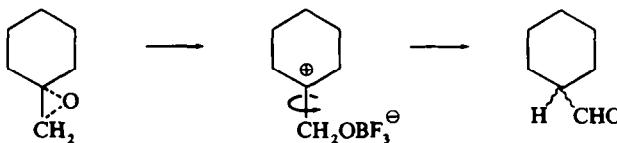


FIG. 2

consequence of a hydride shift from a rotating  $-\text{CH}_2\text{OBF}_3$  group. A consideration of the stereochemistry of the reacting molecule suggests an explanation (other than the discarded concerted reaction hypothesis) for the consistent bias in the product ratios.

For an exocyclic epoxide, rearranging on treatment with  $\text{BF}_3$ , the ionisation of the ring-carbon to oxygen bond would result in the conformational changes shown in Fig. 3. Even when complete formation of a carbonium ion is assumed (A' and B')

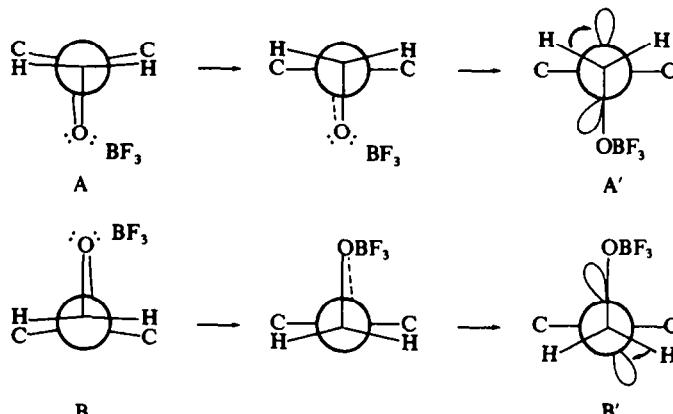


FIG. 3.

for the epimeric epoxides (A and B), the stereochemistry of hydride migration (and hence the product aldehydes) would be loaded in favour of top-side migration for (A') and bottom-side migration for (B') because of the initial asymmetric location of the potential hydride groups (in A' and B') with respect to the vacant p-orbitals of the carbonium ions.

#### EXPERIMENTAL

Rotations were measured for  $\text{CHCl}_3$  soln at  $20^\circ$ . NMR spectra were determined at 60 Mc in  $\text{CDCl}_3$ , with  $\text{CHCl}_3$  and TMS as internal standards. Alumina was P. Spence, Grade H, deactivated by the addition of 5% of 10% aqueous  $\text{AcOH}$ .  $\text{BF}_3$ -etherate was B.D.H., freshly redistilled before use. Light petroleum refers to that fraction b.p. 50–70°.

*Preparation of 3,3'-epoxycholestanes*

To a soln of 3,3'-methylenecholestane (6 g) in benzene (700 ml) was added a soln of monoperoxyphthalic acid in ether (0.2M; 135 ml) and the resulting soln kept at 20° for 24 hr. The steroid material, isolated by means of ether, was adsorbed onto alumina (500 g).

Elution with light petroleum, and crystallization from MeOH, gave 3 $\alpha$ , 3'-epoxycholestane (6) as plates (2.92 g), m.p. 129.5–130.5°,  $[\alpha]_D$  + 31° (c 1.03),  $\nu_{max}$  1380, 924 cm<sup>-1</sup>. (Found: C, 83.7; H, 12.1.  $C_{28}H_{48}O$  requires: C, 84.0; H, 12.0%).

Further elution with light petroleum gave, after crystallization from MeOH–ether, 3 $\beta$ ,3'-epoxycholestane (7) as leaflets (0.7 g) m.p. 175–175.5°,  $[\alpha]_D$  + 20° (c 1.16),  $\nu_{max}$  1380, 924 cm<sup>-1</sup>. (Found: C, 83.8; H, 12.0.  $C_{28}H_{48}O$  requires: C, 84.0; H, 12.0%).

Mixed fractions (ca. 2.7 g) on re-chromatography on alumina gave further pure samples of each epoxide.

*LAH reduction of 3,3'-epoxides*

(a) 3 $\alpha$ ,3'-Epoxide (6). To a soln of the epoxide (228 mg) in dry ether (20 ml) was added LAH (150 mg) and the mixture heated under reflux for 30 min. Isolation of the steroid material by use of ether, and crystallization of the crude material from MeOH gave 3 $\beta$ -methylcholestane-3 $\alpha$ -ol (178 mg) as needles, m.p. and mixed m.p. 125.5–126.5°,  $[\alpha]_D$  + 29° (c 1.08). IR and NMR spectra identical with an authentic sample.<sup>2</sup>

(b) 3 $\beta$ ,3'-Epoxide (7). The epoxide (127 mg), reacted with LAH as above, gave on crystallization from MeOH 3 $\alpha$ -methylcholestane-3 $\beta$ -ol as plates (78 mg), m.p. and mixed m.p. 147.5–148.5°,  $[\alpha]_D$  + 31° (c, 1.09). IR and NMR spectra identical with an authentic sample.<sup>2</sup>

*3 $\beta$ -Acetoxy-6,6'-methylenecholestane (8)*

An ethereal soln of n-BuLi (1.3N; 190 ml) was added to suspension of methyltriphenyl phosphonium bromide (88 g) in dry ether (1 l.) and the soln stirred for 3 hr. A soln of 3 $\beta$ -hydroxycholestane-6-one (10 g) in dry ether (500 ml) was added and the soln stirred overnight. Tetrahydrofuran (700 ml) was added while the ether was removed by distillation. The tetrahydrofuran mixture was treated under reflux for 6 hr, then cooled, diluted with water and the steroid material isolated by means of ether. The crude product was acetylated using pyridine–Ac<sub>2</sub>O at 100° for 1 hr. The acetylated product was adsorbed onto alumina (800 g). Elution with light petroleum and crystallization from MeOH gave 3 $\beta$ -acetoxy-6,6'-methylenecholestane (8.4 g) as needles, m.p. 114–115°,  $[\alpha]_D$  – 3.0° (c 1.2),  $\nu_{max}$  1735, 1645, 1240 and 887 cm<sup>-1</sup>. (Found: C, 81.6; H, 11.4.  $C_{30}H_{50}O_2$  requires: C, 81.4; H, 11.4%).

*3 $\beta$ -Acetoxy-7,7'-methylenecholestane (13)*

Reaction of 3 $\beta$ -hydroxycholestane-7-one (13.5 g), as above, gave the 7,7'-methylene compound (13) which on crystallization from MeOH gave needles (8.3 g), m.p. 64–66°,  $[\alpha]_D$  – 35° (c, 1.01),  $\nu_{max}$  1740, 1645, 1238 and 879 cm<sup>-1</sup>. (Found: C, 81.0; H, 11.4.  $C_{30}H_{50}O_2$  requires: C, 81.4; H, 11.4%).

*3 $\beta$ -Acetoxy-6 $\alpha$ ,6'-epoxycholestane (9)*

To a soln of 3 $\beta$ -acetoxy-6,6'-methylenecholestane (5 g) in dry benzene (500 ml) was added an ethereal soln of monoperoxyphthalic acid (0.3M; 120 ml) and the resulting soln kept at 20° for 2 days. The steroid material, isolated by means of ether, was adsorbed onto alumina (300 g).

Elution with light petroleum gave strating material (440 mg), m.p. 118.5–119.5°,  $[\alpha]_D$  – 1° (c, 1.03).

Elution with light petroleum–benzene (20:1) gave, after crystallization from MeOH, the 6 $\alpha$ ,6'-epoxide (9) as needles (2.85 g), m.p. 107–108°,  $[\alpha]_D$  + 27° (c, 1.02),  $\nu_{max}$  1740, 1250, 895 and 820 cm<sup>-1</sup>. (Found: C, 78.9; H, 11.0.  $C_{30}H_{50}O_3$  requires: C, 78.6; H, 11.0%).

*3 $\beta$ -Acetoxy-6 $\beta$ ,6'-epoxycholestane (10)*

Sodium hydride (1 g) was added to DMSO (60 ml) and the resulting suspension heated to 65–70° under N<sub>2</sub> until hydrogen evolution ceased. THF (20 ml) was added and the soln cooled to –10°. A soln of 6-ketocholestane-3 $\beta$ -ol (4 g) in THF (10 ml) was added, and the resulting soln allowed to warm to 20° (1 hr). The steroid material, isolated by use of ether, was acetylated with pyridine (20 ml) and Ac<sub>2</sub>O (15 ml) at 20° for 24 hr. The crude product isolated by means of ether was adsorbed onto alumina (250 g).

Elution with light petroleum–benzene (20:1) and crystallization from MeOH gave the 6 $\beta$ ,6'-epoxide (10) as prisms (2.9 g), m.p. 74–75°,  $[\alpha]_D$  – 11° (c, 0.92),  $\nu_{max}$  1740, 1250 and 900 cm<sup>-1</sup>. (Found: C, 78.5; H, 10.8.  $C_{30}H_{50}O_3$  requires: C, 78.6; H, 11.0%).

**LAH reduction of 6,6'-epoxides**

(a) **6 $\alpha$ ,6'-Epoxide (9).** To a soln of the epoxide (300 mg) in dry ether (20 ml) was added LAH (150 mg) and the mixture heated under reflux for 4 hr. Isolation by means of ether gave the crude 6 $\beta$ -methylcholestane-3 $\beta$ ,6 $\alpha$ -diol, m.p. 153–155°. Acetylation of the diol with Ac<sub>2</sub>O (2 ml) in pyridine (10 ml) at 20° for 24 hr, and isolation by means of ether, gave on crystallization from MeOH, 3 $\beta$ -acetoxy-6 $\beta$ -methylcholestane-6 $\alpha$ -ol (130 mg) as needles, m.p. 62–64°,  $[\alpha]_D + 21^\circ$  (c, 0.81),  $v_{\max}$  3580, 1735 and 1240 cm<sup>-1</sup>. (Found: C, 78.4; H, 11.3. C<sub>30</sub>H<sub>52</sub>O<sub>3</sub> requires: C, 78.2; H, 11.4%).

(b) **6 $\beta$ ,6'-Epoxide (10)** To a soln of the epoxide (194 mg) in dry ether (15 ml) was added LAH (100 mg) and the mixture heated for 1 hr. Isolation of the crude product by means of ether gave 6 $\alpha$ -methylcholestane-3 $\beta$ ,6 $\beta$ -diol (130 mg), m.p. 194–195° (lit. value,<sup>4</sup> m.p. 193–194°). Acetylation of the diol in the usual manner gave, after crystallization from MeOH, 3 $\beta$ -acetoxy-6 $\alpha$ -methylcholestane-6 $\beta$ -ol (118 mg), m.p. 160–161°,  $[\alpha]_D + 8^\circ$  (c, 1.01),  $v_{\max}$  3600, 1740 and 1250 cm<sup>-1</sup>. (lit. value,<sup>4</sup> m.p. 163°,  $[\alpha]_D + 6^\circ$ ).

**Preparation of 3 $\beta$ -acetoxy-7,7'-epoxycholestanes (14 and 15)**

To a soln of 3 $\beta$ -acetoxy-7,7'-methylenecholestane (5:1 g) in benzene (400 ml) was added monoperoxy-phthalic acid in ether (0.7M; 120 ml) and the resulting soln kept at –5° for 2 days. The steroidal material, isolated by means of ether, was adsorbed onto alumina (400 g).

Elution with light petroleum–benzene (3:1) and crystallization from MeOH gave the 7 $\beta$ ,7'-epoxide (14) as needles (602 mg), m.p. 107.5–108°,  $[\alpha]_D + 12^\circ$  (c, 1.01),  $v_{\max}$  1740, 1250, 828 and 766 cm<sup>-1</sup>. (Found: C, 78.5; H, 10.9. C<sub>30</sub>H<sub>50</sub>O<sub>3</sub> requires: C, 78.6; H, 11.0%).

Elution with light petroleum–benzene (3:1 and 3:2) gave fractions (total 3.6 g), shown (TLC) to be mixtures of the 7 $\alpha$ ,7- and 7 $\beta$ ,7'-epoxides.

Elution with light petroleum–benzene (3:1) gave, after crystallization from MeOH, 15 as plates (401 mg), m.p. 79–80°,  $[\alpha]_D - 16^\circ$  (c, 1.04),  $v_{\max}$  1740, 1250 and 725 cm<sup>-1</sup>. (Found: C, 78.7; H, 10.9. C<sub>30</sub>H<sub>50</sub>O<sub>3</sub> requires: C, 78.6; H, 11.0%).

Rechromatography of the mixed fractions gave further samples of the pure epoxides.

**LAH reduction of 7,7'-epoxides.**

(a) **7 $\alpha$ ,7'-Epoxide (15).** To a soln of the epoxide (150 mg) in dry ether (20 ml) was added LAH (100 mg) and the resulting suspension heated under reflux for 30 min. The steroidal material, isolated by means of ether, was acetylated using pyridine–Ac<sub>2</sub>O at 20°, and the crude product on crystallization from MeOH gave the 7 $\alpha$ -hydroxy compound (17) as plates (95 mg), m.p. 110–112°,  $[\alpha]_D + 19^\circ$  (c, 1.03),  $v_{\max}$  3575, 1737, 1240 cm<sup>-1</sup>. (Found: C, 78.2; H, 11.3. C<sub>30</sub>H<sub>52</sub>O<sub>3</sub> requires: C, 78.2; H, 11.4%).

(b) **7 $\beta$ ,7'-Epoxide (14).** Epoxide (200 mg), treated as above, gave on crystallization from MeOH the 7 $\beta$ -hydroxy compound (16) as needles (140 mg), m.p. 160–163°,  $[\alpha]_D + 9^\circ$  (c, 0.99),  $v_{\max}$  3580, 1735, 1238 cm<sup>-1</sup>. (Found: C, 78.0; H, 11.4. C<sub>30</sub>H<sub>52</sub>O<sub>3</sub> requires: C, 78.2; H, 11.4%).

**Dehydration of 7-hydroxy-7-methyl-compounds with thionyl chloride-pyridine**

(a) **7 $\alpha$ -Hydroxy-7 $\beta$ -methyl compound (17).** A soln of the 7 $\alpha$ -hydroxy compound (920 mg) in pyridine (10 ml) at –20° was treated with SOCl<sub>2</sub> (1 ml) and kept at –20° for 30 min. Isolation by use of pentane gave an oil (880 mg),  $v_{\max}$  1740, 1250 cm<sup>-1</sup>, shown (TLC) to contain two compounds identified (NMR) as 13 and 3 $\beta$ -acetoxy-7-methylcholest-6-ene.

(b) **7 $\beta$ -Hydroxy-7 $\alpha$ -methyl compound (16).** The 7 $\beta$ -alcohol (277 mg), treated as above, gave a crude product (essentially one compound: TLC) which on crystallization from MeOH yielded 3 $\beta$ -acetoxy-7-methylenecholestane (185 mg) as needles m.p. and mixed m.p. 64–66°,  $[\alpha]_D - 35^\circ$ .

**Reaction of 3 $\beta$ -acetoxycholestane-7-one with methyl magnesium iodide**

A soln of 3 $\beta$ -acetoxycholestane-7-one (4.9 g) in dry ether (60 ml) was added to an ethereal soln of MeMgI (1.5M; 40 ml) and the resulting suspension heated under reflux for 3 hr. The steroidal material, isolated by means of ether, was reacetylated using pyridine–Ac<sub>2</sub>O at 20° for 12 hr, and adsorbed onto alumina (400 g). Elution with light petroleum–benzene (1:2) and crystallization from MeOH gave 3 $\beta$ -acetoxy-7 $\beta$ -hydroxy-7 $\alpha$ -methylcholestane as needles (300 mg), m.p. 160–163°,  $[\alpha]_D + 9^\circ$  (c, 1.01). Further elution with light petroleum–benzene (1:2 to 2:3) gave mixtures (3.4 g; TLC) of the 7 $\beta$ -OH and 7 $\alpha$ -OH compounds. Finally elution with light petroleum–benzene (2:3) gave fractions which on crystallization from MeOH gave the 7 $\alpha$ -OH compound (880 mg) as plates, m.p. 110–112°  $[\alpha]_D + 18^\circ$  (c, 1.04). The relative yields of 7 $\alpha$ -OH:7 $\beta$ -OH compounds were estimated (TLC) as 3:1.

**3 $\beta$ -(2"-Tetrahydropyranoxy)cholest-6,6'-ene (20)**

To soln of 3 $\beta$ -hydroxy-6,6'-methylenecholestane (1.3 g) in dry ether (30 ml) and 2,3-dihydropyran (4 ml) was added *p*-toluene sulphonic acid (80 mg) and the soln kept at 20° for 24 hr. Isolation of the steroid material by means of ether, and crystallization from MeOH gave the *pyranyl ether* (20) as needles (1.1 g), m.p. 75–80°,  $[\alpha]_D$  +12.7° (c, 1.2),  $\nu_{max}$  1640, 885  $\text{cm}^{-1}$ . (Found: C, 81.8; H, 11.6.  $\text{C}_{33}\text{H}_{56}\text{O}_2$  requires: C, 81.8; H, 11.6%).

**3 $\beta$ -(2"-Tetrahydropyranoxy)-6 $\beta$ -hydroxymethylcholestane (21)**

Diborane, generated externally, was bubbled into a soln at 0° of the olefin (20; 1 g) in THF (50 ml) until the soln was saturated. The soln was kept at 20° for 3 days. After addition of water to decompose the excess diborane, aqueous NaOH aq (3M; 1.5 ml) was added dropwise, followed by addition of  $\text{H}_2\text{O}_2$  (30%; 1.5 ml) over 30 min. The steroid material, isolated by means of ether, was adsorbed onto alumina (80 g).

Elution with light petroleum gave the olefin (20; 84 mg), m.p. and mixed m.p. 75–80°.

Elution with benzene and crystallization from aqueous MeOH gave the *hydroxypyranyl ether* (21A) as needles (360 mg), m.p. 103–105°,  $[\alpha]_D$  −69° (c, 1.6),  $\nu_{max}$  3600  $\text{cm}^{-1}$ . (Found: C, 78.65; H, 11.6.  $\text{C}_{33}\text{H}_{58}\text{O}_3$  requires: C, 78.8; H, 11.6%).

Further elution with benzene and benzene–ether mixtures gave first mixtures (85 mg) followed by the second pure *hydroxypyranyl ether* (21B) as needles (342 mg; from acetone), m.p. 111–113°,  $[\alpha]_D$  +5° (c, 0.8),  $\nu_{max}$  3600  $\text{cm}^{-1}$ . (Found: C, 78.7; H, 11.6.  $\text{C}_{33}\text{H}_{58}\text{O}_3$  requires: C, 78.8; H, 11.6%).

**Hydrolysis of hydroxypyranyl ethers**

(a) *Compound 21A*. To a soln of 21A (50 mg) in EtOH (20 ml) was added HCl (0.1 ml; 12N) and the mixture warmed to 50° for 30 min. Isolation of the steroid material by use of ether and crystallization from MeOH gave 3 $\beta$ -hydroxy-6 $\beta$ -hydroxymethylcholestane (22) as needles (30 mg), m.p. 220–221°,  $[\alpha]_D$  −13° (c, 0.5),  $\nu_{max}$  3600, 3300  $\text{cm}^{-1}$ . (Found: C, 79.9; H, 11.9.  $\text{C}_{28}\text{H}_{50}\text{O}_2$  requires: C, 80.3; H, 12.0%).

(b) *Compound 21B*. Hydrolysis of 21B (50 mg) as above gave the diol (22; 29 mg), m.p. and mixed m.p. 222–223°,  $[\alpha]_D$  −14° (c, 0.6).

**Oxidation of hydroxypyranyl ether (21)**

A soln of either 21A or 21B (100 mg) in acetonitrile (15 ml) was stirred with  $\text{MnO}_2$  (2 g) at 20° for 7 hr. The crude steroid material, isolated by means of ether, gave an NMR spectrum with signals  $\delta$  9.85 ppm;  $W^1$  1.8 cs ( $\text{CHO}$ ) and  $\delta$  0.79 ppm (19-Me) and  $\nu_{max}$  2700, 1720  $\text{cm}^{-1}$ .

 **$\text{BF}_3$  Catalysed rearrangements of epoxides**

The epoxides were treated as 10% solns in dry benzene with freshly redistilled  $\text{BF}_3$ -etherate (1 ml/g steroid) at 20° for 1 min during which time the reactions were complete (TLC). The ratios of epimeric aldehydes (Table 1) formed from the epoxides were determined by repeated integration of the signals due to the aldehyde protons (Table 2 for positions) in the NMR spectra at 60 Mc for 15% solns (w/v) in  $\text{CDCl}_3$  with  $\text{SiMe}_4$  and  $\text{CHCl}_3$  as internal standards. For the 3,3'-, 6,6'- and 7,7'-epoxides the epimeric aldehydes were the only significant products formed (TLC etc).

**REFERENCES**

- 1 J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **23**, 3511 (1967).
- 2 D. H. R. Barton, A. da S. Campas-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).
- 3 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **84**, 866 (1962).
- 4 L. F. Fieser and J. Rigaudy, *Ibid.* **73**, 4660 (1951).
- 5 N. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry*, p. 19 et seq. Holden-Day, San Francisco (1964).
- 6 T. J. King and J. P. Yardley, *J. Chem. Soc.* 4308 (1961); E. Wenkert, P. W. Jeffs and J. R. Mahajan, *J. Am. Chem. Soc.* **86**, 2218 (1964); W. R. Chan, C. Willis, M. P. Cava and R. P. Stein, *Chem. & Ind.* 495 (1963).
- 7 I. T. Harrison, *Proc. Chem. Soc.* 110 (1964).