# 463. *The Synthesis of 4,5-Epoxy-4-methyl-steroids.*

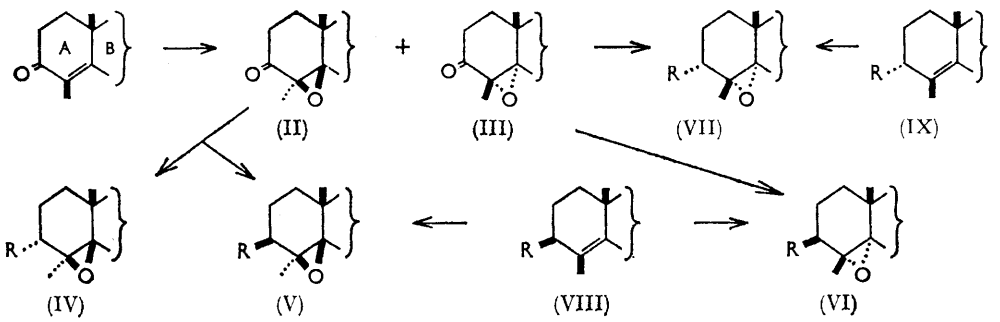
By J. M. Coxon, M. P. Hartshorn, and D. N. Kirk.

4-Methylcholest-4-en-3-one has been converted into its isomeric 4,5-epoxides, which were reduced by sodium borohydride to the corresponding epoxy-alcohols. Sodium borohydride reduction of 4-methylcholest-4-en-3-one gave a separable mixture of 3α- and 3β-hydroxycholest-4-ene. Epoxidation of the former gave only the 4α,5-epoxide.

In the course of other investigations we required the 4,5-epoxy-4-methylcholestanes of both the 3-acetoxy- and 3-oxo-series. Earlier investigators showed that alkaline hydrogen peroxide usually converts $\Delta^4$-3-ketones into a mixture of the α- and β-epoxy-ketones,[1] the relative yields being affected [2] by the nature of distant functional groups on the steroid nucleus.

Reaction of 4-methylcholest-4-en-3-one (I) with alkaline hydrogen peroxide gave the expected mixture of 4α,5- and 4β,5-epoxides, which were incompletely separated by chromatography. The epoxy-ketone ($[\alpha]_D$ +100°) eluted first was assigned the 4β,5-epoxide structure (II) by reason of its Cotton curve [3] (*a* +109); the second epoxy-ketone (III) ($[\alpha]_D$ −18°), assigned the α-epoxide structure, gave a negative Cotton curve (*a* −179). The specific rotations are consistent [1,4] with the above assignments. The α : β epoxide ratio for 4-methylcholestenone was *ca.* 2 : 3, compared with exclusive formation [2b] of the β-epoxide from cholestenone.

Sodium borohydride reduction of the β-epoxy-ketone (II) gave a product from which the major component, the 4β,5-epoxy-3α-hydroxy-compound (IVa), could be obtained by direct crystallisation. Acetylation of the residues from this crystallisation gave a mixture of the epoxy-acetates (IVb) and (Vb) which were separable by chromatography, the latter being identical with that reported by Julia and Lavaux.[5] Acetylation of the epoxy-alcohol (IVa) gave the epoxy-acetate (IVb).




[a: R = OH ; b: R = OAc]

Similarly, sodium borohydride reduction of the α-epoxy-ketone (III) gave, as the main product, the *trans*-epoxy-alcohol (VIa), the residues from the isolation of which, on acetylation, gave a separable mixture of the two epoxy-acetates (VIb) and (VIIb). The alcohol (VIa) on acetylation gave the acetate (VIb), identical with that reported earlier.[5] As the

[1] Camerino, Patelli, and Vercellone, *J. Amer. Chem. Soc.*, 1956, **78**, 3540; Ringold, Batres, Mancera, and Rosenkranz, *J. Org. Chem.*, 1956, **21**, 1432.
[2] (*a*) Henbest, *Proc. Chem. Soc.*, 1963, 159; (*b*) Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1822.
[3] Klyne, private communication.
[4] Bible, Placek, and Muir, *J. Org. Chem.*, 1957, **22**, 607.
[5] Julia and Lavaux, *Bull. Soc. chim. France*, 1963, 1231, and references therein.

epoxy-acetates (Vb) and (VIb) were obtained [5] by reaction of 3β-acetoxy-4-methylcholest-4-ene (VIIIb) with a peracid, the configurations of the four epoxy-acetates (IVb), (Vb), (VIb), and (VIIb) are firmly established.

Our observations that the *trans*-epoxy-alcohols (IVa) and (VIa) were the major sodium borohydride reduction products of the epoxy-ketones (II) and (III) agree with earlier results.[6]

As the report [5] of the epoxidation of 3β-acetoxy-4-methylcholest-4-ene (VIIIb) was not available at the time of the above work, we attempted to confirm the configurations of the acetates and ketones by preparation of the *cis*-epoxy-alcohols (Va) and (VIIa) by the *cis*-epoxidation [7] of the allylic alcohols (VIIIa) and (IXa). The alcohols were obtained by sodium borohydride reduction of the cholestenone (I), and separated chromatographically, the first-eluted isomer, m. p. 103—104°, $[\alpha]_D$ +133°, being assigned [8] the 3α-hydroxy-structure (IXa) whilst the second, m. p. 147—148°, $[\alpha]_D$ +60°, was assigned the 3β-structure (VIIIa). The constants quoted here for the 3β-compound do not agree with those quoted by Julia and Lavaux [5] (m. p. 152°, $[\alpha]_D$ +80°) but mixed crystals of the epimers had higher melting points than either isomer. Acetylation gave the corresponding acetates (VIIIb) and (IXb). The physical constants of the 3β-acetate (VIIIb), more readily purified than the alcohol, agreed with those quoted by Julia and Lavaux.[5]

Treatment of the 3α-hydroxy-compound (IXa) with peracid [7] gave only the 4α,5-epoxy-3α-hydroxy-compound (VIIa), which, on acetylation, gave a product identical with the minor reduction product of the α-epoxy-ketone (III). This result confirms the previous assignment of the C-3 configurations of epoxy-acetates (VIb) and (VIIb).

The correlation of structures of compounds derived from peracid treatment of the 3β-hydroxy-compound (VIIIa) was more difficult since, in this case, the epoxidation was not stereospecific. A mixture (A) of epoxy-alcohols, m. p. 122—123°, $[\alpha]_D$ +36°, which separated readily from a pentane solution of the crude epoxidation product, crystallised unchanged from pentane or methanol. Chromic acid oxidation [9] of mixture (A) gave a low yield (*ca.* 20%) of the α-epoxy-ketone (III), indicating that epoxidation of the 3β-hydroxy-compound (VIIIa) was not stereospecific. In accord with this conclusion, seeding of a methanol solution of sample (A) with 4α,5-epoxy-3β-hydroxy-compound (VIa) gave the epoxy-alcohol (VIa) in reasonable yield. Acetylation of (A) gave a crude product from which the 3β-acetoxy-4α,5α-epoxy-compound (VIb) was obtained (*ca.* 20%) by crystallisation; the residue, on chromatography, afforded the β-epoxy-epimer (Vb).

Since the major product from epoxidation of the allylic alcohol (VIIIa) was expected to be the *cis*-epoxy-alcohol (Va), we examined the pentane-soluble material (*ca.* 50%) remaining after removal of mixture (A). Crystallisation from aqueous methanol gave the *cis*-epoxy-alcohol (Va), which could be converted into the known acetate (Vb). The relative proportions of *cis*- and *trans*-epoxy-3β-alcohols (Va) and (VIa) were *ca.* 3 : 1.

## Experimental

Rotations were measured for chloroform solutions at room temperature unless otherwise stated. Infrared spectra were recorded for carbon disulphide solutions. Alumina was Peter Spence, Grade H, deactivated by the addition of 5% of 10% acetic acid. Light petroleum had b. p. 50—70°.

4,5-*Epoxy*-4-*methylcholestan*-3-*ones*, (II) and (III).—A solution of 4-methylcholest-4-en-3-one (I) (4 g.) in methanol (1·4 l.) was added to 4N-sodium hydroxide (16 c.c.) and hydrogen peroxide (40 c.c.; 30%), and the mixture stirred at 20° for 2 days. The product, isolated with ether, was chromatographed on alumina (200 g.). Elution with light petroleum–benzene

[6] Camerino and Cattapan, *Farmaco* (*Pavia*) *Ed. sci.*, 1958, **13**, 39; (*Chem. Abs.*, 1958, **52**, 13,767).
[7] Henbest and Wilson, *J.*, 1957, 1958.
[8] Mills, *J.*, 1952, 4976; *Chem. and Ind.*, 1953, 218.
[9] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.

(400 : 1) gave 49 fractions. Fractions 1—3 gave 4β,5-*epoxy*-4α-*methylcholestan*-3-*one* (II) (474 mg.) as prisms, m. p. 92—93° (from methanol), $[\alpha]_D$ +100° (*c* 1·02) (Found: C, 81·25; H, 11·0. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·3%), $\nu_{max.}$ 1709 cm.$^{-1}$ (C=O), rotatory dispersion in methanol: [*M*] (3275 Å), +5600°; (2800), −5340°. Fractions 17—21 gave 4α,5-*epoxy*-4β-*methylcholestan*-3-*one* (III) (251 mg.) as needles, m. p. 126—127° (from methanol), $[\alpha]_D$ −18° (*c* 1·04) (Found: C, 81·3; H, 11·0%), $\nu_{max.}$ 1709 cm.$^{-1}$ (C=O), [*M*] (in methanol) (3225 Å), −6800°; (2725), +11,150°. Fractions 4—16 and the mother-liquors from the above crystallisations were combined (2·8 g.); further samples of the β-epoxide (1·02 g.) and the α-epoxide (740 mg.) were obtained by repeated chromatography. The mixed epoxide residue (800 mg.) had $[\alpha]_D$ +65°, corresponding to an α : β ratio of 5 : 2. Fractions 22—49 were combined and crystallised from methanol, to give starting material (490 mg.), m. p. 102—103°, $[\alpha]_D$ +113° (*c* 0·98).

*Reduction of* 4β,5-*Epoxy*-4α-*methylcholestan*-3-*one* (II).—A solution of sodium borohydride (200 mg.) in water (2 c.c.) was added to a solution of the epoxy-ketone (1 g.) and sodium hydroxide (100 mg.) in methanol (100 c.c.). After 1 hr. at 20° the solution was diluted with water and extracted with ether to give 4β,5-*epoxy*-4α-*methylcholestan*-3α-*ol* (IVa) (670 mg.) as needles, m. p. 126·5—127·5° (from methanol), $[\alpha]_D$ +26° (*c* 1·1) (Found: C, 80·7; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%), $\nu_{max.}$ 3610 cm.$^{-1}$ (OH). The residue (320 mg.) was treated with pyridine (3 c.c.) and acetic anhydride (0·4 c.c.), and kept at 20° for 24 hr. The product, isolated in ether, was adsorbed on alumina. Elution with light petroleum–benzene (25 : 1) gave 50 fractions. Crystallisation of fractions 1—8 from methanol gave 3β-acetoxy-4β,5-epoxy-4α-methylcholestane (Vb) (31 mg.) as needles, m. p. 83—84°, $[\alpha]_D$ +16° (*c* 0·98 in dioxan) (lit.,[5] m. p. 81°, $[\alpha]_D$ +14°). Fractions 38—50 were crystallised from methanol, to give 3α-*acetoxy*-4β,5-*epoxy*-4α-*methylcholestane* (IVb) (45 mg.) as needles, m. p. 95—96·5°, $[\alpha]_D$ +12° (*c* 1·02 in dioxan) (Found: C, 78·8; H, 11·0. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%), $\nu_{max.}$ 1748 and 1236 cm.$^{-1}$ (OAc). Further samples of epoxy-acetates (IVb) and (Vb) were obtained by chromatography of the combined residues from the above crystallisations and mixed fractions 9—37.

3α-*Acetoxy*-4β,5-*epoxy*-4α-*methylcholestane* (IVb).—A solution of the epoxy-alcohol (IVa) (830 mg.) in acetic anhydride (0·85 c.c.) and pyridine (5 c.c.) was kept at 20° for 24 hr. Isolation with ether gave the epoxy-acetate (IVb) (650 mg.) as needles, m. p. 95—96·5° (from methanol), $[\alpha]_D$ +12° (*c* 1·19 in dioxan).

*Reduction of* 4α,5-*Epoxy*-4β-*methylcholestan*-3-*one* (III).—A solution of the epoxy-ketone (1·2 g.) and sodium hydroxide (120 mg.) in methanol (120 c.c.) was treated with sodium borohydride (240 mg.) in water (2·4 c.c.). After 1 hr. at 20° the crude product was isolated with ether, to give 4α,5-*epoxy*-4β-*methylcholestan*-3β-*ol* (VIa) (422 mg.) as needles, m. p. 148—149° (from methanol), $[\alpha]_D$ +65° (*c* 0·99) (Found: C, 80·5; H, 11·7. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%), $\nu_{max.}$ 3636 cm.$^{-1}$ (OH). The residues (780 mg.) were treated with pyridine (4·8 c.c.) and acetic anhydride (0·78 c.c.), and kept at 20° for 24 hr. Isolation with ether gave 3β-acetoxy-4α,5-epoxy-4β-methylcholestane (VIb) (247 mg.) as needles, m. p. 134—135·5° (from methanol), $[\alpha]_D$ +74° (*c* 1·01) (lit.,[5] m. p. 131°, $[\alpha]_D$ +80°). After removal of solvents from the above mother-liquor, the residue (632 mg.) was adsorbed on alumina (60 g.), and elution with light petroleum–benzene (4 : 1) gave 30 fractions. Fractions 1—5, on crystallisation from methanol, gave 3α-*acetoxy*-4α,5-*epoxy*-4β-*methylcholestane* (VIIb) (21 mg.) as needles, m. p. 122—124°, $[\alpha]_D$ +57° (*c* 0·71) (Found: C, 78·45; H, 10·9. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%), $\nu_{max.}$ 1745 and 1244 cm.$^{-1}$ (OAc). Fractions 22—30 gave more 3β-acetoxy-compound (VIb) (52 mg.). Further samples of epoxy-acetates (VIb) and (VIIb) were obtained by chromatography of the combined residues from the above crystallisations and mixed fractions 6—21.

3β-*Acetoxy*-4α,5-*epoxy*-4β-*methylcholestane* (VIb).—A solution of the epoxy-alcohol (275 mg.) in acetic anhydride (0·3 c.c.) and pyridine (2 c.c.) was kept at 20° for 24 hr. Isolation with ether gave the epoxy-acetate (VIb) (230 mg.) as needles, m. p. 134—135·5° (from methanol), $[\alpha]_D$ +74° (*c* 0·98).

*Reduction of* 4-*Methylcholestenone* (I) *with Sodium Borohydride*.—A boiling solution of the ketone (4 g.) in methanol (200 c.c.) was treated with a solution of sodium borohydride (800 mg.) and sodium hydroxide (800 mg.) in water (8 c.c.). The solution was heated under reflux for 1·5 hr., diluted with water (200 c.c.), and allowed to cool. The crude 4-methylcholest-4-en-3-ols which were deposited, m. p. 135—143°, $[\alpha]_D$ +71° (*c* 1·06 in dioxan), were dissolved in light petroleum and adsorbed on alumina (280 g.). Elution with light petroleum–benzene (9 : 1)

gave first 4-*methylcholest*-4-*en*-3α-*ol* (IXa), m. p. 103—104°, $[\alpha]_D$ +133° (*c* 1·0) (Found: C, 83·75; H, 12·3. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%), $\nu_{max.}$ 3597 cm.$^{-1}$ (OH). A series of mixed fractions was next eluted, and the final fractions gave 4-methylcholest-4-en-3β-ol (VIIIa) (2·7 g.) as needles, m. p. 147—148° (from methanol), $[\alpha]_D$ +60° (*c* 0·92 in dioxan) (Found: C, 83·9; H, 12·3%), $\nu_{max.}$ 3597 cm.$^{-1}$ (lit.,[5] m. p. 152°, $[\alpha]_D$ +80° for impure material).

3α-*Acetoxy*-4-*methylcholest*-4-*ene* (IXb).—The 3α-hydroxy-compound (60 mg.) was treated with acetic anhydride (0·5 c.c.) in pyridine (1 c.c.) at 20° for 20 hr. Isolation with ether gave the *acetate* as leaflets, m. p. 98—99° (from ethanol), $[\alpha]_D$ +136° (*c* 1·13 in dioxan) (Found: C, 81·2; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%), $\nu_{max.}$ 1739 and 1238 cm.$^{-1}$ (OAc).

3β-*Acetoxy*-4-*methylcholest*-4-*ene* (VIIIb).—Acetylation of the alcohol (VIIIa) as above gave the acetate as needles, m. p. 109—110° (from methanol), $[\alpha]_D$ +46·5° (*c* 1·03 in dioxan), $\nu_{max.}$ 1737 and 1238 cm.$^{-1}$ (OAc) (lit.,[5] m. p. 110—111°, $[\alpha]_D$ +45°).

*Epoxidation of* 4-*Methylcholest*-4-*en*-3α-*ol* (IXa).—A solution of the alcohol (60 mg.) and monoperphthalic acid (45 mg.) in ether (2 c.c.) was kept at 20° for 19 hr. The crude epoxy-alcohol, isolated with ether, was treated with pyridine (0·5 c.c.) and acetic anhydride (0·06 c.c.), at 20°, for 24 hr. The product, isolated with ether, was adsorbed on alumina (6 g.). Elution with light petroleum gave 3α-acetoxy-4α,5-epoxy-4β-methylcholestane (VIIb) (42 mg.) as needles, m. p. (from methanol) and mixed m. p. 120—121°, $[\alpha]_D$ +58° (*c* 0·70).

*Epoxidation of* 4-*Methylcholest*-4-*en*-3β-*ol* (VIIIa).—A solution of monoperphthalic acid (1·85 g.) in ether (20 c.c.) was added to a solution of the alcohol (2·4 g.) in chloroform (5 c.c.), and the mixture kept at 20° for 18 hr. The product, isolated with ether, formed needles (600 mg.), m. p. 123—124° (from pentane). This material (A), $[\alpha]_D$ +36° (*c* 1·5 in dioxan), was a mixture (*ca.* 1 : 1) of the α- (VIa) and the β-epoxy-compound (Va). Further crops of mixture (A) (350 mg.) were obtained from the pentane solution. Treatment of the pentane-soluble residues with aqueous methanol afforded 4β,5-*epoxy*-4α-*methylcholestan*-3β-*ol* (Va) as needles, m. p. 105—107° (from aqueous acetone), $[\alpha]_D$ +17° (*c* 1·24 in dioxan) (Found: C, 80·4; H, 11·8. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%), $\nu_{max.}$ 3571 cm.$^{-1}$ (OH).

The combined residues (1·28 g.) from above were acetylated and the product was adsorbed on alumina (50 g.). Elution with light petroleum gave 3β-acetoxy-4-methylcholest-4-ene (VIIIb) (155 mg.), m. p. and mixed m. p. 109—110°. Light petroleum–benzene (20 : 1) eluted the 3β-acetoxy-4β,5β-epoxide (Vb) (840 mg.), m. p. and mixed m. p. 83—84°, $[\alpha]_D$ +16° (*c* 0·78 in dioxan), then the α-epoxide (VIb) (115 mg.), m. p. and mixed m. p. 133—135°, $[\alpha]_D$ +73° (*c* 1·0 in dioxan).

3β-*Acetoxy*-4β,5-*epoxy*-4α-*methylcholestane* (Vb).—Acetylation of the epoxy-alcohol (Va) (100 mg.) in acetic anhydride–pyridine (1 : 1; 3 c.c.) at 20° for 18 hr. and isolation with ether gave the epoxy-acetate (Vb) (72 mg.), m. p. (from methanol) and mixed m. p. 83—84°, $[\alpha]_D$ +16° (*c* 0·79 in dioxan).

The authors thank Professor W. Klyne for the measurement of the optical rotatory dispersion curves.

UNIVERSITY OF CANTERBURY,
CHRISTCHURCH, NEW ZEALAND.

[*Received, November 18th,* 1963.]