788. *Steroidal αβ-Epoxy-ketones. Part I. Rearrangement of 4α,5-Epoxy-5α-cholestan-3-one and its 4β,5β-Isomer by means of the Boron Trifluoride–Ether Complex.*

By D. J. Collins.

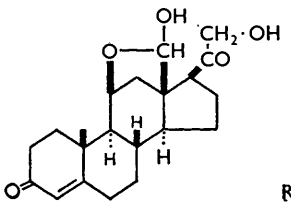
The preparation of 4α,5-epoxy-5α-cholestan-3-one is described. Treatment of 4α,5-epoxy-5α-, and 4β,5-epoxy-5β-cholestan-3-one with the boron trifluoride–ether complex in benzene solution gave, in each case, a mixture of 4-hydroxy-cholest-4-en-3-one, and A-nor-5β-cholestan-3-one. The latter is formed by spontaneous deformylation of 5-formyl-A-nor-5ξ-cholestan-3-one (XXXI), whose synthesis it had been hoped to achieve.

The usual approach [1] to the partial synthesis of aldosterone (I) from steroids lacking an 18-oxygen function involves opening ring D, introducing a potential aldehyde function at position 18, and re-forming ring D. Recently, two independent groups of workers [2] reported the direct introduction, into the *intact* tetracyclic steroid molecule, of a nitrogen

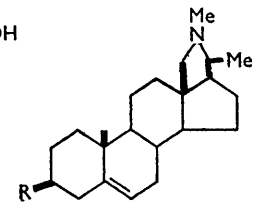
[1] Heusser, Wohlfahrt, Müller, and Anliker, *Helv. Chim. Acta*, 1955, **38**, 1399; Anliker, Müller, Wohlfahrt, and Heusser, *ibid.*, p. 1404; Barton, Campos-Neves, and Scott, *J.*, 1957, 2698.

[2] Corey and Hertler, *J. Amer. Chem. Soc.*, 1958, **80**, 2903; Buchschacher, Kalvoda, Arigoni, and Jeger, *ibid.*, p. 2905.

function on to $C_{(18)}$, to give steroids of the type (II). Subsequently, the Swiss group [3] announced the conversion of conessine (II; R = NMe_2) into 18-hydroxyprogesterone. The various total syntheses of aldosterone [4] involve closure of ring D in a tricyclic intermediate containing a potential 18-aldehyde function.



(I)



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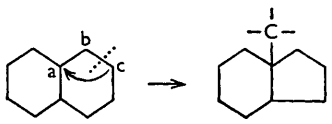


(III) (IV)

It would be useful if an angular aldehyde group could be created by the formal rearrangement (III) ⟶ (IV), which involves fission of bond b–c and concomitant ring closure of c to a.

In a detailed study of the acid-catalysed rearrangement of αβ-epoxy-ketones, House and Wasson [5] showed that treatment of the epoxy-ketone (V) with the boron trifluoride–ether complex in benzene, gave a mixture of the keto-aldehyde (VI) (33%), the ketone (VII) (28%), and the α-diketone (VIII) (3%). In principle, a similar rearrangement of the perhydrochrysene derivative (IX) should afford the keto-aldehyde (X), and the α-diketone (XI). Actually, the ratio of the products (X) and (XI) may be controlled by steric and stereoelectronic factors different from those operating in the case of the cyclohexane derivative (V). The more accessible compound (XII; R = C_8H_{17}), and its hitherto unknown isomer (XIII; R = C_8H_{17}), were chosen for the study of the rearrangement of αβ-epoxy-ketones in which the β-carbon is at a ring junction.

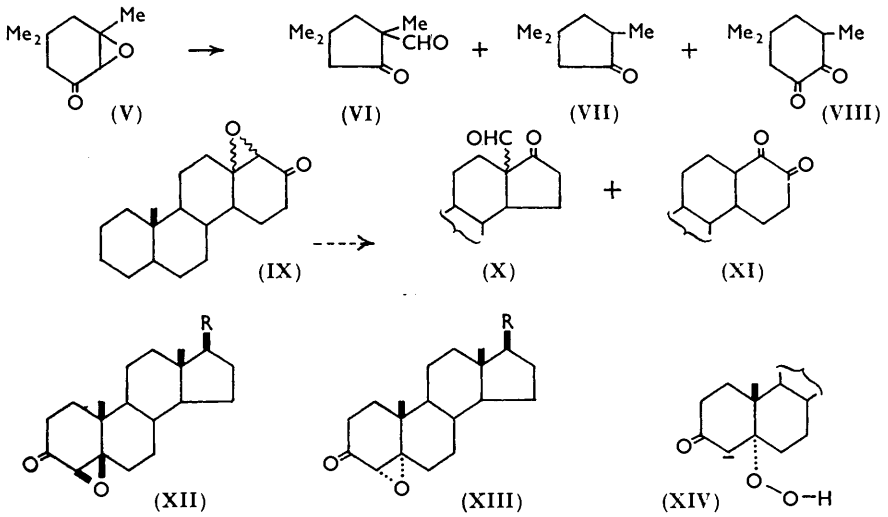
4β,5-Epoxy-5β-cholestan-3-one (XII; R = C_8H_{17}) was prepared by the action of alkaline hydrogen peroxide on cholest-4-en-3-one.[6] None of the 4α,5α-epoxide (XIII; R = C_8H_{17}), an expected by-product (cf. refs. 7—10), could be isolated from the mother-liquors of the isomer (XII; R = C_8H_{17}). If α-approach of the hydroperoxide ion to give the carbanion intermediate (XIV) (cf. ref. 11) is favoured, the predominant formation of the 4β,5β-epoxide must be due to subsequent inversion at position 5; the lack of stereospecificity of this reaction cannot be fully explained.[12]

The 4α,5α-epoxy-ketone (XIII; R = C_8H_{17}) was prepared as follows. The mixture of epimeric alcohols (XVI; R = H) and (XVII), obtained by reduction of cholest-4-en-3-one (XV) with lithium aluminium hydride,[13] was acetylated and chromatographed on alumina to give 3β-acetoxycholest-4-ene (XVI; R = Ac). Epoxidation of the latter with perbenzoic acid gave 3β-acetoxy-4α,5-epoxy-5α-cholestane (XVIII; R = Ac).[14]

When the Δ^4-acetate (XVI; R = Ac) was treated with perbenzoic acid solution which

[3] Buzzetti, Wicki, Kalvoda, and Jeger, *Helv. Chim. Acta*, 1959, **42**, 388.
[4] Lardon, Schindler, and Reichstein, *ibid.*, 1957, **40**, 666; Heusler, Ueberwasser, Wieland, and Wettstein, *ibid.*, p. 787; Schmidlin, Anner, Billeter, Heusler, Ueberwasser, Wieland, and Wettstein, *ibid.*, pp. 1034, 1438, 2291; Wieland, Heusler, Ueberwasser, and Wettstein, *ibid.*, 1958, **41**, 74, 416; Heusler, Wieland, and Wettstein, *ibid.*, p. 997; Johnson, Collins, Pappo, and Rubin, *J. Amer. Chem. Soc.*, 1958, **80**, 2585.
[5] House and Wasson, *J. Amer. Chem. Soc.*, 1957, **79**, 1488.
[6] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1822.
[7] Camerino, Patelli, and Vercellone, *J. Amer. Chem. Soc.*, 1956, **78**, 3540.
[8] Bible, Placek, and Muir, *J. Org. Chem.*, 1957, **22**, 607.
[9] Ringold, Batres, Mancera, and Rosenkranz, *ibid.*, 1956, **21**, 1432.
[10] Camerino and Patelli, *Il Farmaco (Pavia) Ed. Sci.*, 1956, **11**, 579; *Chem. Abs.*, 1957, **51**, 2007.
[11] Bunton and Minkoff, *J.*, 1949, 665.
[12] House and Ro, *J. Amer. Chem. Soc.*, 1958, **80**, 2428.
[13] (*a*) McKennis and Gaffney, *J. Biol. Chem.*, 1948, **175**, 217; (*b*) Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1949, **32**, 265.
[14] Henbest and Wilson, *J.*, 1957, 1958.

contained a trace of sulphuric acid, the sole product was 3β-acetoxy-5α-cholestan-4β,5-diol (XIX; R = Ac). The latter has been tentatively assigned the 4β,5α-configuration since it was also obtained by mild acid hydrolysis of the epoxide (XVIII; R = Ac), and diaxial fission of 4α,5α-epoxides usually gives the α-configuration at position 5.[7]



Hydrolysis of the epoxy-acetate (XVIII; R = Ac) with 2% methanolic potassium hydroxide to 4α,5-epoxy-5α-cholestan-3β-ol (XVIII; R = H), followed by oxidation with chromic anhydride in pyridine, or with chromic acid in acetone, gave 4α,5-epoxy-5α-cholestan-3-one (XIII; R = C_8H_{17}), m. p. 124—125°, $[\alpha]_D$ −44°. The molecular-rotation difference of the latter and cholest-4-en-3-one (ΔM_D = −532°) is consistent with the corresponding values for other 4α,5α-epoxy-3-keto-steroids (see Table).

Molecular-rotation differences of 4α,5α-epoxy-3-keto-steroids and the parent Δ⁴-3-keto-steroids.

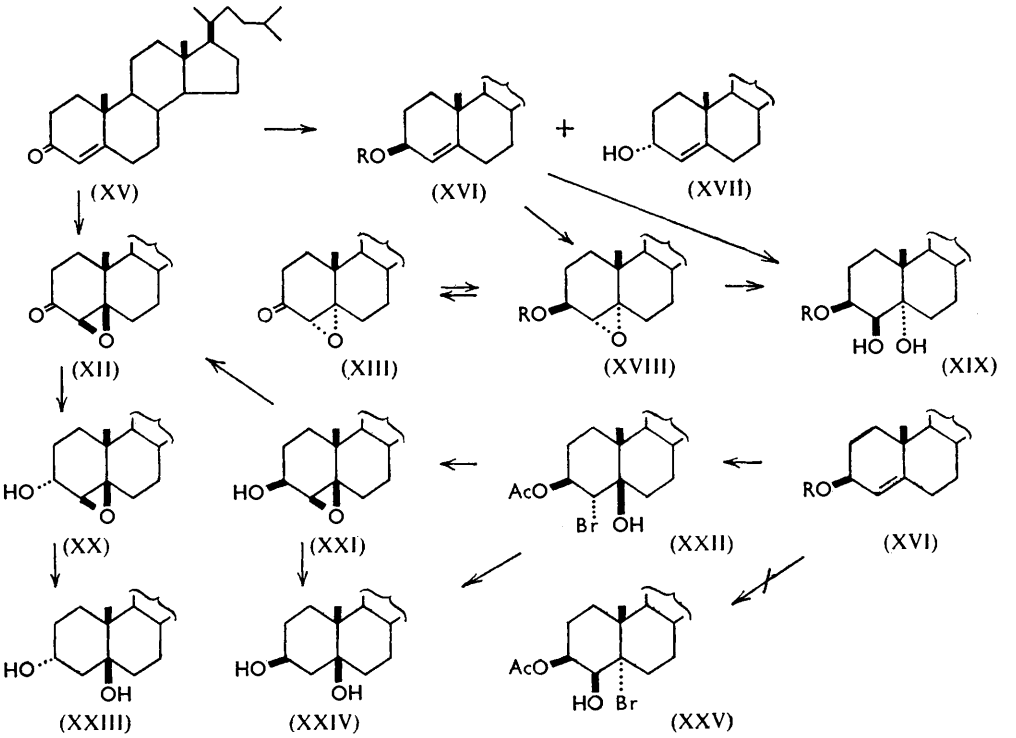
Steroid	M_D	ΔM_D	Ref.
4α,5-Epoxy-5α-cholestan-3-one	−175°	−532°	
Cholest-4-en-3-one	+357		15
4α,5-Epoxy-17β-hydroxy-17α-methyl-5α-androstan-3-one	−278	−509	9
17α-Methyltestosterone	+231		9
4α,5-Epoxy-17α,21-dihydroxy-5α-pregnane-3,11,20-trione 20-(ethylene ketal)	−46	−669	9
Cortisone 20-(ethylene ketal)	+623		16
4α,5-Epoxy-5α-androstan-3-one	−100	−440	7
Testosterone	+340		17
4α,5-Epoxy-5α-pregnane-3,20-dione	+48	−583	8
Progesterone	+631		17

The infrared spectrum of the epoxy-ketone (XIII; R = C_8H_{17}) showed bands at 889 and 861 cm.$^{-1}$, which are characteristic of steroidal αβ-epoxy-ketones.[18] The isomeric epoxy-ketone (XII) showed corresponding bands at 876 and 860 cm.$^{-1}$. Reduction of 4α,5-epoxy-5α-cholestan-3-one (XIII) with sodium borohydride regenerated 4α,5-epoxy-5α-cholestan-3β-ol (XVIII; R = H). Similar reduction of the isomeric 4β,5β-epoxy-ketone (XII) again gave an equatorial alcohol, namely, 4β,5-epoxy-5β-cholestan-3α-ol (XX).

A possible route to the 4α,5α-epoxide (XIII) from 3β-acetoxycholest-4-ene (XVI;

[15] Barton and Jones, *J.*, 1943, 602.
[16] Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *J. Org. Chem.*, 1953, **18**, 70.
[17] Barton and Cox, *J.*, 1948, 783.
[18] Sallmann and Tamm, *Helv. Chim. Acta*, 1956, **39**, 1340; cf. Günthard, Heusser, and Fürst, *ibid.*, 1953, **36**, 1900; Patterson, *Analyt. Chem.*, 1954, **26**, 823.

R = Ac) *via* a diaxial bromohydrin with a 4α- or 5α-hydroxyl group was investigated. Addition of the elements of hypobromous acid to Δ^{2}-,[19] Δ^{11}-,[20] Δ^{16}-,[21] and $\Delta^{9(11)}$-steroids [22,23] has been accomplished by using *N*-bromosuccinimide or *N*-bromoacetamide in perchloric

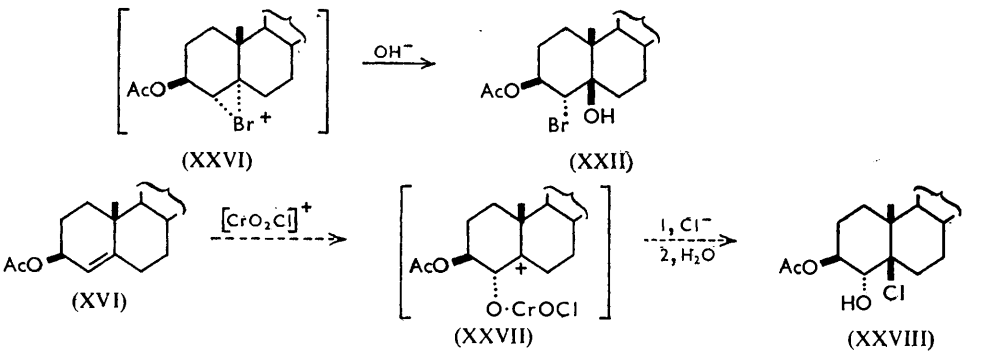


acid.[22] The reaction of Δ^{4}-steroids with this reagent does not appear to have been recorded. 3β-Acetoxycholest-4-ene (XVI; R = Ac) with *N*-bromosuccinimide in perchloric acid gave the undesired 4α-bromo-5β-acetoxy-compound (XXII), whose structure was established as follows. With methanolic potassium hydroxide it gave 4β,5-epoxy-5β-cholestan-3β-ol (XXI), m. p. 95—96°, (lit.,[6] m. p. 95—96°), which with chromic acid in acetone gave 4β,5-epoxy-5β-cholestan-3-one (XII). The bromohydrin must therefore have a β-oriented hydroxyl group, and must be (XXII) rather than (XXV) since it was unaffected by chromic acid in acetone. Reduction of the bromohydrin with lithium aluminium hydride gave, albeit in poor yield, the 3β,5β-diol (XXIV), which was similarly obtained from the epoxy-alcohol (XXI).[24] This does not permit distinction between structures (XXII) and (XXV), since reduction of the bromohydrin may proceed *via* the epoxide (XXI) (cf. the reduction of certain α-bromo-ketones [25]) which could be obtained from either (XXII) or (XXV). Supporting evidence for structure (XXII) for the bromohydrin is the fact that the frequency of the 3β-acetate carbonyl absorption band (1748 cm.$^{-1}$) is higher than normal (*ca.* 1736 cm.$^{-1}$), a phenomenon which has been observed for 3β-acetoxy-5β-hydroxy-steroids and has been attributed to interaction of the two groups by virtue of their proximity in space.[26] The structure of the bromohydrin (XXII) can be rationalised by assuming

[19] Slates and Wendler, *J. Amer. Chem. Soc.*, 1956, **78**, 3749.
[20] Herz, Fried, and Sabo, *ibid.*, p. 2017.
[21] Löken, Kaufmann, Rosenkranz, and Sondheimer, *ibid.*, p. 1738.
[22] Fried and Sabo, *ibid.*, 1953, **75**, 2273; 1957, **79**, 1130.
[23] Herr, Hogg, and Levin, *ibid.*, 1956, **78**, 500.
[24] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1885.
[25] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.
[26] Nickon, *J. Amer. Chem. Soc.*, 1957, **79**, 243.

α-attack of bromonium ion to give the cation (XXVI), followed by β-attack of hydroxyl ion to give the bromohydrin (XXII). This mechanism requires abnormal fission of the 5α-axial bond of the 4α,5α-bromonium ion (XXVI), rather than the expected 4α-equatorial bond-fission * [cf. the hydrolysis of the 4α,5α-epoxide (XVIII; R = Ac) mentioned above].

It has been shown [19] that treatment of a Δ^2-steroid with chromyl chloride affords a chlorohydrin which is *positionally* isomeric with that which is obtained by the action of hypohalous acid. However, the reaction of the Δ^4-steroid (XVI) with chromyl chloride



failed to give the expected chlorohydrin (XXVIII), which theoretically could have been formed *via* the cation (XXVII) (cf. Cristol and Eilar [27]).

The boron trifluoride–ether complex has been used in the rearrangement of αβ-unsaturated-,[28] α-hydroxy-,[29] and simple steroidal epoxides.[30] Also, its reaction with 3-substituted 5α,6α- and 5β,6β-epoxy-steroids has been studied,[31] but no systematic examination of its effect on steroidal αβ-epoxy-ketones has been recorded. In a preliminary report on the preparation of 4-substituted testosterone analogues, Camerino *et al.*[7] stated that treatment of 4α,5-epoxy-17β-hydroxy-5α-androstan-3-one (XIII; R = OH), and its 4β,5β-isomer (XII; R = OH), with the boron trifluoride–ether complex in benzene gave 4-hydroxytesterone. The yield was not given, and no mention was made of any by-products.

When 4β,5-epoxy-5β-cholestan-3-one (XII) was treated with one equivalent of the boron trifluoride–ether complex in benzene for 5 min., a mixture of the starting epoxy-ketone and 4-hydroxycholest-4-en-3-one (XXXVI) was obtained. With a reaction period of 18½ hr. there resulted a complex mixture from which was isolated 35% of the enolic diketone (XXXVI), and 3% of 5β-A-norcholestan-3-one (XXXIII). The latter must be formed *via* the desired keto-aldehyde (XXXI) by deformylation either in the reaction mixture or during the subsequent chromatography for which neutral alumina was used. In an attempt to trap the angular aldehyde group *in situ*, the 4β,5β-epoxy-ketone (XII) was refluxed for 6 hr. with ethylene glycol and the boron trifluoride–ether complex in benzene under a water-separator. Chromatography of the gummy product gave 4% of 5β-A-norcholestan-3-one (XXXIII), and 2·6% of a substance, m. p. 176—177°,

* Grateful acknowledgment is made to one of the referees for drawing attention to this point.

[27] Cristol and Eilar, *J. Amer. Chem. Soc.*, 1950, **72**, 4353.

[28] Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Heusser, Heusler, Eichenberger, Honegger, and Jeger, *ibid.*, 1952, **35**, 295; Heusler and Wettstein, *ibid.*, 1953, **36**, 398; Budziarek, Johnson, and Spring, *J.*, 1952, 3410; Bladon, Henbest, Jones, Lovell, Wood, and Woods; Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921; Elks, Evans, Robinson, Thomas, and Wyman, *ibid.*, p. 2933; Henbest and Wagland, *J.*, 1954, 728.

[29] Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936; Djerassi and Lemin, *J. Amer. Chem. Soc.*, 1954, **76**, 5672.

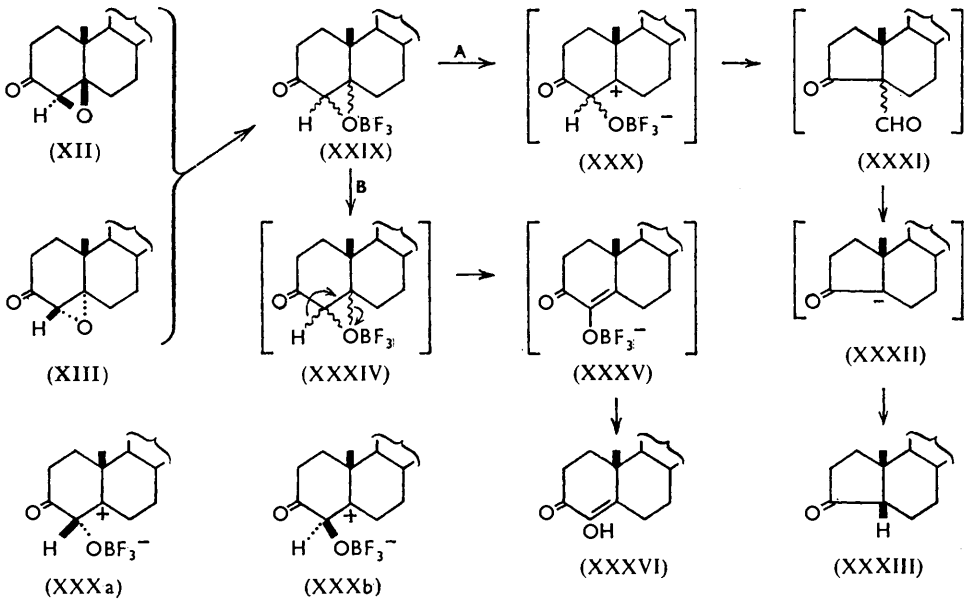
[30] Henbest and Wrigley, *J.*, 1957, 4596.

[31] *Idem, ibid.*, p. 4765.

which showed neither hydroxyl nor carbonyl absorption in the infrared spectrum and gave analyses for the bis(ethylene ketal) of (XXXI) or of the keto-form of (XXXVI). Acid-hydrolysis and deformylation of the former should have afforded the A-nor-3-ketone (XXXIII); the compound, m. p. 176—177°, was unaffected by aqueous acetic acid in dioxan at 100°. Owing to the low yield of this substance it was not studied further.

4α,5-Epoxy-5α-cholestan-3-one (XIII) was recovered unchanged after treatment with the boron trifluoride–ether complex in benzene for 15 min., but with a reaction period of 23 hr. there was obtained 5β-A-norcholestan-3-one (XXXIII) (25%), and 4-hydroxycholest-4-en-3-one (XXXVI) (30%). It has been observed that the substitution of ether for benzene as solvent greatly retards the rate of rearrangement of αβ-unsaturated epoxides by the boron trifluoride–ether complex (Bladon *et al.*[28]), and in the case of benzylideneacetophenone oxide [32] causes the formation of a fluorohydrin rather than a β-keto-aldehyde. In the present instance, the 4α,5α-epoxy-ketone (XIII) was unaffected by the boron trifluoride–ether complex in refluxing ether.

The rearrangement of the epoxy-ketones (XII) and (XIII) may be regarded as proceeding by the two paths A and B (cf. House [5,32]). The initially formed co-ordination complex (XXIX) could afford the carbonium ion (XXX), which by acyl-migration would give the



keto-aldehyde (XXXI). Deformylation of either the 5α- or the 5β-isomer of the latter, involving formation and protonation of the anion (XXXII), would give the A/B-*cis*-fused A-nor-3-ketone (XXXIII). The undescribed 5α-isomer of (XXXIII) was not isolated in any of these experiments. Alternatively, loss of a proton by the electron-shift (XXXIV), and hydrolysis of the intermediate (XXXV), would give the enolic diketone (XXXVI). The yield of the A-nor-3-ketone (XXXIII) was approximately ten times greater from the rearrangement of the 4α,5α-epoxy-ketone (XIII) than from its 4β,5β-isomer (XII). This is explicable on the basis that the intermediate carbonium ion (XXXa) is more stable than its isomer (XXXb) owing to the 1,3-diaxial interactions of the bulky, quasi-axial $-O\cdot BF_3$ group in the latter. Also, the stereochemistry at position 4 in the carbonium ion (XXX) may affect the rate of acyl-migration.

If the presumed intermediate β-keto-aldehyde (XXXI) has the 5α-configuration, it may be possible to prevent deformylation by having present in the molecule a 7α-hydroxyl

[32] House, *J. Amer. Chem. Soc.*, 1956, **78**, 2298.

group which would be favourably situated for hemiacetal formation. The main problem is to promote rearrangement by path A (β-keto-aldehyde formation) rather than by path B (α-diketone formation). It is intended to do further work in this direction.

Experimental

Infrared spectra were measured with a Perkin–Elmer model 21 double-beam spectrophotometer. Ultraviolet spectra were measured with a Unicam SP. 500 spectrophotometer for ethanol solutions. Optical rotations refer to chloroform solutions. Unless stated otherwise, B.D.H. alumina was used. Light petroleum refers to the fraction of b. p. 40—70°.

4β,5-Epoxy-5β-cholestan-3-one (XII; R = C_8H_{17}).—4β,5-Epoxy-5β-cholestan-3-one was prepared by the action of alkaline hydrogen peroxide on cholest-4-en-3-one.[6] The epoxy-ketone crystallised from chloroform–methanol as prisms, m. p. 118—119°, $[\alpha]_D$ +124°, $\nu_{max.}$ (in Nujol) 1718s (C=O), 1247m, 876m, and 860s (epoxide) (lit.,[6] m. p. 116—117°, $[\alpha]_D^{21}$ +134°, 136°).

The mother-liquors were evaporated and chromatographed on alumina. Although it is almost certainly present, the 4α,5α-epoxy-ketone (XIII; R = C_8H_{17}) could not be obtained.

Reduction of 4β,5-Epoxy-5β-cholestan-3-one with Sodium Borohydride.—A solution of 4β,5-epoxy-5β-cholestan-3-one (200 mg.) in 80% dioxan–water (14 ml.) was treated with sodium borohydride (40 mg.) in the same solvent (4 ml.). The mixture was kept for 48 hr. at room temperature, then excess of reagent was decomposed with acetic acid (2 drops), and the mixture was poured into ice-water (100 ml.). The precipitate, m. p. 135—148°, was chromatographed in 50% benzene–light petroleum on alumina. Elution with benzene (130 ml.) gave a solid (170 mg.), which after several recrystallisations from methanol gave 4β,5-epoxy-5β-cholestan-3α-ol (XX) as laths, m. p. 161—162°, $[\alpha]_D$ +25° (lit.,[6] m. p. 158—159°, $[\alpha]_D$ +31·4°).

5β-Cholestane-3α,5-diol (XXIII).—The epoxy-alcohol (XX) (150 mg.) was reduced with lithium aluminium hydride (100 mg.) in the usual way. Recrystallisation of the product from methanol gave 5β-cholestane-3α,5-diol (XXIII) as laths m. p. 190—192·5°, $[\alpha]_D$ +35° (lit.,[6] m. p. 192—193°, $[\alpha]_D$ +47·3°).

3β-Acetoxycholest-4-ene (XVI; R = Ac).—Cholest-4-en-3-one (12·0 g.) was reduced with lithium aluminium hydride (1·5 g.) in ether to a mixture of the epimeric alcohols (XVI; R = H), and (XVII).[13] The crude product was treated at room temperature overnight with acetic anhydride (25 ml.) in pyridine (120 ml.). The mixture was poured on ice-water (1·5 l.). The gummy acetates were isolated with benzene, and chromatographed in light petroleum on acid-washed alumina (170 g.). Elution with light petroleum (350 ml.) gave a solid (10·1 g.), which after crystallisation from ethanol gave 3β-acetoxycholest-4-ene (7·5 g.), m. p. 86°, $[\alpha]_D$ +10° (lit.,[13a] m. p. 85°).

Reduction of this acetate with lithium aluminium hydride gave cholest-4-en-3β-ol (XVI; R = H), m. p. 131—132°, $[\alpha]_D$ +53°, needles from ethanol (lit.,[13b] m. p. 131—132°, $[\alpha]_D^{22}$ +44·6°).

Action of Perbenzoic Acid on 3β-Acetoxycholest-4-ene.—(a) *3β-Acetoxy-4α,5-epoxy-5α-cholestane* (XVIII; R = Ac). To a cooled solution of 3β-acetoxycholest-4-ene (1·0 g.) in chloroform (50 ml.) was added a cold 0·28M-chloroform solution (10 ml.) of perbenzoic acid. The mixture was kept overnight at room temperature, washed with water, dried (Na_2SO_4), and passed through neutral alumina (30 g.; Woelm grade 1). Evaporation of the chloroform eluate (100 ml.) under reduced pressure gave a solid which on trituration with methanol gave crystals, m. p. 100—112°. Two recrystallisations from methanol afforded 3β-acetoxy-4α,5-epoxy-5α-cholestane (640 mg., 62%), m. p. 119—120° $[\alpha]_D$ +55° (lit.,[14] m. p. 117—119°, $[\alpha]_D$ +60°).

(b) *3β-Acetoxy-5α-cholestane-4β,5-diol* (XIX; R = Ac). To a solution of 3β-acetoxycholest-4-ene (1·0 g.) in chloroform (50 ml.) at 0° was added a 0·51M-chloroform solution (7 ml.) of perbenzoic acid containing a trace of sulphuric acid. After being kept overnight at room temperature, the chloroform solution was washed with 10% sodium carbonate solution and water, dried (Na_2SO_4), and evaporated. Several recrystallisations of the residue from acetone–methanol gave *3β-acetoxy-5α-cholestane-4β,5-diol* (500 mg.) as matted needles m. p. 199°, $[\alpha]_D$ +23°, $\nu_{max.}$ (in Nujol) 3528, 3589 (OH), 1712 cm.$^{-1}$ (OAc) (Found: C, 75·4; H, 10·9. $C_{29}H_{50}O_4$ requires C, 75·3; H, 10·9%).

Mild Acid-hydrolysis of 3β-Acetoxy-4α,5-epoxy-5α-cholestane.—A solution of the epoxy-acetate (100 mg.) in acetone (25 ml.) and water (2·5 ml.) containing 2N-sulphuric acid (0·2 ml.) was kept at room temperature for 48 hr. After removal of the acetone under reduced pressure, water was added, and the product was isolated with ether. Three recrystallisations from

acetone–methanol gave needles, m. p. 198—199° alone or mixed with 3β-acetoxy-5α-cholestane-4β,5-diol obtained as described above.

5α-Cholestane-3β,4β,5-triol (XIX; R = H).—(*a*) Hydrolysis of 3β-acetoxy-5α-cholestane-4β,5-diol (100 mg.) for 2 hr. with refluxing 2% methanolic potassium hydroxide (12 ml.) afforded the *triol monohydrate*, m. p. 215—216°, $[\alpha]_D$ +43° in pyridine, needles (from aqueous methanol) (Found: C, 74·1; H, 11·6. $C_{27}H_{48}O_3,H_2O$ requires C, 73·9; H, 11·5%).

The same triol was obtained by reduction of the monoacetate (XIX; R = Ac) with lithium aluminium hydride.

4α,5-Epoxy-5α-cholestan-3-one (XIII; R = C_8H_{17}).—3β-Acetoxy-4α,5-epoxy-5α-cholestane (XVIII; R = Ac) (100 mg.) was refluxed with 2% methanolic potassium hydroxide (12 ml.) for 1 hr. Removal of most of the methanol *in vacuo* and addition of water gave a solid, m. p. 135—136°. Recrystallisation of this from aqueous ethanol gave 4α,5-epoxy-5α-cholestan-3β-ol (XVIII; R = H) as needles m. p. 136—137°, $[\alpha]_D$ +54°.

To a stirred solution of this epoxy-alcohol (1·0 g.) in acetone (100 ml.) was added dropwise 1·45 ml. of chromic acid solution which was prepared by dissolving chromic anhydride (6·67 g.) in water (10 ml.) and concentrated sulphuric acid (5·33 ml.) and diluting it to 25 ml. with water.[33] After addition of a few drops of methanol, the product was isolated in the usual manner and adsorbed on alumina (40 g.) from light petroleum. Elution with 8 : 92 benzene–light petroleum gave a solid which on crystallisation from methanol afforded *4α,5-epoxy-5α-cholestan-3-one* (610 mg.) as blades, m. p. 123—124·5°, $[\alpha]_D$ −44°, $\nu_{max.}$ (in Nujol) 1714s (C=O), 1244m, 889m, 861m cm.$^{-1}$ (epoxide) (Found: C, 81·3; H, 11·0. $C_{27}H_{44}O_2$ requires C, 80·94; H, 11·1%).

Oxidation of the epoxy-alcohol (XVIII; R = H) with chromic anhydride in pyridine gave a slightly better yield of the epoxy-ketone (XIII), but the formation of a stable emulsion during isolation of the product made this method inconvenient.

Reduction of 4α,5-Epoxy-5α-cholestan-3-one (XIII; R = C_8H_{17}) *with Sodium Borohydride.*—To a solution of the epoxy-ketone (100 mg.) in 4 : 1 dioxan–water (8 ml.) was added a solution of sodium borohydride (20 mg.) in the same solvent (2 ml.). After the mixture had been kept at room temperature for 45 hr., excess of reagent was decomposed with acetic acid (2 drops), and the mixture poured into ice-water (20 ml.). The crude product, m. p. 120°, was adsorbed on alumina (5 g.) from 1 : 4 benzene–light petroleum. Elution with 1 : 99 ether–benzene gave a solid (75 mg.) which on crystallisation from aqueous methanol gave 4α,5-epoxy-5α-cholestan-3β-ol (XVIII; R = H), m. p. 136—137°, undepressed on admixture with the epoxy-alcohol obtained by hydrolysis of 3β-acetoxy-4α,5-epoxy-5α-cholestane (XVIII; R = Ac).

4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate (XXII).—To a solution of 3β-acetoxycholest-4-ene (900 mg.) in dioxan (30 ml.) was added powdered *N*-bromosuccinimide (4·8 g.). The suspension was cooled in an ice-bath, and 10% aqueous perchloric acid (22·5 ml.) added dropwise with stirring. The mixture was stirred for a further 3 hr., then 5% sodium hydrogen sulphite solution (10 ml.) and water (60 ml.) were added. The white precipitate melted at 140°. Several recrystallisations from light petroleum gave *4α-bromo-5β-cholestane-3β,5-diol 3-acetate*, as plates, m. p. 147° (decomp.), $[\alpha]_D$ +32°, $\nu_{max.}$ (in CS_2) 3650 (OH), 1748 cm.$^{-1}$ (acetate C=O) (Found: C, 66·2; H, 9·4; Br, 15·7. $C_{29}H_{49}O_3Br$ requires C, 66·3; H, 9·4; Br, 15·2%).

4β,5-Epoxy-5β-cholestan-3β-ol (XXI).—To a suspension of the above bromohydrin (120 mg.) in methanol (10 ml.) was added a solution of potassium hydroxide (100 mg.) in water (0·15 ml.) and methanol (1·0 ml.). The solid rapidly dissolved. The solution was refluxed for 30 min., then concentrated *in vacuo* and diluted with water (10 ml.). Recrystallisation of the precipitate from aqueous methanol gave 4β,5-epoxy-5β-cholestan-3β-ol as needles, m. p. 96—97° (lit.,[13b] m. p. 95—96°).

Oxidation of this epoxy-alcohol (17 mg.) in acetone (2 ml.) with 0·3 ml. of chromic acid solution (prepared as described above), and two recrystallisations of the product from chloroform–methanol afforded 4β,5-epoxy-5β-cholestan-3-one, m. p. and mixed m. p. 118—119°.

Attempted Oxidation of the Bromohydrin (XXII) *with Chromic Acid.*—To a solution of the bromohydrin (100 mg.) in acetone (10 ml.) was added chromic acid solution (0·15 ml.; prepared as before), dropwise with shaking. The product crystallised from methanol as plates, m. p. and mixed m. p. with the starting material, 147°. The hydroxyl group of the bromohydrin must therefore be tertiary.

Reduction of the Bromohydrin (XXII) *with Lithium Aluminium Hydride.*—A solution of the bromohydrin (100 mg.) in ether (20 ml.) was added dropwise to a slurry of lithium aluminium

[33] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.

hydride (60 mg.) in ether (30 ml.), and the mixture was refluxed 30 min. The product was adsorbed on alumina (3·0 g.) from 1 : 1 benzene–light petroleum. Elution with 4 : 96 ether–benzene (60 ml.) gave 5β-cholestane-3β,5-diol (25 mg.) which crystallised from aqueous methanol as needles, m. p. 143—144°, undepressed on admixture with a specimen prepared as below.

Elution with 1 : 4 ether–benzene (100 ml.) gave a solid (50 mg.), m. p. 178—188°, which gave a negative Beilstein test for halogen. Two recrystallisations from aqueous methanol gave needles of a substance, m. p. 185—190°, which was depressed on admixture with 5β-cholestane-3α,5-diol, m. p. 190—192·5°. Since the physical constants of the other epimeric 3,5-diols are different, the product of m. p. 185—190° is probably a dimer formed by bimolecular reduction.

5β-*Cholestane*-3β,5-*diol* (XXIV).—Reduction of 4β,5-epoxy-5β-cholestan-3β-ol (XXI) with lithium aluminium hydride, and crystallisation of the product from light petroleum gave the 3β,5β-diol as prisms, m. p. 147—149°, $[\alpha]_D$ +40° (lit.,[24] m. p. 148—149°, $[\alpha]_D$ +52·3°).

Action of Chromyl Chloride on 3β-*Acetoxycholest*-4-*ene*.—Treatment of 3β-acetoxycholest-4-ene with chromyl chloride (cf. Slates and Wendler [19]) gave a green halogen-containing gum which with methanolic potassium hydroxide or with chromic acid in acetone, followed in each case by chromatography on alumina, failed to give a crystalline epoxide or ketone respectively.

Action of the Boron Trifluoride–Ether Complex on 4β,5-*Epoxy*-5β-*cholestan*-3-*one* (XII; R = C_8H_{17}).—(*a*) To a solution of the epoxy-ketone (1·0 g.) in dry benzene (20 ml.) was added freshly distilled boron trifluoride–ether complex (0·31 ml.). The mixture, which became greenish-yellow, was kept at room temperature for 5 min., diluted with ether (25 ml.), and washed with 10% aqueous sodium hydrogen carbonate, then with water, dried (Na_2SO_4), and evaporated. The gummy residue was dissolved in light petroleum and adsorbed on neutral alumina (30 g.; Woelm grade 1). Elution with 8 : 92 benzene–light petroleum and with benzene gave a total of 330 mg. of a solid, crystallisation of which from methanol gave 4β,5-epoxy-5β-cholestan-3-one, m. p. and mixed m. p. 117—119°. Elution with ether, and recrystallisation of the solid thus obtained, gave 4-hydroxycholest-4-en-3-one (250 mg.) as needles, m. p. 147—148°, $[\alpha]_D$ +84°, $\lambda_{max.}$ 279 mμ (13,260 in EtOH), $\nu_{max.}$ (in Nujol) 3420 (ON), 1665, 1632 cm.$^{-1}$ (enolic α-diketone) {Lit.,[34] m. p. 151°, $[\alpha]_D$ +80°, $\lambda_{max.}$ 278 mμ (13,000 in EtOH)}.

(*b*) The reactants (same quantities) were mixed and kept at room temperature for 18½ hr. The product was isolated as before and chromatographed on neutral alumina (30 g.; Woelm grade 1). Elution with 1 : 99 ether–benzene (100 ml.) gave a solid (35 mg., 4%), which after two recrystallisations from methanol gave 5β-A-norcholestan-3-one (XXXIII) as prisms, m. p. 76·5°, $[\alpha]_D$ +130°, $\nu_{max.}$ (in Nujol) 1740 cm.$^{-1}$ (5-ring ketone) (lit.,[35] m. p. 73·5—74·5°, $[\alpha]_D$ +105° (measured before purification), $\nu_{max.}$ (in CS_2) 1736 cm.$^{-1}$}. Elution with ether gave 4-hydroxycholest-4-en-3-one (350 mg.), m. p. 144—146°.

Action of the Boron Trifluoride–Ether Complex and Ethylene Glycol on 4β,5-*Epoxy*-5β-*cholestan*-3-*one* (XII; R = C_8H_{17}).—A mixture of the epoxy-ketone (1·0 g.), ethylene glycol (2 ml.), and the boron trifluoride–ether complex (0·3 ml.) in benzene (50 ml.) was refluxed for 6 hr. under a water-separator. The cooled mixture was washed with water, dried (Na_2SO_4), and evaporated. The residue was adsorbed on neutral alumina (30 g.; Woelm grade 1). Elution with 3 : 1 benzene–light petroleum (100 ml.) gave 31 mg. (2·6%) of crystals, m. p. 175°, which after two recrystallisations from chloroform–methanol afforded needles of a *bis-dioxolan*, m. p. 176—177° (the infrared spectrum showed neither hydroxyl nor carbonyl absorption) (Found: C, 76·4; H, 10·7. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%). This compound resisted hydrolysis with aqueous acetic acid in dioxan at 100°.

Elution with 1 : 99 ether–benzene gave 5β-A-norcholestan-3-one (40 mg.), m. p. and mixed m. p. 76°. No other crystalline products were obtained.

Action of the Boron Trifluoride–Ether Complex on 4α,5-*Epoxy*-5α-*cholestan*-3-*one* (XIII; R = C_8H_{17}).—(*a*) A solution of the epoxy-ketone (250 mg.) in benzene (6 ml.) was treated with freshly distilled boron trifluoride–ether complex (0·08 ml.). The mixture rapidly became yellow, then pale orange. After 23 hr. the mixture was diluted with ether (30 ml.), washed with 10% aqueous sodium hydrogen carbonate, then with water, dried (Na_2SO_4), and evaporated *in vacuo*. The pale lemon oily residue was chromatographed in light petroleum on neutral

[34] Fieser and Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728.
[35] Smith and Nace, *J. Amer. Chem. Soc.*, 1954, **76**, 6119.

alumina (10 g.; Woelm grade I). Elution with 1 : 1 benzene–light petroleum gave 5β-A-norcholestan-3-one (64 mg., 25%), m. p. and mixed m. p. 74—75°. Elution with ether gave 4-hydroxycholest-4-en-3-one, m. p. 146—148° (30%).

When the same quantities of reactants were used and the reaction period was 15 min., the only crystalline material isolated was the starting epoxy-ketone (120 mg.).

(*b*) A solution of the epoxy-ketone (250 mg.) in dry ether (15 ml.) was treated with the boron trifluoride–ether complex (0·08 ml.) and left at room temperature for 22 hr., then diluted with ether (40 ml.) and worked up as before. The product crystallised from methanol as needles, m. p. 124—125°, undepressed on admixture with the starting material.

When a solution of the epoxy-ketone (250 mg.) and the boron trifluoride–ether complex (0·08 ml.) in dry ether (15 ml.) was refluxed for 4 hr., the product from the washed, dried (Na_2SO_4) ether extract, melted at 120—123° and did not depress the m. p. of the starting material.

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