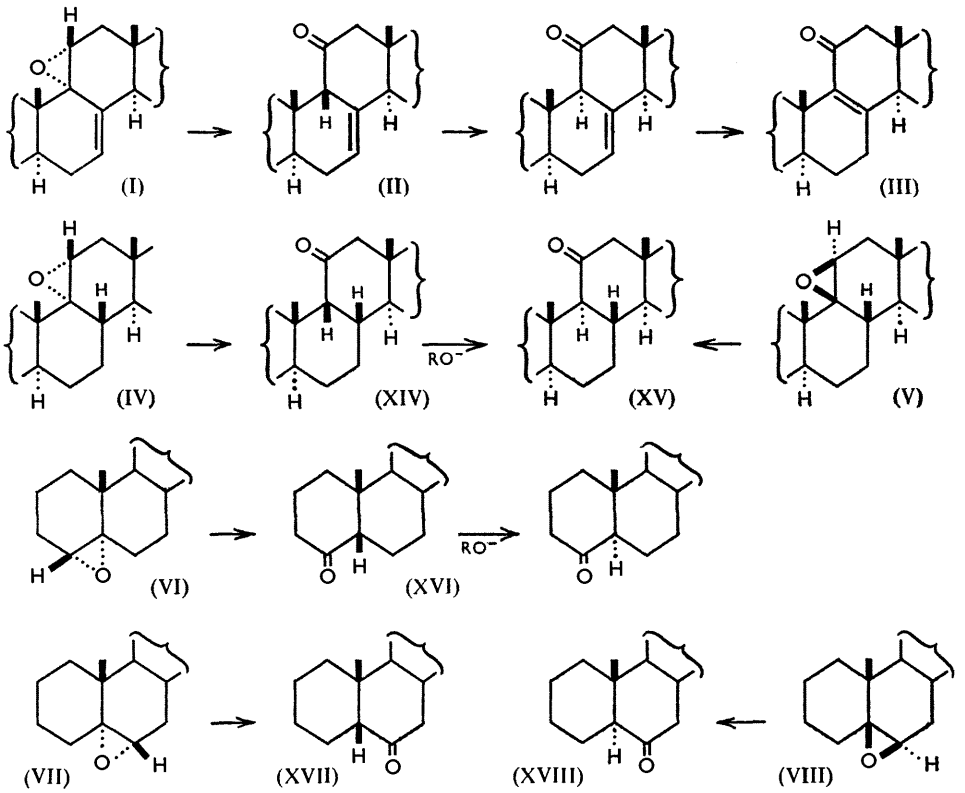
923. *Aspects of Stereochemistry. Part VI.* Reactions of Some Epoxy-steroids with the Boron Trifluoride–Ether Complex.*

By H. B. Henbest and T. I. Wrigley.

The reactions of several simple tri- and tetra-alkylated epoxides of the steroid series with the boron trifluoride–ether complex in benzene solution have been examined. Ketones or conjugated dienes appear to be formed as primary reaction products, the former arising by stereospecific hydride shifts.

Two more examples of the formation of vicinal epoxides by reduction of bromo-ketones with lithium aluminium hydride are described. These reactions proceed *via* the complex anions of diaxial bromohydrins, diequatorial bromohydrins not cyclising under the same conditions.

Rearrangements of vicinal epoxides to carbonyl compounds are catalysed by many electrophilic reagents, such as Lewis acids. In the case of purely aliphatic epoxides the most extensive previous work has been carried out by the French school [1] using magnesium



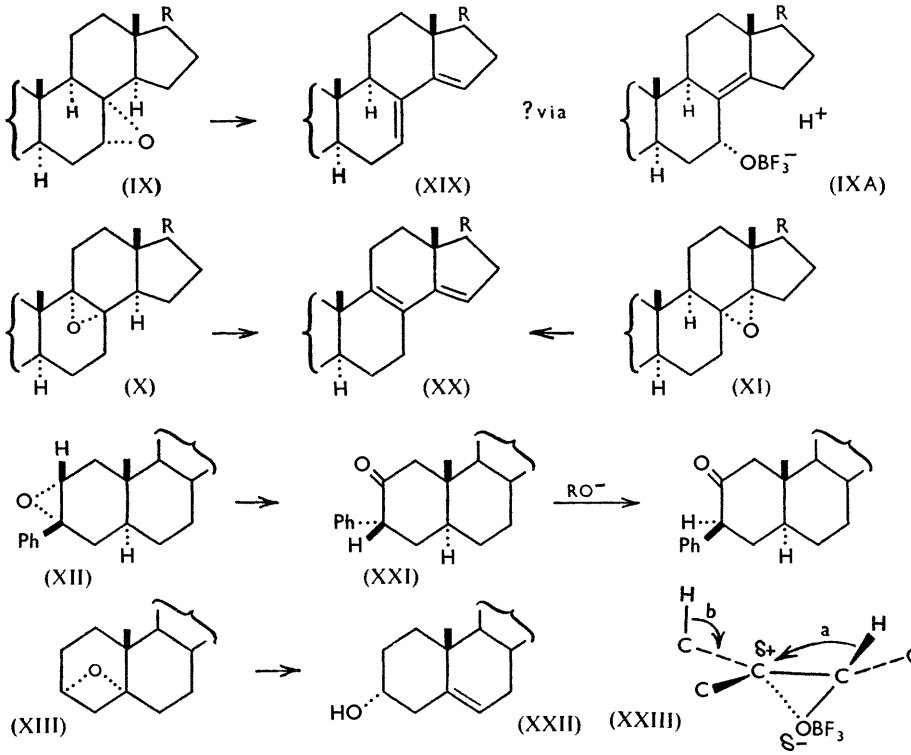
bromide in ethereal solution as catalyst. In general it was found that magnesium derivatives of bromohydrins, >CBr·C(O·MgBr)<, were formed first in such reactions, but that when heated or kept these derivatives were transformed into aldehydes or ketones with loss of magnesium bromide. In more recent years the availability and reactivity of boron trifluoride have led to the employment of this Lewis acid in a variety of reactions. In

* Part V, *J.*, 1957, 1982.

[1] Cf., *inter al.*, Tiffeneau and Tchoubar, *Compt. rend.*, 1938, **207**, 918.

particular, House and his co-workers [2] have studied its reactions with the epoxy-stilbenes and with many aryl substituted αβ-epoxy-ketones, and have shown that isomerisations of the epoxy-function to a carbonyl group may be accompanied by 1 : 2-shifts of phenyl or benzoyl groups.

In order to initiate enquiry into the reactions of purely aliphatic epoxides with boron trifluoride, compounds of the steroid series have been chosen for study. Apart from material aspects of availability of suitable epoxides and the crystallinity of starting materials and products, advantages of investigation in this series were (*a*) that stereochemical changes could be expected to be discerned easily and (*b*) that the reactions could be followed polarimetrically, thus providing information about relative velocities as well



as making it easier to stop each experiment when the initial stage of the reaction was complete. This last consideration proved of some importance as it was found that the reactive catalyst was usually able to cause further (slower) reactions, thus complicating the isolation of primary products. The only steroid reaction subjected previously to thorough scrutiny illustrates the value of polarimetric measurements, for after the first report [3] that the 9α : 11α-epoxy-Δ^7-compound (I) * could be isomerised by boron trifluoride to an 11-oxo-Δ^8-steroid (III), it was shown [4,5] that the strongly lævorotatory 9β-compound (II) was an intermediate which could be isolated in excellent yield after a brief reaction time.

The epoxides (IV—XI) have now been treated with boron trifluoride in benzene

* Partial steroid formulæ are used in this paper.

[2] House and his co-workers, *J. Amer. Chem. Soc.*, 1954, **76**, 1235; 1955, **77**, 6525; 1956, **78**, 2298, 4394.

[3] Heusser, Eichenberger, Kurath, Dallenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106.

[4] Bladon, Henbest, Jones, Lovell, Wood, and Woods; Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

[5] Heusler and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 398.

solution at room temperature to give the products shown (XIV—XX). Also included in the formulæ are the phenyl-substituted epoxide (XII), a preliminary report of whose isomerisation to the ketone (XXI) has been given,[6] and 3 : 5-epoxycholestane (XIII) which has been shown [7] to be readily isomerised to *epi*cholesterol.

The ketonic products of these reactions all arise by *cis*-shifts of hydrogen, thus establishing the general nature of the reaction first observed with the formation of the ketone (II) from the epoxide (I). In five cases it may be noted that this stereospecificity causes the formation of the ketonic isomer with the less stable adjacent bridgehead configuration.

Previous work,[1,2] with magnesium bromide and boron trifluoride (both in ethereal solution) has shown that bromohydrins and fluorohydrins can be initial products, but may be converted by the same Lewis acids into carbonyl compounds. On the other hand, with boron trifluoride in benzene, only carbonyl products were isolated from αβ-epoxy-ketones, the question whether these were formed *via* fluorohydrins under these conditions being left open.[2] With the saturated alicyclic epoxides (IV—VIII), halogenohydrin formation is likely to proceed predominantly or wholly by *trans*-opening of the epoxide ring. Satisfactory routes for the formation of the observed ketones from *trans*-fluorohydrin intermediates being difficult to visualise, we incline to the belief that these aliphatic ketones arise directly by hydride shifts under the present experimental conditions. A possible explanation for the previously observed greater tendency for halogenohydrin formation in ether than in benzene may be connected with the lower electrophilic activity of boron trifluoride in the oxygenated solvent (cf. the much slower rates of the conversions, I ⟶ II, VII ⟶ XVII, and XI ⟶ XX in ether than in benzene). In consequence, in ether, opening of the epoxide ring may more often require the combined attack of a halide nucleophil and the Lewis acid.

The facts now available appear to be consistent with the proposal that the powerfully electrophilic boron trifluoride promotes considerable ionisation of the bond from oxygen to the more alkylated carbon centre (cf. XXIII): the presence of a suitably placed olefinic bond [cf. (I)] will obviously assist such ionisation. Depending on the energy paths available, the intermediate represented by (XXIII) can either yield a ketone by a hydride shift (a) or lose an adjacent proton (b). For further discussion the reactions of the steroid epoxides will now be considered in three groups, depending on whether the electron-deficient centre in the intermediate can be placed on $C_{(9)}$, $C_{(5)}$, or $C_{(8)}$.

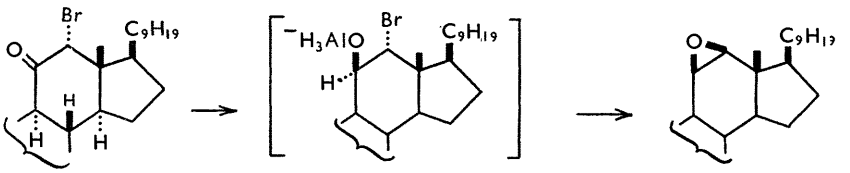
Under the chosen conditions the times for complete reaction of the epoxides (I), (IV), and (V) were <0·5 min., ~70 hr., and ~5 min. The 9α : 11α-epoxide (IV) was by far the least reactive of all of the compounds studied. This behaviour cannot be ascribed solely to an inaccessibility towards the catalyst as the 9β : 11β-epoxide (V) isomerises without difficulty. It seems more likely that relatively unfavourable energy relations are connected with the necessity of converting ring B or ring C into a boat conformation [4] in the formation of the 9β : 11-ketone (XIV): a similar conformational inhibition does not arise in the production of the 9α-11-ketone (XV). The exceedingly rapid isomerisation of the unsaturated epoxide (I), despite the concomitant creation of a 9β-configuration, is clearly caused by resonance participation of the 7 : 8-double bond.

The reactions of boron trifluoride with the epoxides (VI) and (VIII) were complete within a few minutes and the ketonic products (XVI) and (XVIII) were readily isolated. Under similar conditions the 5α : 6α-epoxide (VII) was partly unchanged and only by careful chromatography was it possible to separate the expected ketone (XVII) from non-crystalline products. In exhibiting some reluctance for the occurrence of a hydride shift to an unfavourable bridgehead configuration, this epoxide resembles the 9α : 11α-epoxide discussed above. The ease of reaction with the 4α : 5α-epoxide (which also affords a 5β-compound) may be connected with the greater flexibility of the terminal ring wherein reaction takes place.

[6] Cookson and Hudec, *Proc. Chem. Soc.*, 1957, 24.
[7] Clayton, Henbest, and Smith, *J.*, 1957, 1982.

A 1 : 3-hydride shift (or two 1 : 2-shifts) does not take place on treatment of the 3α : 5α-epoxide (XIII) with boron trifluoride. Loss of a proton from $C_{(6)}$ by the alternative reaction gives *epi*cholesterol in high yield.[7]

Although a hydride shift in the 7α : 8α-epoxide (IX) would yield a 7-ketone with a stable 8β-configuration, the 7 : 14-diene (XIX) is formed instead in a rapid reaction. The allylic alcohol derivative (cf. IXA) formed initially in this reaction contains the very stable 8(14)-double bond, and this circumstance apparently contributes driving force for the reaction observed. As the formation of the 8(14)-olefinic intermediate is in effect a *cis*-elimination it may be produced *via* a strongly developed 8-carbonium ion. The subsequent transformation of an intermediate such as (IXA) into the 7 : 14-diene (XIX) may be represented in several ways. The 7 : 14-diene actually obtained was not quite pure (from optical rotation evidence): other possible products are (*a*) the 6 : 8(14)-diene formed by loss of boron trifluoride and water towards $C_{(6)}$ from the intermediate (IXA), (*b*) the 7 : 9-diene produced *via* an 8(9)-unsaturated intermediate analogous to (XA), and (*c*) the 8(9) : 14-diene formed by partial isomerisation of the 7 : 14-diene. That the last isomerisation can occur (? catalysed by hydrogen fluoride) under the reaction conditions was shown by the isolation of the 8(9) : 14-diene (XX) when the reaction solution was kept for 24 hr. This isomerisation was first detected polarimetrically. As the 8(9) : 14-diene so formed was also not pure (not sufficiently lævorotatory) it seems probable that some non-isomerisable 7 : 9-diene is formed initially along with the 7 : 14-diene. Treatment of the 7 : 8-epoxide (IX) with mineral acid in aqueous dioxan has been shown to yield a 3 : 2 mixture of 7 : 9- and 7 : 14-dienes.[8] The two tetrasubstituted epoxides (X) and (XI) both gave the 8(9) : 14-diene (XX) in rapid reactions, and intermediates similar to (XA) may be suggested. No information is available concerning the relative importance of $C_{(8)}$, $C_{(9)}$, and $C_{(14)}$ as electron-deficient centres in the initial stages of these reactions.



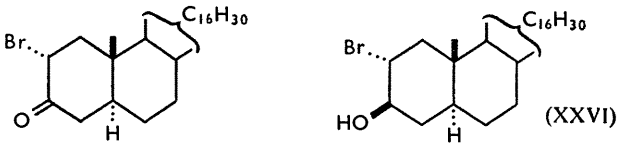
(XXIV) (XXV)

Reduction of Bromo-ketones with Lithium Aluminium Hydride.—For the foregoing investigation, compounds were required with an epoxide group in various positions in the steroid molecule. Many were known or were prepared by standard methods, but two epoxides have been obtained by reactions of suitable bromo-ketones with controlled amounts of lithium aluminium hydride. This reaction was discovered [9] in the case of a 9α-bromo-11-ketone where it may be visualised as proceeding *via* the complex anion of the diaxial bromohydrin. The 9α-bromo-11-ketone (3β-acetoxy-9α-bromoergostan-11-one) was isomerised by hydrogen bromide to a 12α-bromo-11-ketone (cf. XXIV), the reaction being accelerated by the addition of some benzoyl peroxide. Controlled reduction of this new bromo-ketone with hydride afforded an 11β : 12β-epoxide (cf. XXV). With an excess of the reducing agent the 11β-alcohol was formed. Together with infrared evidence, these reactions suffice to prove the structure of the bromo-ketone (XXIV).

This method has also been used to prepare 5β : 6β-epoxycoprostane (cf. VIII) from the new 5α-bromocholestan-6-one. This β-epoxide had been isolated previously [10] (unspecified yield and rotation) as a by-product in the reaction of cholest-5-ene with a peroxyacid. In our hands this reaction gave material inferior in quality to that obtained by the hydride reaction. Later another method was devised which gave even purer β-epoxide.[11]

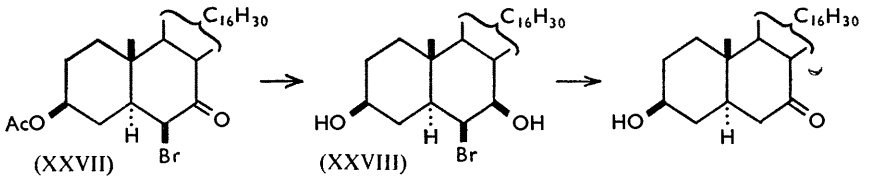
[8] Alt and Barton, *J.*, 1954, 1356.
[9] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.
[10] Furter, Ruzicka, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 327.
[11] Hallsworth and Henbest, following paper.

Three other bromo-ketones have been reduced with lithium aluminium hydride. 2α-Bromocholestan-3-one afforded a good yield of the diequatorial 2α-bromo-3β-alcohol (XXVI). Previous workers [12, 13] reduced this ketone with sodium borohydride, obtaining mixtures of the 3α- and the 3β-alcohol.



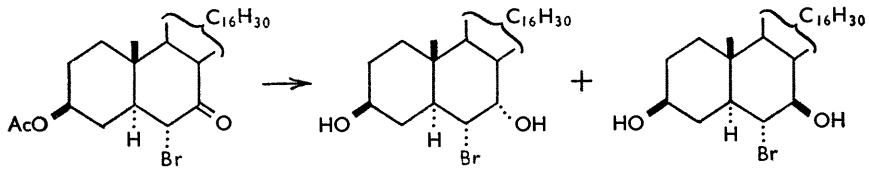
(XXVI)

Reduction of the 6β-bromo-7-ketone (XXVII) with lithium aluminium hydride gave a single bromohydrin (XXVIII), the *cis*-relation of the groups being established by conversion into the 7-ketone on treatment with potassium *tert.*-butoxide in *tert.*-butyl alcohol. Similar reduction of the unbrominated 7-ketone has been reported [13] to give about equal parts of the epimeric 7-alcohols: the axial 6β-bromine in compound (XXVII) clearly discourages the approach of hydride from the β-face and/or rearrangement of an initial hydride–ketone complex on to the β-face of the molecule.



(XXVII) (XXVIII)

Reduction of the isomeric 6α-bromo-7-ketone (XXIX) gave a mixture of two bromohydrins, separated chromatographically. The more easily eluted *cis*-compound (XXX) was converted into the 7-ketone with alkali, whereas its *trans*-isomer afforded the 6β : 7β-epoxide, prepared previously from the 7α-bromo-6β-alcohol.[15]



(XXIX) (XXX) (XXXI)

Of the five examples of the reduction of bromo-ketones with lithium aluminium hydride, epoxides are formed directly in three cases (5 : 6-, 9 : 11-, and 11 : 12-β-oxides) where *trans*-diaxial bromohydrins (as complex anions) must be formed as intermediates; in the two cases where the complex anions of *trans*-diequatorial bromohydrins are first formed, the bromohydrins themselves are finally isolated (*i.e.*, XXVI and XXXI), more drastic alkaline conditions being required to transform them subsequently into epoxides.* Simple geometrical considerations indicate that a diaxial bromohydrin should be more readily converted into an epoxide than its diequatorial isomer, as more work must be expended in the latter case in order to twist the groups into positions favourable for intramolecular nucleophilic displacement.

* The much faster ring closure of diaxial than of diequatorial halogenohydrins in alkaline solutions has been observed (cf. ref. 16).

[12] Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 4832.
[13] Fieser and Huang, *ibid.*, p. 4837.
[14] Fieser, Fieser, and Chakravarti, *ibid.*, 1949, **71**, 2226.
[15] Corey, *ibid.*, 1954, **76**, 175.
[16] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 67.

Reactions of the appropriate olefins with peroxyacids have been used to prepare 8 : 9- and 8 : 14-α-epoxides.

Experimental

In all experiments with the boron trifluoride–ether complex the reagent was freshly redistilled and the apparatus and the purified steroid epoxide were thoroughly dried. "AnalaR" benzene, dried over sodium, was usually employed as solvent. Reactions were terminated by addition of aqueous sodium hydrogen carbonate with shaking. The infrared absorptions of products were in each case consistent with the structures assigned. Rotations were determined for $CHCl_3$ solutions. M. p.s were determined on a Kofler block.

Coprostan-4-one (cf. XVI).—A solution of 4α : 5α-epoxycholestane (0·148 g.) in benzene (14 c.c.) was treated with the boron trifluoride–ether complex (0·12 c.c., 3 mol.). The specific rotation of the solution changed from +57° to a constant value of +38° within 2 min. at 20°. The product was isolated quickly and crystallised from acetone, to yield coprostan-4-one (74 mg.), m. p. 108—110°, $[\alpha]_D$ +44° {Dr. R. Stevenson (Glasgow) has recorded m. p. 109—110°, $[\alpha]_D$ + 41°}. A solution of this ketone (28 mg.) in benzene (1 c.c.) was adsorbed on to alumina (4 g.). After 20 hr. benzene was added to elute a solid (25 mg.), which crystallised from aqueous acetone, to give cholestan-4-one, m. p. and mixed m. p. 96—98°, infrared spectrum identical with that of an authentic sample.

Coprostan-6-one (cf. XVII).—A solution of 5α : 6α-epoxycholestane (2·31 g.) in benzene (31 c.c.) was treated with the boron trifluoride–ether complex (1·2 c.c., 1·8 mol.). Within 2 min. the specific rotation changed from −55° to a constant value of −5° (8 days were required for this change in ether solution), and the product was then isolated and chromatographed on deactivated alumina (150 g.). Elution with light petroleum gave impure starting material (0·32 g., 12%), m. p. 72—75°, $[\alpha]_D$ −47°. Elution with light petroleum–benzene (20 : 1) gave an oil (0·57 g., 33%), $[\alpha]_D$ +36°, showing hydroxyl but no carbonyl absorption in the infrared spectrum. Further elution with the same solvent mixture gave coprostan-6-one (0·555 g., 30%), m. p. 131—132° (from acetone), $[\alpha]_D$ −40° (lit.,[17] m. p. 133°, $[\alpha]_D$ −44°). Elution with benzene–ether (20 : 1) gave an oil (0·41 g., 18%), $[\alpha]_D$ +6°, showing hydroxyl but no carbonyl absorption (infrared).

A solution of coprostan-6-one (2·4 g.) in benzene (50 c.c.) was adsorbed on to alumina (100 g., impregnated with potassium hydroxide [18]). After 2 hr. addition of benzene eluted cholestan-6-one (2·4 g.), m. p. and mixed m. p. 98—100° after crystallisation from acetone.

Cholestan-6-one (cf. XVIII).—A solution of 5β : 6β-epoxycholestane (91 mg.) in benzene (10 c.c.) was treated with the boron trifluoride–ether complex (0·1 c.c., *ca.* 3 mol.). The specific rotation of the solution changed from −9° to a constant value of 0° during 4 min., and the product (90 mg.) was then isolated. One crystallisation from acetone yielded cholestan-6-one, m. p. and mixed m. p. 97—98°, infrared spectrum identical with that of an authentic sample.

3β-*Acetoxy*-9β-*ergostan*-11-*one* (cf. XIV).—A solution of 3β-acetoxy-9α : 11α-epoxyergostane (0·511 g.) in benzene (15 c.c.) was treated with the boron trifluoride–ether complex (0·4 c.c., 3 mol.) at 20°. The solution attained a constant specific rotation after 70 hr., then the product was isolated with ether and chromatographed on deactivated alumina (40 g.). Elution with light petroleum–benzene (4 : 1) afforded 3β-acetoxy-9β-ergostan-11-one (0·14 g., 25%), m. p. and mixed m. p. 155—157°, $[\alpha]_D$ +41°, infrared spectrum identical with that of an authentic sample. Elution with benzene gave an oil (0·27 g.) showing hydroxyl absorption (infrared).

3β-*Acetoxyergostan*-11-*one* (cf. XV).—A solution of 3β-acetoxy-9β : 11β-epoxyergostane [9] (0·143 g.) in benzene (14 c.c.) was treated with the boron trifluoride–ether complex (0·08 c.c., 3 mol.) at 20°. The specific rotation of the solution changed from +23° to a constant value of −2° during 5 min. The product was chromatographed on deactivated alumina (10 g.), elution with light petroleum–benzene (4 : 1) affording 3β-acetoxyergostan-11-one (51 mg.), m. p. and mixed m. p. 138—140° (from methanol), $[\alpha]_D$ +38°, infrared spectrum identical with that of authentic material. Elution with light petroleum–benzene (1 : 1) gave an oil (60 mg.), showing hydroxyl absorption (infrared).

[17] James and Shoppee, *J.*, 1955, 2885.
[18] Cf. Castells and Fletcher, *J.*, 1956, 3245.

Action of Boron Trifluoride on a 7α : 8α-*Epoxide* (IX).—A solution of 3β-acetoxy-7α : 8α-epoxyergost-22-ene [8] (0·42 g.) in benzene (15 c.c.) was treated with the boron trifluoride–ether complex (0·3 c.c., 2·9 mol.) at 20°. The specific rotation of the solution changed from −12° to −188° during 30 sec. The product was twice crystallised from methanol–acetone, giving slightly impure 3β-acetoxyergosta-7 : 14 : 22-triene (0·26 g.), m. p. 142—144°, $[\alpha]_D$ −182° (Found: C, 82·5; H, 10·7. Calc. for $C_{30}H_{46}O_2$: C, 82·15; H, 10·55%), $\lambda_{max.}$ 2420 Å (ε 11,000) in EtOH {lit., m. p. 140—141°, $[\alpha]_D$ −212°, $\lambda_{max.}$ 2420 Å (ε 9900)}.

In another experiment [starting from epoxide (0·378 g.)] the solution was kept at 20° for 24 hr., by which time the rotation had reached a constant value of −25°. The product (0·322 g.) was chromatographed on alumina (20 g.). Elution with light petroleum–benzene (4 : 1) afforded a solid which on crystallisation from methanol yielded impure 3β-acetoxyergosta-8 : 14 : 22-triene, m. p. 138—141°, $[\alpha]_D$ −28°, $\lambda_{max.}$ 2500 Å (ε 15,400) (in EtOH) {lit., m. p. 140—141°, $[\alpha]_D$ −54°, $\lambda_{max.}$ 2490 Å (ε 15,500)}.

Action of Boron Trifluoride on an 8α : 9α-*Epoxide* (X).—A solution of 3β-acetoxy-8α : 9α-epoxyergostane (46 mg.; preparation below) in benzene (7 c.c.) was treated with the boron trifluoride–ether complex (0·05 c.c., 3·9 mol.) at 20°. The rotation rapidly attained a constant negative value, and the product was isolated after 2 min. Crystallisation from methanol afforded 3β-acetoxyergosta-8 : 14-diene, m. p. and mixed m. p. 138—140°, $[\alpha]_D$ −31°, $\lambda_{max.}$ 2490 Å (ε 18,400) (in EtOH) (lit., m. p. 137—138°, $[\alpha]_D$ −28·5°).

Action of Boron Trifluoride on an 8α : 14α-*Epoxide* (XI).—Treatment of 3β-acetoxy-8α : 14α-epoxyergostane (0·564 g.; preparation below) with the boron trifluoride–ether complex (3 mol.) in benzene (25 c.c.) at 20° resulted in a change of rotation from +12° to +34° within 2 min. The product was then isolated and chromatographed on deactivated alumina (40 g.), light petroleum–benzene (1 : 1) eluting 3β-acetoxyergosta-8 : 14-diene (0·495 g.), m. p. and mixed m. p. 140—141°, $[\alpha]_D$ −38°, $\lambda_{max.}$ 2490 Å (ε 18,600) in EtOH.

A similar reaction in ether required 15 days for the rotation to reach a constant value. Isolation gave the same diene as before.

Preparation of Epoxides.—3β-*Acetoxy*-11β : 12β-*epoxyergostane* (cf. XXV). A solution of 3β-acetoxy-12α-bromoergostan-11-one (0·39 g.) and lithium aluminium hydride (23 mg., 0·83 mol.) in ether (25 c.c.) was heated under reflux for 45 min. The product was isolated with ether, acetylated, and chromatographed on deactivated alumina (30 g.). Elution with light petroleum–benzene (5 : 1) gave the 11β : 12β-*epoxide* (123 mg.), m. p. 133—135° (from methanol), $[\alpha]_D$ +29° (Found: C, 78·2; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). No other crystalline products were obtained by further elution of the chromatogram.

When a solution of the 12α-bromo-11-ketone (0·15 g.) and lithium aluminium hydride (0·2 g.) in tetrahydrofuran (20 c.c.) was heated under reflux for 4 hr., and the product isolated with ether and crystallised from methanol, ergostane-3β : 11β-diol, m. p. and mixed m. p. 177—179°, was obtained. Acetylation gave 3β-acetoxyergostan-11β-ol, m. p. and mixed m. p. 132—133°.

5β : 6β-*Epoxycholestane* (cf. VIII). A solution of cholestan-6-one (0·939 g.) in ether (25 c.c.) and acetic acid (7 c.c.) was treated with a solution of bromine in acetic acid (4·69 c.c. of a 2·8% v/v solution, 1·05 mol.). The bromine colour was discharged during 30 sec. at 20°. Water was then added and the steroid isolated with ether. Crystallisation from acetone gave 5α-*bromocholestan-6-one* (0·827 g., 70%), m. p. 101—102°, $[\alpha]_D$ −134° (Found: C, 70·15; H, 9·85; Br, 17·75. $C_{27}H_{45}OBr$ requires C, 69·65; H, 9·65; Br, 17·25%).

The molecular-rotation difference between this bromo-ketone and cholestan-6-one is −635°, in excellent agreement with that (−630°) between 3β-acetoxy-5α-bromocholestan-6-one and its 5-hydrogen analogue, but different from that (+282°) between 3β-acetoxy-7α-bromocholestan-6-one and the unbrominated compound.

A solution of the bromo-ketone (0·638 g.) and lithium aluminium hydride (14 mg., 0·27 mol.) in ether (20 c.c.) was heated under reflux for 10 min. The product was isolated with ether and chromatographed on alumina (25 g.). Elution with light petroleum gave 5β : 6β-epoxycholestane (0·142 g.), m. p. 55—57° (from acetone), $[\alpha]_D$ −9° (Found: C, 83·7; H, 12·0. Calc. for $C_{27}H_{46}O$: C, 83·85; H, 12·0%). Further elution with the same solvent afforded impure starting material (87 mg.), m. p. 81—93° (from acetone). Elution with benzene gave a gum (0·245 g.).

5α : 6α-*Epoxycholestane* (cf. VII). Perbenzoic acid in benzene (475 c.c. of a 0·21M-solution; 1·3 mol.) was added to a solution of cholest-5-ene (29 g.) in benzene (50 c.c.), and the mixture was kept at 20° for 2 hr. Organic acids were washed out with aqueous potassium hydrogen

carbonate, and the benzene solution was filtered through deactivated alumina (650 g.), the adsorbent being washed with more benzene. Removal of solvent gave material (29 g.) which after 5 crystallisations from acetone gave the pure α-epoxide (8·4 g.), m. p. 74—75°, $[\alpha]_D$ −55°. A portion of this product was separated into 16 fractions by chromatography on deactivated alumina; the rotation of each fraction was $[\alpha]_D$ −56° ± 3°, and crystallisation of some of the fractions only altered the m. p. slightly, to 75—76°.

Reduction of the α-epoxide (0·729 g.) with an excess of lithium aluminium hydride in boiling ether gave cholestan-5α-ol (0·591 g., 81%), m. p. 100—102°. No cholestan-6β-ol was obtained.

Material (8 g.) from the first mother-liquor from crystallisation of the α-epoxide was chromatographed on deactivated alumina (800 g.). Light petroleum (b. p. 40—60°) was used as eluting solvent and most of the material was eluted in thirty 100 c.c. fractions. The rotations of all of these were within −16° to −19°. Crystallisation of the products from various fractions gave impure β-epoxide: a typical sample had m. p. 60—63°, $[\alpha]_D$ −18°.

2α-Bromocholestan-3β-ol (cf. XXVI).—A solution of 2α-bromocholestan-3-one (0·528 g.) and lithium aluminium hydride (0·3 g.) in ether (30 c.c.) was heated under reflux for 2 hr. The product (0·41 g.) was isolated with ether, and a portion (0·246 g.) was chromatographed on deactivated alumina (20 g.). Elution with light petroleum–benzene (1 : 1) afforded pure 2α-bromocholestan-3β-ol (0·215 g.), double m. p. 76° and 112—114° (from methanol), $[\alpha]_D$ +19°. Acetylation yielded 3β-acetoxy-2α-bromocholestane, m. p. 106—107° (from methanol), $[\alpha]_D$ −4°. Recorded values [12, 13] are: for the bromohydrin, m. p. 111·5—112·5° $[\alpha]_D$ +14° and m. p. 113—114°, $[\alpha]_D$ +12°, and for the acetate, m. p. 106—107°, $[\alpha]_D$ −82°. Professor L. F. Fieser, Harvard, has informed us that this rotation should be −8·2°.

Reduction of 3β-Acetoxy-6β-bromocholestan-7-one (XXVII).—A solution of the steroid (0·935 g.) and lithium aluminium hydride (0·2 g.) in ether (150 c.c. was heated under reflux for 1 hr. Isolation with ether followed by crystallisation from acetone yielded the *bromohydrin* (XXVIII) (0·56 g.), m. p. (decomp.) 183—186°, $[\alpha]_D$ +44° (Found: C, 67·15; H, 9·5; Br, 16·55. $C_{27}H_{47}O_2Br$ requires C, 67·1; H, 9·75; Br, 16·55%).

A solution of the bromohydrin (1·8 g.) in anhydrous *tert.*-butyl alcohol (50 c.c.) was treated with molar potassium *tert.*-butoxide in the alcohol (15 c.c.) at 20°. Potassium bromide separated almost immediately and after 5 min. the product was isolated with ether and crystallised from methanol, to give 3β-hydroxycholestan-7-one (1·1 g.), m. p. 166—168°, $[\alpha]_D$ −31°.

Acetylation and crystallisation of the product from methanol afforded 3β-acetoxycholestan-7-one, m. p. and mixed m. p. 149—150°, $[\alpha]_D$ −34°.

Reduction of 3β-Acetoxy-6α-bromocholestan-7-one (XXIX).—A solution of the steroid (2·638 g.) and lithium aluminium hydride (0·158 g., 0·83 mol.) was heated under reflux for 1 hr. The product was isolated with ether and chromatographed on deactivated alumina (140 g.). Elution with benzene–ether (9 : 1) gave *6α-bromocholestane-3β : 7α-diol* (0·83 g.), m. p. 131—132° (from acetone), $[\alpha]_D$ +59° (Found: C, 67·4; H, 9·8. $C_{27}H_{47}O_2Br$ requires C, 67·1; H, 9·75%). Further elution with this solvent mixture afforded *6α-bromocholestane-3β : 7β-diol* (0·65 g.), m. p. 209—212° (from acetone), $[\alpha]_D$ +64° (Found: C, 67·3; H, 9·8; Br, 16·85%).

A solution of the 6α-bromo-3β : 7β-diol (0·75 g.) in benzene (10 c.c.) and anhydrous *tert.*-butyl alcohol (50 c.c.) was treated at 20° with M-potassium *tert.*-butoxide solution in the alcohol (12 c.c.). Potassium bromide was precipitated almost immediately and after 10 min. the product (0·622 g.) was isolated with ether. Chromatography on deactivated alumina yielded 6β : 7β-epoxycholestan-3β-ol [0·515 g., eluted with benzene–ether (9 : 1)], m. p. 154—156° (from acetone), $[\alpha]_D$ −10° (lit.,[15] m. p. 157—158°, $[\alpha]_D$ −14·5°) (Found: C, 80·5; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·55; H, 11·5%). Acetylation gave *3β-acetoxy-6β : 7β-epoxycholestane*, m. p. 137—139° (crystallised from methanol), $[\alpha]_D$ −23° (Found: C, 78·4; H, 11·05. $C_{29}H_{48}O_3$ requires C, 78·2; H, 10·9%).

A solution of the 6α-bromo-3β : 7β-diol (0·246 g.) in *tert.*-butyl alcohol (15 c.c.) was treated with M-potassium *tert.*-butoxide solution in the alcohol (10 c.c.). The mixture was kept at 20° for 5 hr., then the steroid was isolated with ether. The product still gave a positive Beilstein test and was purified by chromatography on deactivated alumina (10 g.). Elution with benzene afforded 3β-hydroxycholestan-7-one (0·104 g.), m. p. and mixed m. p. 165—167°.

3β-Acetoxy-8α : 9α-epoxyergostane (cf. X).—A solution of 3β-acetoxyergost-8-ene [21] (0·3 g.)

[19] Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397.
[20] Barton and Cox, *J.*, 1948, 783; 1949, 5397.
[21] Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

in benzene (11 c.c.) was treated with perbenzoic acid (5·45 c.c. of a 2·5M-solution in benzene; 2 mol.). One equivalent of peroxy-acid was consumed during 72 hr. at 0°, and the steroid was then isolated and filtered in light petroleum–benzene (2 : 1) solution through deactivated alumina (15 g.). The *epoxide* (0·264 g., 85%) had m. p. 180—183° (from methanol), $[\alpha]_D$ +4° (Found: C, 78·75; H, 11·45. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%).

3β-*Acetoxy*-8α : 14α-*epoxyergostane* (cf. XI).—Anhydrous formic acid (25 c.c.) and hydrogen peroxide (25 c.c. of a 30% solution in water) were added to a solution of 3β-acetoxyergost-8(14)-ene (5 g.) in chloroform (100 c.c.), and the two-phase system was then stirred for 13 hr. at 20°. After organic acids had been washed out, the chloroform was evaporated to give a yellow gum (5·1 g.) which was chromatographed on deactivated alumina (300 g.). Elution with light petroleum–benzene (9 : 1) gave the 8 : 14-*epoxide* (2·6 g., 50%), m. p. 139—140° (from methanol), $[\alpha]_D$ +15° (Found: C, 78·35; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%).

3β-*Acetoxy*-12α-*bromoergostan*-11-*one* (cf. XXIV).—3β-Acetoxy-9α-bromoergostan-11-one (0·5 g.) and benzoyl peroxide (0·113 g., 0·5 mol.) were dissolved in acetic acid (15 c.c.) and benzene (15 c.c.), and hydrogen bromide (1 c.c. of a 50% w/v solution in acetic acid, *ca.* 12·5 mol.) was added. These operations were performed with nitrogen bubbling through the solution which was shielded from light. The specific rotation of the solution changed from +128° to a constant value of −3° after 41 hr. at room temperature. Isolation with ether and crystallisation from methanol afforded pure 3β-*acetoxy*-12α-*bromoergostan*-11-*one* (0·376 g.), m. p. 135—137°, $[\alpha]_D$ −3° (Found: C, 66·9; H, 9·5; Br, 15·0. $C_{30}H_{49}O_3Br$ requires C, 67·0; H, 9·25; Br, 14·9%). Infrared absorption (in CS_2): carbonyl peak at 1705 cm.$^{-1}$ (as in the unbrominated compound).

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