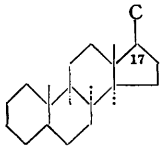
97. *The Reconversion of D-Homoandrostane Compounds into Derivatives of Androstane.*

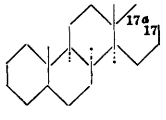
By D. A. Prins and C. W. Shoppee.

Two examples of the reconversion of D-homoandrostane compounds (as II) into derivatives of androstane (as I) are recorded; in both cases ring transposition proceeds to a very limited extent, the bulk of the material remaining as D-homoandrostane compounds. Comparison of the molecular achitecture of rings C and D in (II) with that of *trans*-decahydronaphthalene fails to suggest an explanation of the practical inhibition of the rearrangement (II ⟶ I).

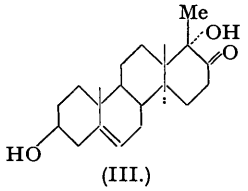
The conversion of steroids (as I) into derivatives of D-homoandrostane or D-homoætiocholane (II), whereby the terminal 5-membered ring of the steroid nucleus becomes 6-membered, occurs readily and is frequently encountered (compare *inter alia* Ruzicka *et al.*, *Helv. Chim. Acta*, 1939, **22**, 421, 626; 1940, **23**, 364, 513; Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 79; 1940, **62**, 489; 1941, **63**, 3127; Goldberg *et al.*, *Helv. Chim. Acta*, 1940, **23**, 376; 1941, **24**, 478, 295E; 1942, **25**, 1553; 1943, **26**, 680, 1142; Reichstein *et al.*, *ibid.*, 1941, **24**, 828, 879; Shoppee and Prins, *ibid.*, 1943, **26**, 185; 201, 2089; Shoppee, *ibid.*, 1944, **27**, 8). The reverse transformation, the regeneration of the steroid structure (I) from the D-homo-structure (II), does not appear to have been recorded; two examples are now given, but both proceed to the extent of a few per cent. only.



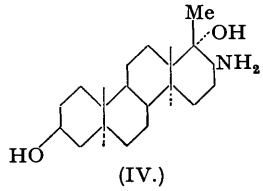
(I.)



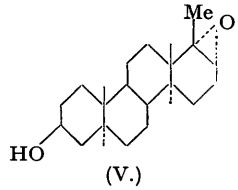
(II.)



(III.)



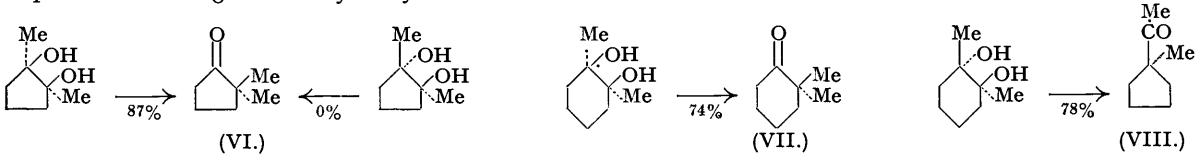
(IV.)



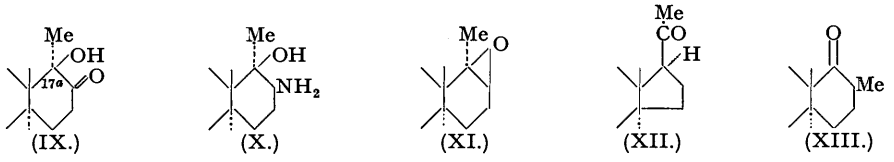
(V.)

Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1321) attempted to achieve the change (II ⟶ I) by deamination of the α-aminoalcohol (IV) obtained by complete reduction of the oxime of the hydroxyketone (III), but isolated only the oxide (V) in 63% yield, although Mousseron and Souche (*Bull. Soc. chim.*, 1935, **2**, 1102; compare *idem*, *ibid.*, 1937, **4**, 1197) had found 2-amino-1-methyl*cyclo*hexanol with nitrous acid to afford acetyl*cyclo*pentane accompanied by a little 2-methyl*cyclo*hexanone. Ruzicka and Meldahl did not, however, make a search for ketonic products possibly present in small amount.

Bartlett and Bavley (*J. Amer. Chem. Soc.*, 1938, **60**, 2416) have shown that dehydration of *cis*-1 : 2-dimethyl-*cyclo*pentane-1 : 2-diol affords 87% of the ketone (VI) but that the *trans*-diol yields only tars, and Bartlett and Pöckel (*ibid.*, 1937, **59**, 820) found dehydration of *cis*-1 : 2-dimethyl*cyclo*hexane-1 : 2-diol to give 74% of the ketone (VII) whilst the *trans*-diol furnished 78% of the isomeride (VIII). Whatever the precise interpretation of these results (compare Bartlett and Brown, *ibid.*, 1940, **62**, 2927) the general implication is that the spatial arrangement of the participating groups may play a determinative rôle in regard to the occurrence and the course of pinacolic rearrangement in cyclic systems.



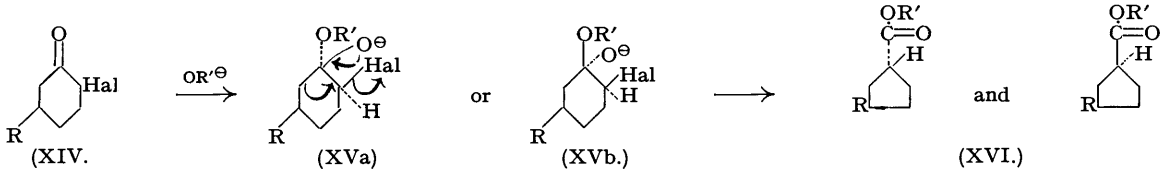
It seemed therefore of interest, when the 17*a*-epimeride (IX) of the hydroxyketone (III) became available (Stavely, *loc. cit.*; Shoppee and Prins, *loc. cit.*) to examine the behaviour of the 17*a*-epimeric α-aminoalcohol (X) on deamination.



The product resulting from the action of nitrous acid on (X) was treated with Girard's reagent-T. Non-ketonic material formed the bulk of the product and furnished the beautifully crystalline *oxide* (XI), characterised as the *acetate*, but no trace of the corresponding diol (Stavely, *loc. cit.*; compare also Godschot and Mousseron, *Bull. Soc. chim.*, 1934, **1**, 1925) was found. The acetoxy-oxide could not be cleaved by hot acetic acid (compare Ruzicka and Meldahl, *loc. cit.*, who were able to split the 17 : 17*a*-epimeric oxide (V) under these conditions) and was recovered unchanged; use of acetic acid containing 5% hydrochloric acid was also ineffective but hydrolysed the 3(β)-acetoxy group to regenerate the oxide (XI). The betaine-hydrazones were fractionally hydrolysed at pH 3 and pH ≪ 1 to give ketonic fractions (K_1 and K_2). Fraction K_1 (21 mg.) was non-crystalline, but on chromatographic analysis gave traces of the oxide (XI), a very small quantity of an unidentified ketone, and a little *allo*pregnane-3(β)-ol-20-one (XII). Fraction K_2 (25 mg.) was crystalline and after chromatographic purification afforded a ketone which, by exclusion, would appear to be 17-*methyl-D-homo-androstane*-3(β)-*ol*-17a-*one* (XIII).

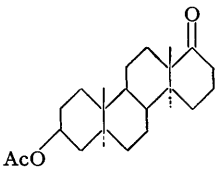
The results of Bartlett *et al.* suggest that of the four C_{17}-isomerides represented by (IV) and (X), only 17(β)-amino-(IV) and 17(α)-amino-(X) should give (XII) whilst only the two remaining epimerides should furnish (XIII); it would seem that the oxides (V) and (XI) could result respectively from either of the 17-amino epimerides represented by (IV) and (X). The configuration of the amino group in (IV) and (X) is not known, and, although both the bases and their oxime precursors were prepared under the same conditions, it is uncertain whether they were homogeneous or mixtures of C_{17}-epimerides. Owing to this configurational uncertainty and its possible significance, we have attempted to eliminate, or at least to minimise, the influence upon rearrangement of the type (II ⟶ I) of the geometrical arrangement of the groups concerned as follows.

The general reaction, originally described by Favorski (*J. Russ. Phys. Chem. Soc.*, 1912, **43**, 580), whereby α-halogenoketones by treatment with alkalis undergo ring-contraction to give carboxylic acids or their esters, can be formulated as a pinacolic process (compare, however, Mousseron and Granger, *Bull. Soc. chim.*, 1943,

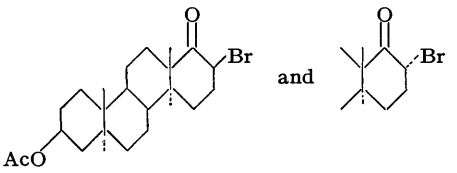


10, 42; also Aston and Greenberg, *J. Amer. Chem. Soc.*, 1940, **62**, 2590); and appears to provide a comparable chance that the two configurations (XVa, XVb; R = H) can arise by addition of the nucleophilic anion. Mousseron, Granger, and Bourrel (*Bull. Soc. chim.*, 1939, **6**, 607) starting from the chloroketone (XIV; R = Me) have isolated both the acids corresponding to (XVI), whilst the production of a similar pair of *trans*-hydrindane-2-carboxylic acids from 3-chloro-*trans*-β-decalone has been reported by Cauquil and Tsatsas (*ibid.*, 1945, **10**, 47).

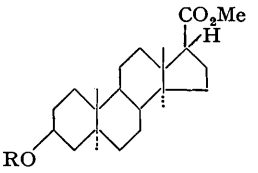
To realise the change (II ⟶ I) by application of the Favorski reaction, we utilised the stereoisomeric bromo-acetoxyketones corresponding to (XVIII) derived from D-homoandrostane-3(β)-ol-17a-one acetate (XVII) (Goldberg and Monnier, *Helv. Chim. Acta*, **1940**, **23**, 376; see also Goldberg and Wydler, *ibid.*, **1943**, **26**, 1142). The isomerides represented by (XVIII) were difficult to separate, and the mixture of crystalline bromo-acetoxy-ketones was used for treatment with various alkaline reagents.



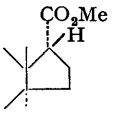
(XVII.)



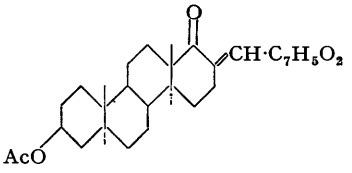
(XVIII.)



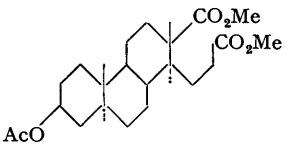
(XIXa; R = H.)
(XIXb; R = Ac.)



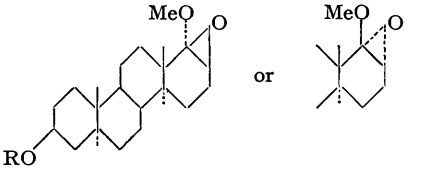
(XIXc; R = Ac.)



(XXI.)



(XXII.)



(XXa; R = H.) (XXb; R = Ac.)

The action of sodium methoxide in methanol on (XVIII) dissolved in ether at 20° yielded no acid fraction directly; the neutral product gave a substance $C_{21}H_{34}O_3$, which is probably one of the stereoisomeric oxides (XXa). The neutral mother liquors could not be hydrolysed by potassium hydroxide to furnish any acidic substance so that the neutral fraction could not have contained the ester (XIXa). The unavoidable presence of small amounts of methanol may be concerned with the non-production here of the ester (XIXa) (compare Aston and Greenberg, *loc. cit.*).

Employment of potassium bicarbonate in methanol (Marker and Wagner, *J. Amer. Chem. Soc.*, **1942**, **64**, 216) also yielded no acidic fraction; the neutral fraction gave a compound, $C_{23}H_{36}O_4$, which however cannot be the unknown ester (XIXc) because it could not be hydrolysed to an acid; the substance did not appear to react with semicarbazide and is probably one of the pair of oxides represented by (XXb). A substance, $C_{24}H_{36-38}O_5$, m. p. 220—222°, was also isolated chromatographically; this involves an increase of 2 C and 2 O atoms with respect to (XVII) ($C_{22}H_{34}O_3$) and suggests that additon of methanol to (XXb) may have occurred (compare Aston and Greenberg, *loc. cit.*).

Treatment with methanolic potassium hydroxide, which should lead directly to acids, gave a small acidic fraction; after esterification with diazomethane, chromatographic analysis furnished traces of an unidentified methyl ester, m. p. 225°, which was eluted only with acetone. Other fractions of the chromatogram failed to crystallise by inoculation with methyl 3(β)-hydroxyætio*allo*cholanate (XIXa). The neutral fraction was discarded.

Use of dry powdery sodium methoxide in anhydrous dioxan and alkaline hydrolysis of the neutral product furnished a mixture of solid acids; chromatographic analysis of the acetylated methyl esters yielded a very small amount of methyl 3(β)-acetoxyætio*allo*cholanate (XIXb), a little *methyl* 3(β)-*acetoxy*allo*homobilianate* (XXII), and traces of an unidentified methyl ester, m. p. 110—112°. The neutral hydrolysis product was not examined.

For comparison with the ester (XXII), a genuine specimen was synthesised as follows: the acetoxyketone (XVII) was converted into the piperonylidene derivative (XXI) and, after reacetylation, this was treated with ozone in acetic acid and the ozonide oxidised in acetic acid with chromium trioxide; esterification with diazomethane, acetylation, and chromatographic purification of the product furnished the dimethyl ester (XXII), double m. p. 139° and 156°.

The rearrangement (II ⟶ I) can thus be realised but proceeds with very considerable difficulty and to a very limited extent, the bulk of the material remaining as D-homoderivatives. It was pointed out by Wightman (*J.*, 1925, 1421) that the *trans*-decahydronaphthalene skeleton could exist in 3 forms, chair-chair (B), chair-boat (E), and boat-boat (G); in the strict strain-free sense all forms containing the chair are rigid, *i.e.*, B and E are rigid and G has a little strain-free motion; on Mohr's postulate, all 3 forms are interconvertible through a very small energy barrier, B and E tending to pass into G. These characteristics are not obviously changed when the *trans*-decahydronaphthalene structure is extended to afford the D-homoandrostane structure (as II). The ready transformation of the *trans*-decahydronaphthalene skeleton to that of *trans*-hydrindane reported by Cauquil and Tsatsas (*loc. cit.*) may not be precisely analogous to the rearrangement (II ⟶ I), but the cause of the difficulty in the latter case remains obscure. It is, however, known (compare Reichstein and Gatzi, *Helv. Chim. Acta*, **1940**, **23**, 1480; Shoppee, *ibid.*, **1941**, **24**, 351) that mutually remote parts of the steroid system (I) can influence one another, and similar effects may well be operative in the D-homoandrostane system (II).

Experimental.

(All m. ps. were determined thermoelectrically on a Kofler block and are corrected : Limits of error ±2°. All solvents used for chromatographic separations were rigorously purified and dried.)

17*a*-Methyl-Δ⁵-D-homoandrostene-3(*β*) : 17*a*(*β*)-diol-17-one (IX) was prepared from 17-ethynyl-Δ⁵-androstene-3(*β*) : 17(*a*)-diol by the method of Stavely (*J. Amer. Chem. Soc.*, 1941, **63**, 3127) as long prisms, m. p. 188—190°, from acetone–ether; a genuine specimen previously prepared by Shoppee and Prins (*Helv. Chim. Acta*, 1943, **26**, 201) and labelled m. p. 176—178° was found now to have m. p. 188—190°, and a mixture of the two preparations had m. p. 188—190°. The *oxime* was obtained by refluxing the dihydroxy-ketone (620 mg.) for 3 hours with the filtrate obtained by dissolving hydroxylamine hydrochloride (620 mg.) and crystalline sodium acetate (1·24 g.) in methanol (25 c.c.). The solution was cooled, poured into water, and the product filtered off and dried in a vacuum. Recrystallisation from alcohol gave successive crops of colourless prisms m. p. (i) 283°, (ii) 285°, (iii) 285°, (iv) 280—283° all decomp. (yield, 555 mg.) (Found (after drying at 80°/0·01 mm.) : C, 72·99; H, 9·82; N, 4·12. $C_{21}H_{33}O_3N$ requires C, 72·60; H, 9·60; N, 4·03%).

17-*Amino*-17a-*methyl*-*D*-*homoandrostane*-3(*β*) : 17a(*β*)-*diol* (X).—PtO_2,H_2O (100 mg.) suspended in acetic acid (12 c.c.) was prehydrogenated; the foregoing oxime (550 mg.) suspended in absolute alcohol (8 c.c.) was added, and the whole shaken in hydrogen at 20°. The reaction was stopped after absorption of 107 c.c. of hydrogen (≡ $3H_2$) in 1¼ hours, and the solution filtered and largely evaporated under reduced pressure at 40°. Water was added, a small precipitate filtered off and rejected, and the clear filtrate made slightly alkaline with 2N-NaOH. The *base* so precipitated was filtered off and dried in high vacuum : it was very insoluble in chloroform, acetone, and dioxan, but separated from alcohol by concentration in microprisms, m. p. 240—244° [Found (after drying at 80°/0·01 mm.) : C, 74·80; H, 10·89. $C_{21}H_{37}O_2N$ requires C, 75·18; H, 11·11%].

Deamination. The amine (400 mg.) was treated with sodium nitrite in 2N-AcOH as described by Ruzicka and Meldahl (*Helv. Chem. Acta*, 1941, **24**, 1321) but with mechanical stirring. The reaction product was extracted with ether, the extract washed with 2N-Na_2CO_3, and with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in methanol (8 c.c.) and, after addition of acetic acid (0·60 c.c.) and Girard's reagent-T (600 mg.), refluxed for 20 minutes. The well-cooled solution was poured into a mixture of 2N-NaOH (4·90 c.c.) and ice-water (*ca.* 100 c.c.) and immediately extracted with ether. The extract was washed with water, 2N-Na_2CO_3, and again with water, dried (Na_2SO_4), and evaporated to yield non-ketonic material (201 mg.). The aqueous solution was made just acid to Congo red with hydrochloric acid, allowed to stand for ½ hour, partly evaporated under reduced pressure to remove methanol, and extracted with ether. The extract was washed with water, 2N-Na_2CO_3, and again with water, dried (Na_2SO_4) and evaporated to furnish fraction K_1 (21 mg.). Finally the aqueous solution was mixed with 10% of its volume of concentrated hydrochloric acid and allowed to stand for ½ hour. The solution was then extracted with ether, the extract washed as above, dried, and evaporated to afford fraction K_2 (25 mg.) which crystallised largely on keeping, m. p. *ca.* 150°.

The non-ketonic fraction crystallised by keeping and, recrystallised from alcohol, gave shining pyramids of 17(*β*) : 17a(*β*)-*epoxy*-17a-*methyl*-*D*-*homoandrostane*-3(*β*)-*ol* (XI), m. p. 210°, which failed to analyse satisfactorily (cf. the experience of Ruzicka and Meldahl with the 17(*a*) : 17*a*(*a*)-isomeride). (Found (after sublimation at 160—170°/0·001 mm.) : C, 80·35; H, 10·60. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·76%). The *acetate*, prepared by treatment with acetic anhydride in pyridine for 18 hours at 20°, was crystallised twice from methanol and formed clusters of colourless prisms, m. p. 171°, $[\alpha]_D^{14°}$ −31·9 ± 3° (*c* = 0·785 in acetone) (Found (after sublimation at 150—160°/0·001 mm.) : C, 76·60; H, 9·90. $C_{23}H_{36}O_3$ requires C, 76·62; H, 10·06%). The epoxyacetate was recovered unchanged, m. p. 170°, after refluxing for 2 hours with CrO_3-stable acetic acid (cf. Ruzicka and Meldahl, *loc. cit.*) (Found : C, 76·10; H, 10·02%); use of "AnalaR" acetic acid containing 5% of concentrated hydrochloric acid was also ineffective, but here hydrolysis of the 3-acetoxy group occurred to regenerate the oxide, m. p. 210°. The ketonic fraction K_1 was non-crystalline; it was dissolved in benzene (0·5 c.c.) and introduced on to a column of alumina (Spence (activity I–II, according to the scale suggested by Brockmann and Schodder, *Ber.*, 1941, **74**, 73), 650 mg.) prepared in pentane (5 c.c.). The chromatogram was developed using the "Durchlauf" method as set out in Table I.

Table I.

Fraction.	Eluant (2·5 c.c.).		Eluate.
1, 2	Benzene–pentane	(1 : 10)	—
3	,,	(1 : 1)	—
4, 5	Benzene		—
6	Ether–benzene	(1 : 15)	Crystallised spontaneously — Recryst. ether–pentane in prisms, m. p. 157—161°.
7	,,	,,	,, by inoculation with Fr. 6
8	,,	,,	—
9, 10	,,	(1 : 7)	Crystallised spontaneously : recryst. ether–pentane, m. p. 200—207°.
11, 12	,,	(1 : 3·5)	,, ,, ,, ether–pentane, m. p. 195—203°.
13, 14	,,	(1 : 1)	,, by inoculation : recryst. ether–pentane, m. p. 170—200°.
15, 16	Ether		,, ,, ,, ether–pentane, m. p. 170—195°.
17	Acetone–ether	(1 : 4)	Little oil.
18	,,	(1 : 1)	,,
19	Acetone		Trace of oil.
20	,,		—

The substance (2 mg.) present in fractions 6 and 7 could not be identified; the m. p. was depressed to 135° on admixture with the ketone (XIII) of m. p. 163°. Fractions 9—12 furnished the oxide (XI) (3 mg.), no m. p. depression being observed on admixture with this compound, and the various melts crystallising immediately on slight cooling. Fractions 13—16 appeared to be mixtures of the oxide (XI) with some other substance(s); fractions 13—18 and the mother-liquors from fractions 11 and 12 were therefore united (9 mg.) and re-chromatographed on a column of alumina (Merck-Brockmann (activity III—IV), 450 mg.) prepared in benzene. Elution with ether–benzene mixtures (1 : 4, 1 : 2) furnished small quantities of the oxide (XI), m. p. 205—210°, whilst ether afforded *allo*pregnane-3(*β*)-ol-20-one (XII) (2 mg.) as leaflets (from ether–pentane), m. p. 193—195°, which did not depress the m. p. of a genuine specimen. Elution with acetone–ether mixtures and with acetone gave only traces of oil which could not be induced to crystallise.

The ketonic fraction K_2 was crystalline, m. p. *ca.* 150°; it was dissolved in benzene (0·5 c.c.) and purified chromatographically on a column of alumina (Spence (activity I–II), 750 mg.) prepared in pentane (5 c.c.), using 2·5 c.c. of each eluant. Elution with ether–benzene (1 : 2) gave traces of crystalline material, and with ether–benzene (1 : 1) furnished 3 fractions (6, 7, and 8) which crystallised spontaneously on evaporation, whilst ether afforded further traces of crystalline material. Fractions 6, 7, and 8 were recrystallised from ether–pentane to give in each case felted needles m. p. 160—163°; they were united and crystallised from ether–pentane to furnish 4 mg. of a ketone, m. p. 163—165°, presumed by exclusion to be 17-*methyl*-D-*homoandrostane*-3(*β*)-*ol*-17a-*one* (XIII). For analysis the substance was sublimed at 150°/

0·001 mm. (Found: C, 79·45; H, 10·74. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·90%). Subsequent eluates obtained by elution with acetone–ether mixtures and with acetone gave no appreciable residues. The second crop of the ketone (XIII) (2 mg.) had m. p. 160—163° and was converted into the semicarbazone, m. p. 270—273°.

D-Homoandrostane-3(β)-ol-17*a*-one acetate (XVII) was originally obtained from Δ⁵-androstene-3(β)-ol-17-one acetate (dehydro*iso*androsterone acetate) by the method of Goldberg and Monnier (*loc. cit.*; cf. Goldberg and Wydler, *loc. cit.*) with slight modification. The cyanohydrin, m. p. 185—186° (decomp.), by complete hydrogenation gave the acetate of the acetoxyamine (X), which separated from methanol–ether in prisms becoming opaque at 150—160°, undergoing transformation at 220—225° without melting to iridescent plates, m. p. 236—237° (without decomp. (cf. Goldberg and Monnier)), the melt recrystallising immediately on slight cooling. Subsequent fractions exhibited the same behaviour, but the final m. p. rose to 242—244° and 244—246°. Deamination gave the acetoxy-ketone (XVII); after crystallisation from ether–pentane and drying at 85°/0·02 mm., it had m. p. 118—120°, $(\alpha)_D^{14}$ −50° ± 2° (*c* = 1,050 in methanol). Chromatographic purification eliminated traces of the isomeric D-homoandrostane-3(β)-ol-17-one acetate, but failed to give the m. p. 124—125° and $[\alpha]_D^{20°}$ −45° found by Goldberg and Monnier. Since catalytic reduction in acetic acid leads to quite considerable amounts of ætiocholane compounds (Reichstein and Lardon, *Helv. Chim. Acta*, 1941, **24**, 955; Wenner and Reichstein, *ibid.*, 1944, **27**, 24), the acetoxyketone (XVII) was obtained from androstane-3(β)-ol-17-one acetate (*iso*androsterone acetate).

Androstane-3(β)-ol-17-one acetate, double m. p. 97° and 102—104°, (3 g.) was dissolved in 96% alcohol (50 c.c.), and the solution was cooled to 20°, and finely powdered potassium cyanide (5·9 g. = 10 mols.) added. Acetic acid (5·4 c.c. = 9·5 mols.) was then added gradually with mechanical stirring, and finally 0·1 c.c. of triethylamine (cf. Lapworth, *J.*, 1928, 2533). After 16 hours at 15°, the mixture was poured into water (500 c.c.) containing acetic acid (2 c.c.) with stirring, and the precipitate filtered off, washed with water, and dried in a vacuum. Crystallisation from ether gave the *cyanohydrin* (1·80 g.) as long prisms, m. p. 125—126° (decomp.), $[\alpha]_D^{14°}$ −28° ± 1·5° (*c* = 1·624 in alcohol) (Found (after drying at 60°/0·01 mm.): C, 73·10; H, 9·06. $C_{22}H_{33}O_3N$ requires C, 73·49; H, 9·25%). The mother liquor yielded further small crops of crystals (380 mg. and 290 mg.) probably consisting essentially of the epimeric *cyanohydrin*, m. p. 146—148° (decomp.), $[\alpha]_D^{14°}$ −24·7° ± 1·5° (*c* = 1·416 in alcohol) (Found (after drying at 60°/0·01 mm.): N, 3·90. $C_{22}H_{33}O_3N$ requires N, 3·90%). The cyanohydrin (1·79) dissolved in pure acetic acid (25 c.c.) was shaken with Pt (from 350 mg. of PtO_2,H_2O) in hydrogen at 20° (H_2 absorbed, 221 c.c. Calc.: 233 c.c.). After filtration, the solution was evaporated at 35—40°/10 mm., and the residual syrup dissolved in methanol (7·5 c.c.); concentration to about ⅓ volume and addition of ether gave the acetoxyamine acetate (1·81 g.) as prisms becoming opaque at 160° and transformed at 225° to flat iridescent plates, m. p. 243—246° with immediate recrystallisation of the melt. This procedure is much to be preferred to that given by Goldberg and Monnier, which involves evaporation under reduced pressure of an aqueous solution of the acetoxyamine acetate whereby extensive frothing occurs only partially overcome by addition of *n*-octyl alcohol. Deamination of the acetoxyamine acetate furnished 1·39 g. of crude product, which by crystallisation from ether–pentane gave D-homoandrostane-3(β)-ol-17*a*-one acetate (770 mg.), m. p. 123—125°, $[\alpha]_D^{15°}$ −45·3° ± 1° (*c* = 2·192 in methanol) (material sublimed at 130—140°/0·02 mm.). A further quantity of the same degree of purity was obtained from the mother liquor by chromatography, together with a little D-homoandrostane-3(β)-ol-17-one, m. p. 104°; mixtures of these two acetoxyketones do not give m. p. depressions.

17-*Bromo-D-homoandrostane*-3(β)-*ol*-17a-*one acetate* (XVIII). The acetoxyketone (680 mg.) dissolved in acetic acid (2 c.c.) was treated with a solution of bromine (314 mg. = 1 mol.) in acetic acid (1·0 c.c.) dropwise. The *bromo-acetoxyketone* crystallised spontaneously; after addition of ether, it was filtered off and washed with ether–pentane (1 : 1) (530 mg., m. p. *ca.* 240°); recrystallisation from chloroform–ether or dioxan–ether gave shining plates (365 mg.), m. p. 246—248°, $[\alpha]_D^{14°}$ −31·7° ± 2° (*c* = 1·483 in chloroform) (Found (after drying at 80°/0·01 mm.): Br, 18·85. $C_{22}H_{33}O_3Br$ requires Br, 18·79%). The mother liquor by concentration gave only a small quantity of crystals; the combined mother liquors by complete evaporation furnished 520 mg. of material which was dissolved in benzene (2 c.c.) and chromatographed on a column of neutralised * alumina (16 g.) prepared in pentane. Elution with benzene–pentane (1 : 1), benzene, and ether–benzene mixtures containing 1—5% of ether yielded crystalline fractions which failed to melt sharply; thus fraction 9 (obtained with benzene), after recrystallisation from ether, had m. p. 182—185° but traces of material in the melt survived to *ca.* 200°; these crystals had $[\alpha]_D^{14°}$ −55·5° ± 3° (*c* = 1·188 in chloroform) and appeared to consist largely of the 17-*epimeric bromo-acetoxyketone* (Found: C, 62·62; H, 8·01. $C_{22}H_{33}O_3Br$ requires C, 62·11; H, 7·82%). As separation appeared difficult, the various crystalline fractions were combined and reduced with zinc in acetic acid in the presence of sodium acetate to afford the acetoxyketone, m. p. 123—124°.

Action of Alkaline Reagents on the Bromo-acetoxyketones (XVIII).—(*a*) The compound (XVIII), m. p. 246—248° (170 mg.), in dry ether was added to a cold solution of sodium methoxide (from 230 mg. "molecular" sodium and dry methanol (1 c.c.)). Sodium bromide was immediately precipitated, and, after standing at 15° for 2 hours, the reaction mixture was poured into ice–water (10 c.c.) containing 2N-HCl (5·5 c.c.), extracted with ether, and separated into neutral and acidic fractions. The neutral fraction (130 mg.) crystallised on concentration of the ether solution; the crystals were filtered off and recrystallised from acetone in prisms, m. p. 226° after softening from 218°, $[\alpha]_D^{18°}$ −38·2° ± 4° (*c* = 0·524 in acetone) (Found (after sublimation at 180°/0·01 mm.): C, 74·70; H, 9·70. $C_{21}H_{34}O_3$ requires C, 75·39; H, 10·25%). The compound did not appear to react with semicarbazide acetate and is regarded as 17 : 17a-*epoxy*-17a-*methoxy-D-homoandrostane*-3(β)-*ol* (XXa). The united mother liquors were evaporated and the residue refluxed with 3·3% methanolic potassium hydroxide (2 c.c.) for 2 hours; after addition of a few drops of water and saturation with carbon dioxide, methanol was removed under reduced pressure, and the product acidified, extracted with ether, and separated into in neutral and acidic fractions. No acidic fraction was obtained; the neutral fraction was rejected.

(*b*) The compound (XVIII) (m. p. *ca.* 240°; 350 mg.) was dissolved in methanol (20 c.c.), a solution of potassium bicarbonate (1 g.) in water (4 c.c.) added, and the mixture refluxed on the steam-bath for 3 hours. After removal of methanol under reduced pressure and addition of water, the product was extracted with ether, and the extract washed with water, dried (Na_2SO_4), and evaporated. The residual oil, dissolved in a little ether–pentane, was left overnight at −15°; the crystals which separated were washed with cooled ether–pentane to give 17 : 17a-*epoxy*-17a-*methoxy-D-homoandrostane*-3(β)-*ol acetate* (XXb) as needles, m. p. 164—166°. For analysis the compound was again recrystallised from methanol; it then had m. p. 164—166°, and sublimed at 140°/0·02 mm. (Found: C, 73, 17; H, 9·53. $C_{23}H_{36}O_4$ requires C, 73·37; H, 9·63%). The compound could not be hydrolysed by methanolic potassium hydroxide to yield an acid, and did not appear to react with semicarbazide acetate. Chromatography of the residue from the original ether–pentane mother liquor afforded with benzene–pentane (1 : 2) a small amount of the foregoing oxide, and with benzene a small quantity of a *substance*, which, recrystallised several times from ether–pentane, formed flat prisms transformed at *ca.* 205° to hair-like needles, m. p. 210—212° with partial recrystallisation and final melting at 220—222° (Found (after drying at 100°/0·02 mm.): C, 71·09; H, 8·92. $C_{24}H_{36}O_5$ requires C, 71·25; H, 8·9; $C_{24}H_{38}O_5$ requires C, 70·90; H, 9·42%). The potassium bicarbonate aqueous liquor on acidification and extraction furnished no acidic material.

* Al_2O_3 (Merck–Brockmann) was digested with 2N-HNO_3, filtered off, washed well with water, and twice refluxed with MeOH; the oxide was filtered off, freed from MeOH in a vacuum and reactivated at 250°/10 mm.

(*c*) The compound (XVIII) (m. p. *ca.* 240°; 160 mg.) was refluxed with 3·3% methanolic potassium hydroxide (containing 3—4% water) (5 c.c.) for 1 hour; after adding a few drops of water, methanol was removed under reduced pressure. Part of the product was insoluble in hot chloroform, but soluble in warm water; the reaction mixture was therefore extracted with chloroform–ether and the extract washed with water. The washing was mixed with the alkaline aqueous liquor and acidified; a precipitate then formed. The acid(s) were extracted with chloroform–ether, and the extract dried and evaporated to afford 40 mg. of oil which was esterified with diazomethane in ether. Chromatography of the product (eluants: benzene–pentane (1 : 1), benzene, ether–benzene mixtures (2—40% ether), ether, and acetone–ether (1 : 1)) furnished only oily fractions which failed to crystallise when inoculated with methyl 3(β)-hydroxyætio*allo*cholanate; elution with acetone and chloroform–acetone (1 : 1) gave traces of an unindentified methyl ester, m. p. *ca.* 225°. The neutral product of the reaction was not further examined.

(*d*) The compound (XVIII) (m. p. 235°; 665 mg.) was dissolved in warm dioxan (10 c.c. freshly distilled over Na) and dry powdery sodium methoxide (cf. Komppa, *Annalen*, 1909, **368**, 137) (*ca.* 200 mg.) was introduced. After standing for 48 hours at 15° with rigid exclusion of moisture, dioxan was removed under reduced pressure. The yellow residue was treated with ice–water, and on addition of 2N-HCl became nearly colourless. Extraction with chloroform, and washing of the extract with 2N-Na_2CO_3 gave an acidic gum (20 mg.) which was rejected. Evaporation of the chloroform extract furnished a yellow oil (570 mg.) which was refluxed for 1 hour with 3·3% methanolic potassium hydroxide (10 c.c.). After addition of a little water, methanol was removed under reduced pressure to leave a yellow product partially insoluble in ether–chloroform; the resulting yellow powder was insoluble in cold water, and was filtered off and washed with chloroform. The ether–chloroform solution, containing unsaponifiable material, was not further examined. The potassium salts were dissolved in hot water and acidified with 2N-HCl (Congo red) to furnish a nearly colourless precipitate of solid acids (44 mg.), m. p. 160—170° (unsharp).

The dried mixture of acids was dissolved in dioxan, esterified with diazomethane in ether, and the residue obtained by evaporation refluxed with acetic anhydride for ½ hour. Acetic anhydride was evaporated in a vacuum, the last traces were removed in a high vacuum, and the product, dissolved in benzene (0·5 c.c.), was chromatographed by the " Durchlauf " method on a column of alumina (Merck–Brockmann (activity III–IV), 1·5 g.) prepared in pentane.

TABLE II.

Fraction.	Eluant (5 c.c.).	Eluate.
1	Benzene–pentane (1 : 20)	—
2	,, (1 : 10)	Trace of oil.
3	,, (1 : 4)	Crystallised spontaneously; recryst. methanol, m. p. 110—111°.
4, 5	,, ,,	Little oil, failed to crystallise.
6, 7	,, (1 : 2)	Oil, crystallised from methanol; plates, m. p. 146—148°.
8, 9	,, (1 : 1)	,, ,, ,, double m. p. 139° and 156°.
10, 11	Benzene	Oil, failed to crystallise.
12	Ether–benzene (1 : 1)	,, ,, ,,
13	Ether	,, ,, ,,

Fractions 6 and 7 gave methyl 3(β)-acetoxyætio*allo*cholanate (1·5 mg.) (XIXb), which gave no depression with a genuine specimen, m. p. 148—150°; the quantity was insufficient to determine the specific rotation, but the opportunity was taken to measure this constant, which has not previously been recorded, for the genuine specimen: $[\alpha]_D^{15°}$ + 42° ± 2° (*c* = 1·064 in acetone).

Fractions 8 and 9 furnished an ester (4 mg.) exhibiting a double m. p. and shown to be *methyl* 3(β)-*acetoxy*allo*homobilianate* (XXII) by mixed m. p. with a genuine specimen, and by the specific rotation $[\alpha]_D^{15°}$ −6° ± 6° (*c* = 0·308 in acetone) (Found (after distillation at 160—170°/0·02 mm.): C, 68·10; H, 9·20. $C_{24}H_{38}O_6$ requires C, 68·22; H, 9·06%).

The trace of ester, m. p. 110—111°, from fraction 3 (<1 mg.) was insufficient for further examination.

Methyl 3(β) *Acetoxy*allo*homobilianate* (XXII) *from D-Homoandrostane*-3(β)-*ol*-17-*one Acetate* (XVII).—The acetoxy-ketone (XVII) (125 mg.) and piperonal (75 mg.) were dissolved in methanol (2·5 c.c.), 10N-KOH (0·1 c.c.) added, and the mixture left at 15° for 16 hours. The yellow needles which separated were filtered off (40 mg.), m. p. 190—192°; the mother liquor despite its yellow colour gave an oily residue (97 mg.) which consisted mainly of unchanged acetoxy-ketone since chromatographic purification furnished this compound (80 mg.), m. p. 124°, mixed m. p. 124°. The piperonylidene derivative was refluxed with acetic anhydride for ½ hour, and the residue obtained by complete evaporation (m. p. 190° was dissolved in chloroform and treated with ozonised oxygen for ½ hour at 0°. After removal of chloroform under reduced pressure, the product was taken up in acetic acid (0·5 c.c.) and a solution of chromium trioxide in acetic acid (1 c.c. of 2%) added; the mixture, after standing overnight at 15°, was worked up in the usual manner to give an oil (17 mg.), which was esterified with diazomethane in ether. The product obtained by evaporation was dissolved in benzene (0·5 c.c.) and introduced onto a column of alumina (Merck–Brockmann, 0·5 g.) prepared in pentane. Elution with benzene–pentane (1 : 2 and 1 : 1) gave eluates which crystallised by rubbing with a trace of methanol; these fractions were united and crystallised twice from methanol to give plates (3 mg.) of the methyl ester (XXII), m. p. 139—140° with resolidification to prisms, m. p. 156°, recrystallising at 154° and remelting at 155—156°, $[\alpha]_D^{20°}$ −8° ± 4° (*c* = 0·250 in acetone on material dried at 80°/0·02 mm.). The ester was recovered from the acetone solution and distilled at 170°/0·02 mm. for analysis (Found: C, 68·08; H, 9·14%).

We wish to thank Dr. K. Miescher of CIBA Limited, Basle, for gifts of dehydro*iso*androsterone and *iso*androsterone acetates, Professor Dr. L. Ruzicka, For. Mem. R.S., for microanalytical facilities at the Eidg. Techn. Hochschule, Zürich, and Prof. Dr. T. Reichstein for the hospitality of his Institute; one of us (C. W. S.) also desires to acknowledge the award of a Rockefeller Research Fellowship, during the tenure of which part of this work was carried out, and the generous support of the British Empire Cancer Campaign and the Jane Coffin Childs Memorial Fund.

PHARMAZEUTISCHE ANSTALT DER UNIVERSITÄT, BASEL.
THE CHESTER BEATTY RESEARCH INSTITUTE,
THE ROYAL CANCER HOSPITAL (FREE), LONDON, S.W. 3. [*Received, December 17th*, 1945.]