619 *Steroids and Walden Inversion Part XL.* The Configurations of the Bromination Products of Androstan-17-one.*

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Bromination of androstan-17-one affords the 16α-bromo- and the 16 : 16-dibromo-ketone. With lithium aluminium hydride the former product gives the 16α-bromo-17β-hydrin whose reactions with chromium trioxide, zinc, and potassium hydroxide (giving unexpectedly androstan-17-one) are reported; use of sodium borohydride gives the 16α-bromo-17α- and -17β-hydrin, whose reactions (as above) are also reported.

16β-Bromoandrostan-17-one is obtained by two methods and its equilibration with the 16α-bromo-ketone by hydrogen bromide is investigated.

Structures and configurations are rigidly proved.

The results differ from Fajkos's experiences with 3β-methoxy- and 3β-acetoxy-5α-androstan-17-one probably owing to long-range effects ascribed to conformational transmission.

The ultraviolet and infrared spectra of the bromo-ketones and bromohydrins are discussed in relation to the geometry of the steroid ring D.

There are two general methods for determination of the configuration at the halogen-substituted position in α-bromo*cyclo*hexanones. The chemical method depends upon reduction with lithium aluminium hydride or sodium borohydride to epimeric bromohydrins; with alkali *trans*-bromohydrins yield epoxides, and *cis*-bromohydrins regenerate the original ketones, whilst catalytic reduction furnishes the epimeric alcohols of established configurations.[1,2] The physical method depends on the circumstance that the frequency of the spectral absorption maximum of the carbonyl group in an α-bromo*cyclo*hexanone is a function of θ, the angle between the C–Br dipole and the trigonal $>C^{+}-O^{-}$ bond projected on a plane perpendicular to the bond joining C–Br and $C^{+}-O^{-}$.[3,4] Thus, in the ultraviolet region, axial α-bromo*cyclo*hexanones (θ ~105°) show displacements of the wavelength ($\Delta\lambda$ +28 mμ) and intensity ($\Delta \log \varepsilon$ + 0·6) of the carbonyl absorption maximum, whereas the equatorial epimerides (θ ~ −15°) exhibit only small differences ($\Delta\lambda$ −5 mμ; $\Delta \log \varepsilon$ 0 to +0·3) with respect to the parent ketones;[4] conversely, in the infrared region, equatorial α-bromo*cyclo*hexanones exhibit an increase in the carbonyl frequency ($\Delta\nu_{max.}$ + 15—20 cm.$^{-1}$), whereas the axial epimerides show little, if any, displacement.[3,5]

Equatorial bromine in α-bromo*cyclo*hexanols [θ 60°] gives one or more intense absorption bands in the 700 cm.$^{-1}$ region, whilst axial bromine [θ 60° or 180°] gives one or more intense bands in the 500—600 cm.$^{-1}$ region;[6] whilst these characteristic frequencies, which reflect the weight and configuration of the bromine atom, are largely independent of the α-hydroxyl group (whether axial or equatorial), α-bromo*cyclo*hexanols with *trans*(diequatorial)- or *cis*(axial-equatorial or equatorial-axial)-geometry, show considerable perturbation of the O–H and C–OH stretching frequencies ($\Delta\nu_{O-H}$: −25 to −48 cm.$^{-1}$; $\Delta\nu_{C-OH}$: +13 to +25 cm.$^{-1}$), the *trans*-diaxial isomerides show little or no perturbation ($\Delta\nu_{O-H}$: −3 to −7 cm.$^{-1}$; $\Delta\nu_{C-OH}$: +2 to +6 cm.$^{-1}$).[7] These last techniques permit determination of both the halogen and the hydroxyl configurations in α-bromo*cyclo*hexanols.

* Part XXXIX, *J.*, 1958, 1657.

[1] Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 700; Fieser and Dominguez, *ibid.*, p. 1704; Fieser and Huang, *ibid.*, p. 4837; cf. Corey, *ibid.*, p. 4832.

[2] James and Shoppee, *J.*, 1954, 4224; James, Rees, and Shoppee, *J.*, 1955, 1370; James and Shoppee, *J.*, 1956, 1064; Shoppee, Jenkins, and Summers, *J.*, 1958, 1657.

[3] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

[4] Cookson, *J.*, 1954, 282; Cookson and Dandegaonker, *J.*, 1955, 352.

[5] Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301, 3297; 1954, **76**, 175; 1955, **77**, 5415, 5418.

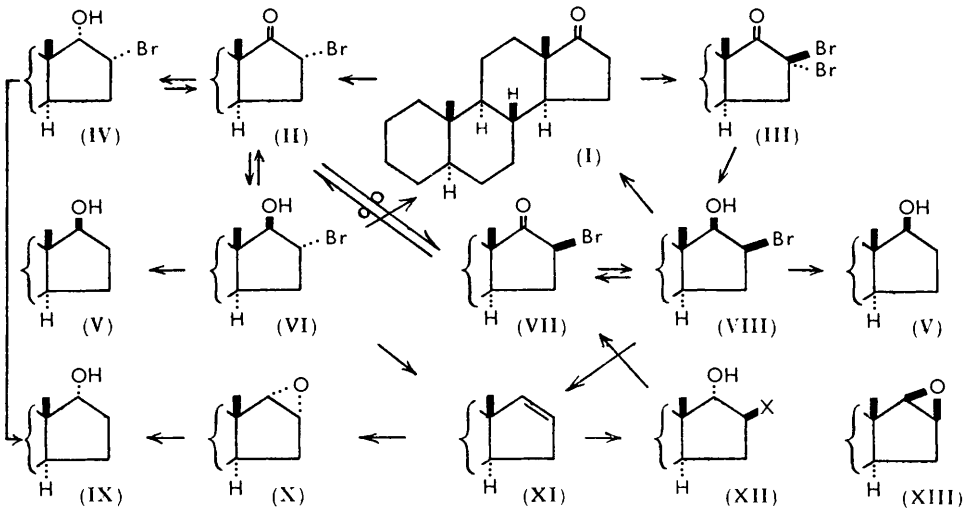
[6] Barton, Page, and Shoppee, *J.*, 1956, 331; Cummins and Page, *J.*, 1957, 3847; cf. Bellamy and Williams, *ibid.*, p. 4294.

[7] Nickon, *J. Amer. Chem. Soc.*, 1957, **79**, 243.

There is relatively little analogous chemical and physical information about α-bromo-*cyclo*pentanones and α-bromo*cyclo*pentanols. 15-, 16-, and 17-Keto-14α-steroids involve *cyclo*pentanone rings of fixed conformation; it seemed therefore of interest to investigate their bromination products, to ascertain the configurations of the α-bromo-ketones and those of the derived bromohydrins by chemical means, and to examine their spectral characteristics in the infrared and the ultraviolet region with a view to correlation with the geometry of ring D. The present paper deals with androstan-17-one and its derivatives.

Monobromination of androstan-17-one [8, 9, 10] (I) in acetic acid at 15° and purification of the product by crystallisation gave 75% of the 16α-bromo-ketone (II), whilst dibromination in ether–acetic acid at 36° gave the 16 : 16-dibromo-ketone (III).

The 16α-bromo-ketone (II) with lithium aluminium hydride in ether at 0° gave a 70% yield of the 16α-bromo-17β-hydrin (VI), m. p. 94°, $[\alpha]_D$ +2° (acetate, m. p. 142°, $[\alpha]_D$ −31°), oxidised by chromium trioxide in acetic acid at 20° to the 16α-bromo-ketone (II), and reductively debrominated with hydrogen and palladium in methanol to androstan-17β-ol [11,12,13] (V). Dehydrobromination with boiling methanolic potassium hydroxide



yielded, not the expected 16β : 17β-epoxide (XIII), but 86% of androstan-17-one (I), whose identity was confirmed by infrared spectroscopy, accompanied by 3% of androstan-17β-ol (V), possibly formed by reduction of the ketone (I) by methanol in the presence of methoxide ions.[14] The 16α-bromo-ketone (II) with sodium borohydride in methanol at 20° gave, after chromatography, the 16α-bromo-17α-hydrin (IV), m. p. 128°, $[\alpha]_D$ −5° (acetate, m. p. 200°, $[\alpha]_D$ −8°), and the 16α-bromo-17β-hydrin (VI), m. p. 90—94°, $[\alpha]_D$ +3°, giving an infrared spectrum identical with that of the material described above; the 16α-bromo-17α-hydrin (IV) with chromium trioxide in acetic acid at 20° gave the 16α-bromo-ketone (II), with hydrogen and palladium in methanol gave androstan-17α-ol [12, 13] (IX), and with hot methanolic potassium hydroxide gave androstan-17-one (I). In two experiments in which the sodium borohydride reduction product was isolated by direct crystallisation a compound of m. p. 147°, $[\alpha]_D$ −4°, was obtained; this gave correct

[8] Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192.
[9] Fernholz and Chakravorty, *Ber.*, 1935, **68**, 353.
[10] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[11] Marker, *ibid.*, 1940, **62**, 2543.
[12] Miescher and Kagi, *Helv. Chim. Acta*, 1939, **22**, 683.
[13] Shoppee, *Chem. and Ind.*, 1950, 454.
[14] Elks and Phillipps, *J.*, 1956, 4320.

analytical figures and appears to be a polymorph of the 16α-bromo-17α-hydrin (IV) (since in a third experiment fractions were obtained melting over the range 128—144°), or a molecular compound of the 17-epimeric bromohydrins (IV) and (VI).

The 16 : 16-dibromo-ketone (III) with sodium borohydride in methanol at 15° gave the 16β-bromo-17β-hydrin (VIII), m. p. 123°, $[\alpha]_D$ +3°, as sole product; its structure follows from its conversion by hydrogen and palladium into androstan-17β-ol (V), and by potassium hydroxide in methanol into androstan-17-one (I). The 16β-bromo-17β-hydrin (VIII) with chromium trioxide in acetic acid at 15° gave the 16β-bromo-ketone (VII), reconverted by reduction with sodium borohydride into the 16β-bromo-17β-hydrin (VIII).

The 16β-bromo-ketone was also obtained in another way. The three epimeric bromohydrins (IV), (VI), and (VIII) on brief treatment with zinc in acetic acid reacted with apparently equal facility, probably by the unimolecular elimination mechanism *E1cB*,[15] to afford androst-16-ene [16, 17] (XI). This hydrocarbon with perbenzoic acid gave the 16α : 17α-epoxide (X), reduced by lithium aluminium hydride to androstan-17α-ol (IX), and converted by hydrogen bromide in acetic acid into the 16β-bromo-17α-hydrin (XII; X = Br), m. p. 126°, $[\alpha]_D$ −4°, which with chromium trioxide in acetic acid at 15° gave the 16β-bromo-ketone (VII), whose infrared spectrum was identical with that of the previous preparation.

Epimerisation of the 16-bromo-ketones by hydrogen bromide was very slow at 15°; the specific rotation of the 16α-bromo-ketone (II) in chloroform containing a few drops of a 40% solution of hydrogen bromide in acetic acid at 20° increased only from +58° to +62° in 15 hr., whilst the specific rotation of the 16β-bromo-ketone (VII) in a 4% solution of hydrogen bromide in acetic acid at 20° fell only from +124° to +115° in 24 hr. At 55° in a 4% solution of hydrogen bromide in acetic acid interconversion of the epimerides was fairly fast, to give an equilibrium mixture with a specific rotation of 93° ± 2° in 6 hr., unchanged during a further 90 hr.; isolation of the product gave material with specific rotations of +95° and +91°, from which the less soluble 16α-bromo-ketone (II) was isolated by crystallisation. On the basis of the rotation values, the equilibrium proportions are 47 ± 3% of (II; 16α) and 53 ± 3% of (VII; 16β). Attempted base-catalysed epimerisation of the 16α-bromo-ketone at 20° with methanolic sodium hydroxide equivalent to the alkalinity generated in reduction with sodium borohydride gave an oil, $[\alpha]_D$ +10°, substantially free from bromine.

An attempt to prepare the 16β : 17β-epoxide (XIII) from the 16α : 17α-epoxide (XI) by the usual inversion procedure [acetolysis of the 16α : 17α-epoxide (XI) to give the 16β : 17α-diol 16-mono-acetate (XII: X = OAc), and treatment of this as the 17-toluene-*p*-sulphonate with potassium hydroxide] had to be abandoned for lack of material.

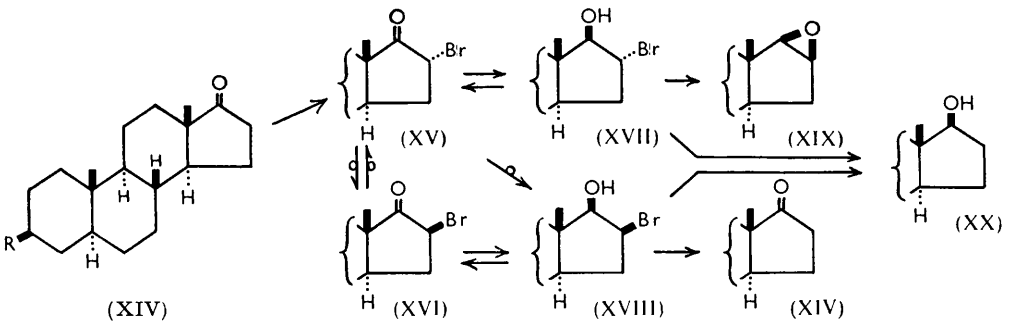
When the foregoing work was almost complete, there appeared a paper by Fajkos [18] describing the epimeric 16-bromo-derivatives of 3β-methoxy- and 3β-acetoxy-androstan-17-one with results so strikingly different from our own as to compel repetition of our work, and to merit brief description of his results.

Bromination in acetic acid of 3β-methoxyandrostan-17-one (XIV; R = MeO) gave the 16α-bromo-ketone (XV; R = MeO) unaccompanied by the 16 : 16-dibromo-ketone. The 16α-bromo-ketone with lithium aluminium hydride in ether at 0° gave 45% of the 16α-bromo-17β-hydrin (XVII; R = MeO), which was oxidised by chromium trioxide in acetic acid at 20° to regenerate the parent 16α-bromo-ketone (XV; R = MeO), dehydrobrominated by potassium hydroxide to the 16β : 17β-epoxide (XIX; R = MeO), and debrominated by palladium in hydrogen to 3β-methoxyandrostan-17β-ol (XX; R = MeO). The 16α-bromo-ketone (XV; R = MeO) however, with sodium borohydride in methanol at 20°, gave 70% of the 16β-bromo-17β-hydrin (XVIII; R = MeO), converted by palladium

[15] James, Rees, and Shoppee, *J.*, 1955, 1370.
[16] Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1944, **27**, 66.
[17] Miescher and Kagi, *ibid.*, 1949, **32**, 761, 764, 766.
[18] Fajkos, *Coll. Czech. Chem. Comm.*, 1955, **20**, 312.

and hydrogen into the 17β-ol (XX; R = MeO), by potassium hydroxide into the 3β-methoxy-ketone (XIV; R = MeO), and by chromium trioxide in acetic acid at 20° into the 16β-bromo-ketone (XVI; R = MeO). This 16β-bromo-ketone was isolated in small quantity by systematic fractional crystallisation of the crude product of the original bromination (being probably formed as the result of hydrogen bromide-catalysed epimerisation of the 16α-bromo-ketone); it was also obtained from the 16α-bromo-ketone by base-catalysed epimerisation at 20°, the equilibrium mixture of the epimeric bromo-3β-methoxy-ketones being estimated on the basis of its specific rotation as 20% of 16α- and 80% of 16β-isomer. It was suggested that reduction of the 16α-bromo-ketone (XV; R = MeO) with sodium borohydride in methanol, as opposed to lithium aluminium hydride in ether at 0°, is preceded by base-catalysed epimerisation at 20°, to give the 16β-bromo-ketone (XVI; R = MeO), which in fact affords 73% of the 16β-bromo-17β-hydrin (XVIII; R = MeO) when reduced with sodium borohydride in methanol.

Bromination of 3β-acetoxyandrostan-17-one (XIV; R = AcO) in acetic acid was much slower and yielded only a small amount of the 16α-bromo-ketone (XV; R = AcO), but in ethanol gave some 30% of the 16α-bromo-ketone accompanied by the 16 : 16-dibromo-ketone. The 16α-bromo-ketone was readily prepared by the action of bromine on the enolic acetate 3β : 17-diacetoxyandrost-16-ene, and afforded 17-epimeric 16α-bromohydrins (XVII and its 17α-epimeride; R = AcO) by reduction with lithium aluminium hydride or with lithium borohydride in ether at 0°, but yielded 60% of the 16β-bromo-17β-hydrin (XVIII; R = AcO) with sodium borohydride in methanol or with lithium borohydride in ethanol at 20°. Oxidation of the 16β-bromo-17β-hydrin (XVIII; R = AcO) with chromium trioxide in acetic acid furnished the 16β-bromo-ketone (XVI; R = AcO), which was prepared independently by Šorm and Fajkos [19] from 3β-acetoxy-16α : 17α-epoxyandrostane by fission with hydrogen bromide and oxidation of the resulting non-crystalline 16β-bromo-17α-hydrin with chromium trioxide. Finally, the 16α-bromo-



ketone (XV; R = AcO) was partly converted into the 16β-bromo-ketone (XVI; R = AcO) by treatment with hydrogen bromide, the equilibrium mixture being estimated on the basis of specific rotation to contain the epimerides in the proportion 16α 60% : 16β 40%.

The chemical evidence for the configurations of the various 16-bromoandrostan-17-ones prepared by us and by Fajkos appears unambiguous. It is supported by the available physical evidence. The molecular rotation data for the various androstan-17-ones and their 16-bromo-derivatives, and for the androstan-17-ols and their 16-bromo-derivatives are collected in Table 1.

It will be seen that, in terms of the configurations assigned, inversion of configuration of a 16-bromo-substituent (16α ⟶ 16β) leads consistently to increased dextrorotation; this is also true for 16-bromo-17α-hydrins (16α : −18°; 16β : −14°). The molecular-rotation data thus support the chemical evidence of configuration. The larger increments observed for the bromo-ketones than for the bromohydrins reflect the larger rotatory contribution of the 17-keto-group (+93°) than of the 17β-hydroxyl group (+11°). In

[19] Šorm and Fajkos, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1478.

the bromo-ketones, the rotatory contribution of a 16α-bromine atom is negative, but that for a 16β-bromine atom is positive; in the bromohydrins, the rotational contribution of a 16α-bromine atom is again negative, whereas that for a 16β-bromine atom is also negative but less. In this connexion it may be recalled that the rotatory contributions for epimeric

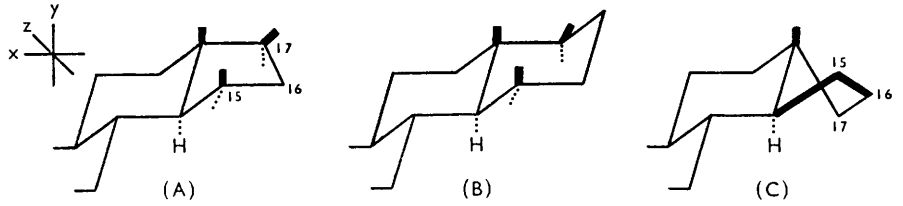
TABLE 1.

3β-Substituent R	Compound	$[\alpha]_D$	$[M]_D$	Δ16β–16α	ΔBr 16α	ΔBr 16β
H	Androstane	+2°	+5°	—	—	—
	17-Ketone (I)	+98	+268	—	—	—
	16α-Bromo-ketone (II)	+58	+204	+234°	−64°	—
	16β-Bromo-ketone (VI)	+124	+438		—	+170°
	16 : 16-Dibromo-ketone (III)	+62	+268	—	−170	+64
MeO	17-Ketone (XIV)	+79	+240	—	—	—
	16α-Bromo-ketone (XV)	+45	+174	+232	−66	—
	16β-Bromo-ketone (XVI)	+106	+406		—	+166
AcO	17-Ketone (XIV)	+69	+229	—	—	—
	16α-Bromo-ketone (XV)	+38	+154	+232	−75	—
	16β-Bromo-ketone (XVI)	+94	+386		—	+157
	16 : 16-Dibromo-ketone	+45	+223		−163	+69
H	17β-Alcohol (V)	+13	+36	—	—	—
	16α-Bromo-17β-hydrin (VI)	+2	+7	+5	−29	—
	16β-Bromo-17β-hydrin (VIII)	+3·5	+12		—	−24
MeO	17β-Alcohol (XX)	+15	+46	—	—	—
	16α-Bromo-17β-hydrin (XVII)	−8	−31	+16	−77	—
	16β-Bromo-17β-hydrin (XVIII)	−4	−15		—	−61

16-hydroxyl groups are both negative: ΔOH-16α −36°, ΔOH-16β −20°, and it can be shown [20] that ΔOH and ΔHal values tend, in the absence of vicinal action, to be similar in both sign and magnitude at the various nuclear positions.

We have also investigated the ultraviolet and the infrared spectral characteristics of androstan-17-one (I) and its bromides (II, VII, and III), less in the expectation that they would support the configurations assigned, than in the hope that they would provide evidence relating to the geometry of ring D and so possibly throw light on the factors controlling the rates of interconversion and the equilibria of pairs of 16-epimerides.

In androstane and other 14α-steroids generally, it is usual to attribute equatorial character to the 15α- and 17β-bonds, and axial character to the 15β- and 17α-bonds (A), either by reference to the conformation of ring C or by analogy with the conformation of



the terminal ring of D-homoandrostane (B). This approximation cannot be applied to the bonds attached to $C_{(16)}$. Spectroscopic measurements [21] and entropy calculations [22,23] indicate that the 5-carbon ring of *cyclo*pentane is puckered as the result of 1 : 2-repulsions between adjacent C–H bonds. The decrease in stability caused by the deformation of the tetrahedral angles is more than compensated by the gain in stability resulting from reduction of the repulsive forces between adjacent C–H bonds by staggering; C_2 symmetry with $C_{(3)}$ lying below and $C_{(5)}$ above a plane containing $C_{(1)}$, $C_{(2)}$, and $C_{(4)}$ has been confirmed by determination of the molar Kerr constants for *cyclo*pentane and the

[20] Shoppee, Howden, and Lack, unpublished work.
[21] Tschamler and Voetter, *Monatsh.*, 1952, **83**, 302, 835, 1228.
[22] Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63**, 2039; 1943, **65**, 341.
[23] Kilpatrick, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2483.

*cyclo*pentyl halides by Le Fèvre and Le Fèvre.[24] The same arrangement is also adopted by *cyclo*pentanone,[24] and supporting evidence has been furnished by Brutcher *et al.*;[25] these workers confirmed the values of the carbonyl stretching frequency in the infrared spectrum found by Corey [5] for *cyclo*pentanone and the α-halogeno*cyclo*pentanones, and compared the frequency displacements with those observed for the planar structures present in indan-2-one and camphor and their α-halogeno-derivatives. Table 2 gives the infrared spectral data, together with the positions of the ultraviolet carbonyl absorption band determined by Kumler and Huitric [25] or recorded by Cookson.[4]

TABLE 2.

	$\nu_{max.}$ (in CCl_4) (cm.$^{-1}$)	$\Delta\nu$	$\lambda_{max.}$ (mμ)	$\Delta\lambda$	log ε	Δ log ε	θ
*cyclo*Pentanone	1742	—	287	—	—	—	—
α-Chloro*cyclo*pentanone	1755	+13	302	+15	—	—	~80°
α-Bromo*cyclo*pentanone	1750	+8	311	+24	—	—	~80
Indan-2-one	1753	—	—	—	—	—	—
1-Chloroindan-2-one	1772	+19	—	—	—	—	60
1-Bromoindan-2-one	1766	+13	—	—	—	—	60
Camphor	1744	—	288	—	1·45	—	—
3-*exo*-Chlorocamphor	1762	+18	306	+18	1·72	0·27	~55
3-*endo*-Chlorocamphor	1763	+19	305	+17	1·75	0·3	~65
3-*exo*-Bromocamphor	1760	+16	312	+24	1·95	0·5	~55
3-*endo*-Bromocamphor	1758	+14	310	+22	1·95	0·5	~65
3 : 3-Dichlorocamphor	1774	+30	310	+22	1·82	0·37	—
3 : 3-Dibromocamphor	1766	+22	323	+35	1·88	0·43	—

The increments Δν are smaller and the differences Δλ are larger for the *cyclo*pentanones than for the indan-2-ones and camphors; it is therefore concluded that the projected angle between the C–Hal dipole and the $^{+}C–O^{-}$ dipole in the former must be greater than 60°; in fact, the Le Fèvre model for *cyclo*pentanone requires an angle of ~78°.

The steroid ring D is a *cyclo*pentane ring of fixed conformation, in which adoption of the puckered C_2 symmetry of *cyclo*pentane is compelled by the *trans*-C/D-ring fusion. Departures from the tetrahedral angle resulting from the ring-fusion and from the introduction of trigonal carbon and other substituents are difficult to estimate, but if the 13β-methyl group and the 14α-hydrogen atom constitute the vertical, then $C_{(13)}$, $C_{(14)}$, and $C_{(16)}$ lie in a plane which makes an angle of 19° 28′ to the horizontal (C). The 16α-C–H and 16β-C–H bonds are symmetrically disposed (*a*) at an angle $\alpha = \sim 55°$ to the plane defined by $C_{(15)}$, $C_{(16)}$, and $C_{(17)}$, and (*b*) at an angle $\beta = \sim 39°$ to the vertical in the plane *z* at right

TABLE 3.

	$\nu_{max.}$ (in CCl_4) (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	$\Delta\lambda$ (mμ)	log ε	Δ log ε
Androstan-17-one (I)	1746	—	292	—	1·72	—
16α-Bromoandrostan-17-one (II)	1752 [a] 1754	+7	314	+22	2·01	0·29
16β-Bromoandrostan-17-one (VII)	1754 [a] 1754	+8	312	+20	1·90	0·18
16 : 16-Dibromoandrostan-17-one (III)	1763	+17	320	+28	1·91	0·19

[a] Independent measurements, which also gave $\nu_{max.}$ 1751 cm.$^{-1}$ for (II) and 1754 cm.$^{-1}$ for (VII) (both in CS_2).

angles to the general plane *x* of the ring-system [given by $\cos\beta = \cos(90° - \alpha) \cdot \cos 19° 28'$]. The infrared and the ultraviolet spectral characteristics for androstan-17-one (I) and its 16-bromo-derivatives (II, VII, III) are set out in Table 3.

It will be seen that the increments Δν and Δλ are approximately equal for both the

[24] Le Fèvre and Le Fèvre, *J.*, 1956, 3549.

[25] Brutcher, Roberts, Barr, and Pearson, *J. Amer. Chem. Soc.*, 1956, **78**, 1507; cf. Kumler and Huitric, *ibid.*, p. 3369.

epimeric 16-bromo-ketones, and correspond in magnitude with those found for α-bromo-*cyclo*pentanone. Fajkos [18] records $\nu_{max.}$ 1753 cm.$^{-1}$ for both 16α- and 16β-bromo-3β-methoxyandrostan-17-one (XV, XVI; R = MeO), but fails to state the solvent; his value for 3β-methoxyandrostan-17-one (XIV) is 1735 cm.$^{-1}$ (solvent unspecified). The interactions of the C–Br dipole and the $^{+}C–O^{-}$ dipole are thus nearly the same, so that the C–Br bonds in both epimers make the same angle with the plane of $C_{(15)}$, $C_{(16)}$, and $C_{(17)}$. This confirms indirectly the validity of the Le Fèvre model for *cyclo*pentanone, which requires a symmetrical arrangement of the 16α-C–H and 16β-C–H bonds for *trans*-C/D-steroid 17-ketones.[26] The Le Fèvre model, however, predicts an unsymmetrical arrangement of the exocyclic bonds of $C_{(15)}$ and of $C_{(17)}$ in *trans*-C/D-steroid 16-ketones, and an experimental study is in progress. For αα-dibromo*cyclo*hexanones, in the ultraviolet region, the equatorial bromine atom reduces by about one half the increment contributed by the axial bromine atom to the position of $\lambda_{max.}$ ($\Delta\lambda$*gem.*-Br_2 + 12 to + 15 mμ),[4] and conversely, in the infrared region the axial bromine atom has little effect on the increase in the carbonyl stretching frequency contributed by the equatorial bromine atom ($\Delta\nu$*gem.*-Br_2 + 17 cm.$^{-1}$);[3] the αα-dibromo*cyclo*pentanone (III) shows $\Delta\lambda$ +28 mμ and $\Delta\nu$ +17 cm.$^{-1}$, and, like 3 : 3-dibromocamphor (see Table 2), does not appear to conform to the homologous pattern.

The principal differences exhibited by our work (3β-substituent = H) and that of Fajkos [18] (3β-OMe, -OAc) are the variation with the nature of the 3β-substituent (i) of the rate of epimerisation of the 16α-bromo-17-ketones as disclosed by the occurrence of retention, as opposed to inversion of configuration at $C_{(16)}$, on reduction with sodium borohydride in methanol at 20°, (ii) of the position of equilibrium amongst the three pairs of epimeric 16-bromo-17-ketones, and (iii) of the production of 16β : 17β-epoxides.

If the inversion at $C_{(16)}$ reported by Fajkos is due to base-catalysed epimerisation of the 16α-bromo-ketones (XV) before reduction, the rate of enolisation must be rapid by comparison with the rate of reduction, for otherwise the process should lead to mixtures of 16-epimeric bromohydrins. Even so, it is not clear why inversion at $C_{(16)}$ is not also observed in the sodium borohydride reductions of the 16β-bromo-ketones (XVI), especially in the case of the 3β-acetoxy-compound (XVI; R = AcO) which at equilibrium is converted to the extent of 60% into the 16α-bromo-epimeride (XV; R = AcO).

In studies of 16-substituted steroids Šorm *et al.* have shown that the thermodynamic stabilities of pairs of epimerides vary from case to case: 16β-OH > 16α-OH; [27,28] 16α-CO_2H > 16β-CO_2H; [29] 16α-COMe > 16β-COMe; [30] and have suggested that the variation depends on the nature of the 16-substituent. It now appears that the nature of the 3-substituent is also a factor in the situation and influences both reaction rates and equilibria at $C_{(16)}$:

3β-Substituent R	Rate of epimerisation of 16α-bromo-ketones: (OH^- at ~20°)	Position of equilibrium 16α : 16β of 16-bromo-ketones (H^+ at ~20°)
H	Slow	47 : 53
MeO	Fast	20 : 80
AcO	Fast	60 : 40

These qualitative or semiquantitative variations in the properties of compounds with identical structures (apart from the 3β-substituent) are inexplicable in terms of 1 : 3-interactions, *e.g.*, 13β-Me/16β-Br and 14α-H/16α-Br, and suggest the operation of influences transmitted across a rigid, saturated, and conformationally unambiguous structure from $C_{(3)}$ in ring A to $C_{(16)}$ in ring D—a distance of about 9 Å. They appear to constitute a

[26] R. N. Jones and Roberts, *Chem. and Ind.*, 1957, 1269.
[27] Fajkos and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 349; 1955, **20**, 1464.
[28] Šorm and Hovak, *ibid.*, 1956, **21**, 926.
[29] Fajkos and Šorm, *ibid.*, 1954, **19**, 766.
[30] Fajkos and Šorm, *Chem. Listy*, 1956, **50**, 791.

further example of the long-range effects in saturated alicyclic systems ascribed to conformational transmission.[31]

We reserve comment on the formation of androstan-17-one (I) from the *trans*-bromohydrin (VI) in contrast to the production of 16β : 17β-epoxides (XIX; R = MeO, AcO) from the *trans*-bromohydrins (XVI; R = MeO, AcO), because various mechanistic possibilities are available which cannot at present be distinguished. *trans*-Geometry may be essential for mechanisms involving synchronous covalency changes, *e.g.*, " internal " S_N2, *E*2, but not for stepwise mechanisms, *e.g.*, S_N1 (*E*1) and *E*1*cB*, in the course of which the original geometry disappears.

Experimental

For general experimental directions see *J.*, 1958, 1657. $[\alpha]_D$ are in $CHCl_3$; $\lambda_{max.}$ were determined for EtOH solutions on a Unicam S.P. 500 spectrometer with corrected scale, and $\nu_{max.}$ for CCl_4 solutions on a Grubb-Parsons double-beam grating instrument. Unless otherwise specified, alumina was of Spence Type II (activity ~II).

16α-*Bromoandrostan*-17-*one* (II).—Androstan-17-one (m. p. 120°; 710 mg.), dissolved in acetic acid (50 c.c.) and ether (20 c.c.), was treated with a 10% solution of bromine in acetic acid (5 c.c., 1·1 mol.), and 2 drops of a solution of hydrogen bromide in acetic acid were added. After being kept overnight at 15°, the colourless solution was worked up in the usual way to an oil, which crystallised on trituration with ether–methanol (m. p. 181—185°). Two recrystallisations from light petroleum (b. p. 60—80°) gave 16α-*bromoandrostan*-17-*one* (900 mg.), m. p. 197°, $[\alpha]_D$ +58° (*c* 1·2) [Found (after drying at 70°/0·01 mm. for 6 hr.): C, 64·7; H, 8·4. $C_{19}H_{29}OBr$ requires C, 64·6; H, 8·2%]. Other preparations had m. p. 193—197°, $[\alpha]_D$ +58° (*c* 1·08).

Lithium Aluminium Hydride Reduction of 16α-*Bromoandrostan*-17-*one*: 16α-*Bromoandrostan*-17β-*ol* (VI).—16α-Bromoandrostan-17-one (1·47 g.) in dry ether (150 c.c.) at 0° was treated with lithium aluminium hydride (600 mg.). After 2 hr., the excess of reagent was destroyed by addition of ice followed by 2N-sulphuric acid. The product, isolated in the usual way, was an oil, which crystallised on addition of light petroleum; it was chromatographed on aluminium oxide (40 g.; Woelm, acid) in light petroleum (b. p. 60—80°). Elution with light petroleum–benzene (1 : 4, 2 × 200 c.c.; and 1 : 2, 200 c.c.) gave fractions 1—3 as oils (49 mg.); elution with benzene (7 × 200 c.c.) gave fractions 4—10, which crystallised from light petroleum (m. p. 90—94°); use of ether–benzene (1 : 19, 3 × 200 c.c.) afforded fractions 11—14, which crystallised (m. p. 86—92°) from light petroleum. Fractions 4—14 were united (1005 mg.) and recrystallised several times from light petroleum, to give 16α-*bromoandrostan*-17β-*ol*, m. p. 92—94°, $[\alpha]_D$ +2° (*c* 0·8) [Found (after drying at 20°/0·02 mm. for 16 hr.): C, 64·0; H, 8·4. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%], $\nu_{max.}$ 3632 $cm.^{-1}$ (O–H stretching), which was converted by acetic anhydride–pyridine in 12 hr. at 20° into the *acetate*, m. p. 142—144°, $[\alpha]_D$ −31° (*c* 1·8) [Found (after drying at 20°/0·02 mm. for 16 hr.): C, 63·2; H, 8·2. $C_{21}H_{33}O_2Br$ requires C, 63·5; H, 8·3%]. Further elution with ether–benzene (1 : 19, 2 × 200 c.c.) gave fractions 15 and 16 (92 mg., 55 mg.) which did not crystallise, whilst use of ether–benzene and chloroform gave only traces of oil (10 mg., 8 mg.).

Reactions of the 16α-*Bromo*-17β-*hydrin* (VI).—(*a*) The bromohydrin (128 mg.) was oxidised with a 2% solution of chromium trioxide in acetic acid at 20°; after 1 hr., the crystalline product was filtered off, and the filtrate worked up in the usual way, to give 16α-bromoandrostan-17-one (120 mg.), m. p. and mixed m. p. 193—196°.

(*b*) The bromohydrin (120 mg.) in methanol (5 c.c.) was shaken with 5% palladium–charcoal (150 mg.) in hydrogen at 20° for 18 hr. The product, isolated in the usual manner, was androstan-17β-ol, m. p. and mixed m. p. 165°, $[\alpha]_D$ +11° (*c* 1·2), after two crystallisations from aqueous acetone; on admixture with androstan-17α-ol, the m. p. was depressed to ~128°. Alternatively, the bromohydrin (60 mg.) in methanol (5 c.c.) was shaken with platinum oxide (60 mg.) in hydrogen at 20° for 16 hr. Filtration and evaporation in a vacuum gave androstan-17β-ol (47 mg.), transition to needles at 138—139°, m. p. 164—165°, whose infrared spectrum was identical with that of a genuine specimen.

(*c*) The bromohydrin (830 mg.) was refluxed with potassium hydroxide (830 mg.) in methanol (83 c.c.) for 48 hr. After partial removal of methanol under reduced pressure, and addition of

[31] Barton and Head, *J.*, 1956, 932; Barton, Head, and May, *J.*, 1957, 935.

water, the product was extracted with ether, washed with water, dried, and evaporated to an oil, which was chromatographed on aluminium oxide (30 g.; Woelm, neutral) in light petrolem. Elution with light petroleum (2 × 100 c.c.) yielded no eluates, but further use of light petroleum (100 c.c.) gave fraction 3, which crystallised (44 mg.). Elution with benzene–light petroleum (1 : 9, 4 × 100 c.c.) gave crystalline fractions 4—7 (382, 87, 16, and 11 mg.); use of benzene–light petroleum (1 : 4, 100 c.c.) gave a crystalline fraction 8, but use of benzene (100 c.c.) gave no eluate. Fractions 4 and 5 were combined and recrystallised to yield androstan-17-one, m. p. 120°, whose infrared spectrum was identical with that of an authentic specimen; fractions 3, 6, 7, and 8 also consisted of this ketone. Finally, elution of the column with ether (100 c.c.) furnished androstan-17β-ol (20 mg.), m. p. 161° (mixed m. p. 161—164°) after recrystallisation from light petroleum.

(*d*) The bromohydrin (130 mg.) was refluxed with zinc dust in ethanol (5 c.c.) for 3 hr.; the product, isolated in the normal manner, was chromatographed on aluminium oxide (4 g.) in pentane. Elution with pentane gave an oil (92 mg.), which crystallised from acetone to give androst-16-ene, m. p. and mixed m. p. 76—77°.

Sodium Borohydride Reduction of 16α-*Bromoandrostan*-17-*one*: 16α-*Bromoandrostan*-17α-*ol* (IV).—(*a*) 16α-Bromoandrostan-17-one (m. p. 193°; 340 mg.) in ether (25 c.c.) was treated with sodium borohydride (100 mg.) in methanol (12 c.c.) at 20° for 18 hr. After the usual working up, the product was chromatographed on aluminium oxide (8 g.; Woelm, neutral) in light petroleum. Elution with light petroleum (4 × 30 c.c.) gave an oil (140 mg.), which crystallised from acetone–methanol to give 16α-*bromoandrostan*-17α-*ol*, m. p. 125—128°, $[\alpha]_D$ −5° (*c* 1·0) [Found (after drying at 20°/0·02 mm. for 12 hr.): C, 64·1; H, 8·8. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%], and was converted by acetic anhydride–pyridine at 20° in 12 hr. into the *acetate*, m. p. 200—203°, $[\alpha]_D$ −5° (*c* 1·0) after two recrystallisations from acetone [Found (after drying at 50°/0·01 mm. for 12 hr.): C, 63·6; H, 8·4. $C_{21}H_{33}O_2Br$ requires C, 63·5; H, 8·3%]. Further elution of the column with benzene–light petroleum (1 : 1, 3 × 40 c.c.) gave an oil (130 mg.), which crystallised from light petroleum to give 16α-bromoandrostan-17β-ol, m. p. 90—94°, $[\alpha]_D$ +3° (*c* 1·25), whose infrared absorption spectrum was identical with that of the preparation, m. p. 92—94°, obtained by use of lithium aluminium hydride. A second experiment gave the same two products.

(*b*) 16α-Bromoandrostan-17-one (120 mg.) in ether (20 c.c.) was treated with sodium borohydride (40 mg.) in methanol (10 c.c.). After 18 hr. at 15°, the solution was diluted with water and extracted with ether. Working up furnished an oil, which crystallised readily from acetone to give either a polymorphic form of 16α-bromoandrostan-17α-ol, or more probably a molecular compound of the 16α-bromo-17-hydrins (IV, VI) (110 mg.), m. p. 144—147°, $[\alpha]_D$ −4° (*c* 1·5) [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 64·0; H, 8·8. Calc. for $C_{19}H_{31}OBr$: C, 64·2; H, 8·7%]. In a second experiment, direct crystallisation of the product, from acetone, again gave the compound, m. p. 146—149°, but a third experiment gave a product of m. p. 128—141°.

Reactions of the 16α-*Bromo*-17α-*hydrin* (IV).—(*a*) The bromohydrin (m. p. 128°; 43 mg.) was oxidised with a 2% solution of chromium trioxide in acetic acid at 20° for 12 hr. The product, isolated in the usual way, gave a nearly quantitative yield of 16α-bromoandrostan-17-one, m. p. and mixed m. p. 191—193°, $[\alpha]_D$ +58° (*c* 1·1).

(*b*) The bromohydrin (m. p. 125—127°; 30 mg.) in methanol (5 c.c.) was shaken with 5% palladium–charcoal (50 mg.) in hydrogen at 20° for 40 hr. The product, isolated in the usual way, was androstan-17α-ol, m. p. and mixed m. p. 142—144° after recrystallisation from aqueous acetone.

(*c*) The bromohydrin (m. p. 125—127°; 40 mg.) was refluxed with potassium hydroxide (120 mg.) in methanol (15 c.c.) for 2·5 hr. After saturation with carbon dioxide, partial removal of methanol under reduced pressure, and dilution with water, the product was isolated in the usual way and crystallised from hexane to give androstan-17-one (30 mg.), m. p. and mixed m. p. 119—121°, $[\alpha]_D$ +94° (*c* 1·1).

(*d*) The bromohydrin (100 mg.) was refluxed with zinc dust (500 mg.) in acetic acid (15 c.c.) for 6 hr.; the warm solution was filtered, acetic acid largely removed at 10 mm., and the product extracted with ether. The usual procedure gave an oil, which was dissolved in pentane and filtered through a column of aluminium oxide (5 g.); the filtrate was evaporated and the product crystallised twice from acetone, to yield androst-16-ene, m. p. and mixed m. p. 74—76°.

16 : 16-*Dibromoandrostan*-17-*one* (III).—Androstan-17-one (2·0 g.), in ether (200 c.c.), was

refluxed with a 50% solution of bromine in acetic acid (5 c.c., 2·1 mol.) for 24 hr. Water was then added to the colourless solution, and the ethereal layer separated and worked up in the usual way. The resultant oil crystallised readily from ether to give in high yield 16 : 16-*dibromoandrostan*-17-*one*, m. p. 179°, $[\alpha]_D$ +62° (*c* 1·1) [Found (after drying at 50°/0·01 mm. for 7 hr.): C, 53·2; H, 6·7. $C_{19}H_{28}OBr_2$ requires C, 52·9; H, 6·5%]. A second preparation had m. p. 182°.

16β-*Bromoandrostan*-17β-*ol* (VIII).—16 : 16-Dibromoandrostan-17-one (220 mg.) in ether (40 c.c.) was treated with a solution of sodium borohydride (50 mg.) in methanol (20 c.c.) at 15° for 18 hr. The mixture was diluted with water and extracted with ether, and the product isolated in the usual way, to give 16β-*bromoandrostan*-17β-*ol* (150 mg.), m. p. 123°, $[\alpha]_D$ +3·5° (*c* 1·7), after recrystallisation from acetone [Found (after drying at 40°/0·01 mm. for 18 hr.): C, 64·6; H, 8·9. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%]. A marked depression of m. p. was observed on admixture with the form of (IV), m. p. 128°, $[\alpha]_D$ −5°, and a second preparation gave material of m. p. 123—124°.

Reactions of the 16β-*Bromo*-17β-*hydrin* (VIII).—(*a*) The bromohydrin (150 mg.) and 20% palladium–charcoal (120 mg.) in methanol (45 c.c.) were shaken in hydrogen at 20° for 4 hr. The product was isolated in the usual manner and chromatographed on a column of aluminium oxide (4·5 g.) prepared in pentane. Elution with pentane gave androstan-17-one (80 mg.), m. p. and mixed m. p. 118°, $[\alpha]_D$ +98° (*c* 1·1). Elution with benzene–pentane (1 : 1) and with benzene gave androstan-17β-ol, m. p. and mixed m. p. 161—163° (from light petroleum).

(*b*) The bromohydrin (340 mg.) was treated with potassium hydroxide (900 mg.) in methanol (35 c.c.) at 15° overnight. The solution was then refluxed for 3 hr., diluted with water, and worked up in the usual way, to give androstan-17-one (270 mg.), m. p. and mixed m. p. 119°.

(*c*) The bromohydrin (130 mg.) was refluxed with zinc dust (500 mg.) in acetic acid (40 c.c.) for 6 hr.; the warm solution was filtered, acetic acid removed at 10 mm., and the product isolated in the usual way as an oil (100 mg.), which crystallised from acetone to give androst-16-ene, m. p. and mixed m. p. 76—77°.

16β-*Bromoandrostan*-17-*one* (VII).—The 16β-bromo-17β-hydrin (493 mg.), dissolved in ether (2 c.c.) and acetic acid (10 c.c.), was oxidised with a 2% solution of chromium trioxide in acetic acid (10 c.c., 2 O) at 15° for 18 hr. Excess of chromium trioxide was destroyed by methanol, the solution diluted with water, and the precipitate filtered off, washed with water, and dried. Recrystal isation from acetone gave 16β-*bromoandrostan*-17-*one* (300 mg.), m. p. 128—129°, $[\alpha]_D$ +124° (*c* 1·4) [Found (after drying at 60°/0·01 mm. for 8 hr.): C, 64·6; H, 8·2. $C_{19}H_{29}OBr$ requires C, 64·6; H, 8·2%]. The m. p. was depressed on admixture with the starting material. A second oxidation gave material, m. p. 126°.

16β-*Bromoandrostan*-17β-*ol* (VIII).—To a solution of 16β-bromoandrostan-17-one (24 mg.) in ether (20 c.c.) was added a solution of sodium borohydride (30 mg.) in methanol (10 c.c.). After 18 hr. at 15° the mixture was diluted with water and extracted with ether, to afford, after the usual isolation procedure, 16β-bromoandrostan-17β-ol (15 mg.), m. p. and mixed m. p. 122—123°.

16α : 17α-*Epoxyandrostane* (X).—Androst-16-ene (200 mg.) in chloroform (4 c.c.) was treated with a chloroform solution of perbenzoic acid (1·2 mol.) at 0° for 3 days. The solution was diluted with water, extracted with ether, and worked up in the usual way to give an oil; this crystallised readily from ethanol, to afford 16α : 17α-*epoxyandrostane* (150 mg.), m. p. 109—110°, $[\alpha]_D$ +1° (*c* 1·05) [Found (after drying at 50°/0·01 mm. for 12 hr.): C, 82·8; H, 11·0. $C_{19}H_{30}O$ requires C, 83·2; H, 10·9%].

16β-*Bromoandrostan*-17α-*ol* (XII).—The 16α : 17α-epoxide (120 mg.) in acetic acid (10 c.c.) was treated at 15° with a 5% solution of hydrogen bromide in acetic acid (2 c.c.) with stirring. After a few minutes a copious precipitate was formed. The mixture was diluted with a few drops of water, and the precipitate filtered off, washed with water, and dried. Crystallisation from acetone gave 16β-*bromoandrostan*-17α-*ol* (110 mg.), m. p. 126—128°, $[\alpha]_D$ −4° (*c* 1·1) [Found (after drying at 50°/0·01 mm. for 8 hr.): C, 64·3; H, 8·8. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%]. The m. p. was depressed on admixture with 16β-bromoandrostan-17β-ol (VIII).

The 16β-bromo-17α-hydrin (99 mg.) in acetic acid (2 c.c.) was oxidised with a 2% solution of chromium trioxide in acetic acid (2 c.c.) at 15° overnight. Excess of the reagent was destroyed by methanol, the solution diluted, and the resultant precipitate filtered off, washed with water, dried, and crystallised from acetone to yield 16β-bromoandrostan-17-one, m. p. and mixed m. p. 128—129°, $[\alpha]_D$ +124° (*c* 1·25).

Androstan-17α-ol (IX).—The 16α : 17α-epoxide (30 mg.) in ether (10 c.c.) was refluxed with lithium aluminium hydride (30 mg.) in ether (20 c.c.) for 6 hr. Excess of the reagent was decomposed with ice and 2N-sulphuric acid, and the product isolated in the usual way. The resulting oil was chromatographed on a column of aluminium oxide (1 g.) prepared in pentane. Elution with benzene–pentane (1 : 9) gave some starting material, m. p. 106—109°; elution with benzene yielded an oil, which crystallised from ethanol to give androstan-17α-ol, m. p. and mixed m. p. 142—146°, $[\alpha]_D$ −6° (*c* 0·8).

Interconversion of 16α- *and* 16β-*Bromoandrostan-17-one.*—(*a*) The 16α-bromo-ketone (II) (m. p. 197°, $[\alpha]_D$ +58°; 145 mg.) was dissolved in acetic acid (9 c.c.), 48% hydrobromic acid (1 c.c.) and a little chloroform (to give a homogeneous solution) were added, and the mixture was set aside at 25° for 4 days. Dilution with water and the usual ether-extraction gave a product (144 mg.), $[\alpha]_D$ +95° (*c* 1·1), which by crystallisation from ethanol gave the 16α-bromo-ketone, m. p. 191—193°. Fractional crystallisation of the mother-liquors gave the 16β-bromo-ketone, m. p. 118—122°, $[\alpha]_D$ +116° (*c* 0·5).

(*b*) The 16β-bromo-ketone (VII) (m. p. 124—126°, $[\alpha]_D$ +124°; 45 mg.) was dissolved in acetic acid (9 c.c.), and a 40% solution of hydrogen bromide in acetic acid (1 c.c.) added; at 20° after 24 hr. $[\alpha]_D$ was +115°. The mixture was kept at 55° for 6 hr., whereafter $[\alpha]_D$ was 91°; after being kept at 20° during a week-end, the product was isolated in the usual way and had $[\alpha]_D$ +91°, whilst crystallisation from ethanol gave the 16α-bromo-ketone, m. p. and mixed m. p. 191°.

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