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222. *Studies in the Steroid Group. Part LXXV.* The Partial Synthesis of 4α,9α-Dimethyl-5α-androstan-3-one, the Enantiomer of a Triterpene Degradation Product.*

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The partial synthesis of 4α,9α-dimethyl-5α-androstan-3-one (III) has been achieved by standard methods except that the 9α-methyl group was introduced by methyl iodide–Grignard reagent treatment of a 9α-bromo-11-ketone (X; R = Br) and the 11-keto-group was reduced by a protracted vigorous Wolff–Kishner procedure. Analytical gas–liquid chromatography (g.l.c.) was invaluable in the later stages of the synthesis. The dimethylsteroid ketone is enantiomeric with a lupeol degradation product, described in the following paper, a relationship which correlates a major portion of the structure and stereochemistry of the pentacyclic triterpenes with that of the steroids.

In Part LXXI [1] a scheme for the conversion of a steroid into the enantiomer of a pentacyclic triterpene [*e.g.*, (I) ⟶ *enantio*-lupeol (II)] was briefly mentioned. In the meantime appreciable progress [2] has been made towards the total synthesis of pentacyclic triterpenes and although in these syntheses full stereochemical control has not yet been

* Part LXXIV, *J.*, 1962, 1312.

[1] Jones, Meakins, and Stephenson, *J.*, 1958, 2156.

[2] *Inter al.*, Stork, Davies, and Meisels, *J. Amer. Chem. Soc.*, 1959, **81**, 5517; Corey, Hess, and Proskow, *ibid.*, p. 5258; Ghera and Sondheimer, Communication at the Second Internat. Symposium Chem. of Natural Products, Prague, 1962; Barltrop, Littlehailes, Rushton, and Rogers, *Tetrahedron Letters*, 1962, 429.

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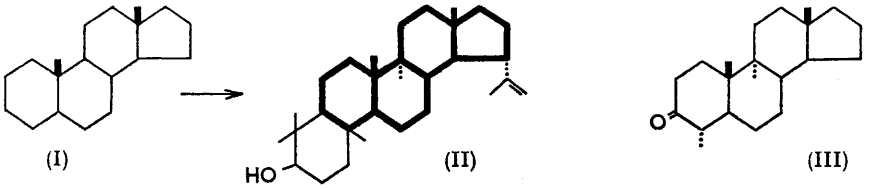
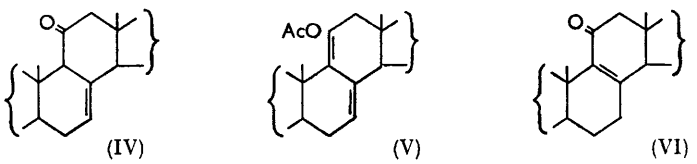
attained, it seemed undesirable to attempt a conversion of the type originally contemplated. A more limited objective was therefore sought. Both the degradation



(I) (II) (III)

of a pentacyclic triterpene to a tetracyclic compound and its partial synthesis from a steroid appeared to be reasonably feasible and to offer the possibility of major structural and stereochemical (6 centres) correlations. As described in the following paper [3] the triterpene lupeol (mirror image of II), has been shorn of its isopropenyl group and of ring A, thereby producing a ketone which should be enantiomeric with 4α,9α-dimethyl-5α-androstan-3-one (III). This paper describes the partial synthesis of the ketone (III) and some related studies.



(IV) (V) (VI)

It was pointed out originally [1] that the introduction of the 9-methyl group was the crucial stage in any projected synthesis. In the ergostane series the methylation of βγ-unsaturated 11-ketones (IV) was successful, but with steroids more suitable for our present purpose such compounds are not readily available. αβ-Unsaturated ketones (*e.g.*, VI) cannot be methylated in good yield because of complications due to base-catalysed isomerisation at C-14,[4] but heteroannular dienyl acetates (V) can be converted smoothly into 9α-methyl derivatives.[5] Methods of obtaining suitable αβ-unsaturated ketones [6] and of the 7,9(11)-dienyl acetates [7] have been devised; in the latter case much experimentation was necessary to determine how to avoid both inversion at C-14 and the production of homoannular 8(14),9(11)-dienyl acetates.

Just as these procedures were being applied to appropriate steroids Dr. Max Tishler kindly informed us that he and his colleagues had succeeded in making 9α-methylhydrocortisone by methylation of a protected 9α-bromo-11-ketone with methyl iodide and methylmagnesium iodide.[8] This method, which involved two stages less than our procedure, was eventually found to be adaptable to our needs. Work which was needed to ascertain the most appropriate substrate for this reaction is described later.

The readily available hydroxy-diketone (VII) of the 5α-pregnane series [the methylation reaction fails in the 5β-series (see below)] was converted [9] into the diacetate (VIII), the side chain was removed by ozonolysis and the resulting 17-keto-group was selectively reduced under mild Wolff–Kishner conditions. Bromination [10] of the keto-acetate (IX) gave the 9α-bromo-compound (X; R = Br), the position of the bromine atom being indicated by a dehydrobromination experiment and the configuration by light absorption and O.R.D. determinations.

[3] Baddeley, Halsall, and Jones, following paper.
[4] Djerassi, Frick, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 3496.
[5] Jones and Wluka, not yet published.
[6] Jones and Wluka, *J.*, 1959, 907.
[7] Cox, Jones, and Wluka, not yet published.
[8] Beyler, Hoffman, Sarett, and Tishler, *J. Org. Chem.*, 1961, **26**, 2426.
[9] Dr. J. Elks, private communication; modification of the conditions of Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.
[10] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.

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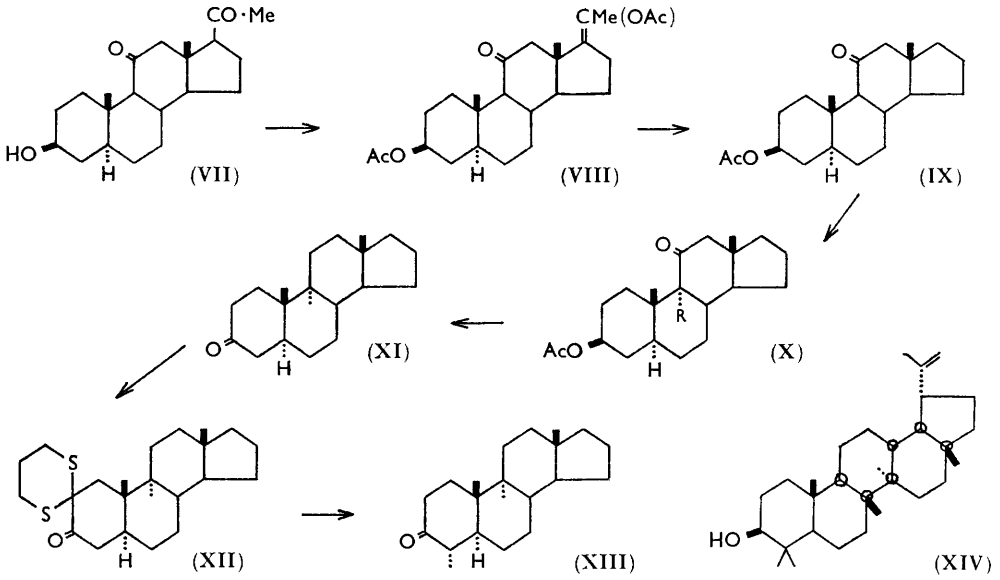
Treatment of the bromo-ketone (X; R = Br) (or the corresponding 3-ethylenedioxy-compound) with methylmagnesium iodide and a small excess of methyl iodide gave, after reacetylation, only the parent debrominated ketone (IX). However, with a large excess (2000 equivalents) of methyl iodide for a longer time another product was detected by



g.l.c. analysis, advantage being taken of Horning's invaluable extension [11] of the technique to steroids. Further experiments enabled the optimum conditions for this methylation reaction to be worked out. Accordingly the bromo-ketone (X; R = Br) was treated first with the Grignard reagent, converting all the bromo-compound into an intermediate, presumably the magnesium enolate (see later), and then with a large excess of the iodide, under reflux, for at least 16 hours. Acetylation and chromatography gave the required keto-acetate (X; R = Me) in 50% yield. Its identity was established by the relative retention time in g.l.c. analysis, the optical rotation together with the rotatory dispersion (as compared with a 9α-methyl-11-ketoergostane derivative), and the n.m.r. spectrum which indicated the presence of three tertiary methyl groups.

Previous attempts [1] to remove the 11-keto-group in 9α-methyl-11-keto-compounds had been unsuccessful and an indirect method involving reduction to the 11-alcohol, pyrolysis of its benzoate, and catalytic hydrogenation of the 11,12-ethylenic bond had been employed. When the most vigorous Wolff–Kishner conditions [12] were used with the ketone (X; R = Me) it was apparently unaffected, but g.l.c. analysis revealed the presence, in the total product after reacetylation, of a very small fraction with a retention time shorter than that of the starting material. The proportion increased with the reaction time and when this was prolonged to 7 days the desired reduction product was isolated in 65% yield. Hydrolysis and oxidation gave 9α-methyl-5α-androstan-3-one (XI) with a rotatory dispersion curve similar to that of 3-keto-steroids of the A/B *trans*-series, the 9α-methyl group making no significant contribution, as predicted by the Octant rule.[13]

Methylation at C-4 necessitated blocking C-2; this was achieved as in the cholestanone series [14] by Woodward's method [15] employing the 2,2′-*spiro*-dithioketal derivative (XII),

[11] Vanden Heuvel, Sweeley, and Horning, *J. Amer. Chem. Soc.*, 1960, **82**, 3482; Vanden Heuvel, Haahti, and Horning, *ibid.*, 1961, **83**, 1513; *J. Org. Chem.*, 1961, **26**, 626.
[12] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[13] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[14] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.
[15] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131.

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which was treated with methyl iodide (5 equivalents) and potassium *t*-butoxide. [Chromatography of a small portion of the methylation product afforded, as major fraction, material (m. p. 194—198°) significantly different from the original dithian (XII) (m. p. 174—176·5°) and with a carbonyl frequency (1700 cm.$^{-1}$) appreciably higher than that (1685 cm.$^{-1}$) of the derivative of 4,4-dimethylcholestanone.[14]] After reduction with Raney nickel, any alcohol formed was oxidised with chromic acid, the mixture was treated with acid to convert any 4β(*ax*)-methyl ketone into the more stable 4α(*eq*)-epimer.[16] G.l.c. analysis was invaluable in following the chromatographic separation indicating the presence of a longer-retention-time by-product, presumably some 4,4-dimethyl ketone and, faster running than the major product on the non-polar stationary phase, some of the unmethylated ketone. Appropriate fractions were combined to give 4α,9α-dimethyl-5α-androstan-3-one (XIII). This differed appreciably in m. p. (162—163·5°) and in retention time from the monomethyl ketone (XI) (m. p. 137—139°) and there were major differences in the infrared spectra, particularly in the C–Me deformation region. The molecular rotation difference (−59°), between compounds (XIII) and (XI), is practically identical with that (−58°) between 4α-methylcholestan-3-one and cholestan-3-one.[14]

The ketone (XIII) was converted into its oxime, and in the Table their properties are compared with those of the corresponding ketone and oxime derived from lupeol (following paper). It is clear that the two sets of compounds are truly enantiomeric thus providing

	4α,9α-Dimethyl-5α-androstan-3-one (XIII)	20,29,30-Trisnordes-A-(10βH)-lupan-5-one (*enantio*-4α,9α-Dimethyl-5α-androstan-3-one)
M. p.	162—163·5° (subl. plates → prisms *ca.* 130°)	162—164° (subl. plates → prisms *ca.* 130°)
Infrared absorption spectrum in solution	Superimposable	
G.l.c. analysis, retention time (min.)	15·2	15·3
$[\alpha]_D$	−19°	+21°
O.R.D. $a([M] \times 10^{-2})$	+55°	−51°
Oximes		
M. p.	215—218°	216—218°
Infrared absorption spectrum in solution	Superimposable	
$[\alpha]_D$	−7°	+6°

confirmation that, for lupeol and all the pentacyclic triterpenes which have been related to it, the structure of rings B—E is identical with that of the steroids and the stereochemistry at the six marked centres is as indicated in formula (XIV).

Before embarking on the partial synthesis described above, conversions of the same type were attempted in the 5β-androstane series. Here it was expected that the methylation reaction in ring A, and the subsequent addition of another ring to complete the pentacyclic system, would be simplified by the *cis*-fusion of rings A and B. Standard procedures were employed to prepare the keto-acetate (XV; R = H) which was converted into the 12α-bromo-compound by direct bromination (cf. ref. 6), to the 3-alcohol by acid hydrolysis, and *via* the 3-ketone to the 3-ethylenedioxy-compound (XVI; R = Br). Methylation [8] yielded a monomethyl compound which, on the basis of rotation, rotatory dispersion, and n.m.r. spectrum measurements is formulated as the 12α-methyl-compound (XVI; R = Me). It was thus established that methylation with the Grignard–methyl iodide procedure would work in the 5β-series, at least in the 12-position. It was then ascertained that a 3-acetoxy-, rather than a 3-ethylenedioxy-compound could be employed, by methylating the bromo-acetate (XV; R = Br) and converting the product into the 12α-methyl-3,11-diketone (XVII), identical with that derived from the ethylenedioxy-derivative (XVI; R = Me).

The 9α-bromo-ketone (XVIII) was prepared from the keto-acetate (XV; R = H) *via*

[16] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

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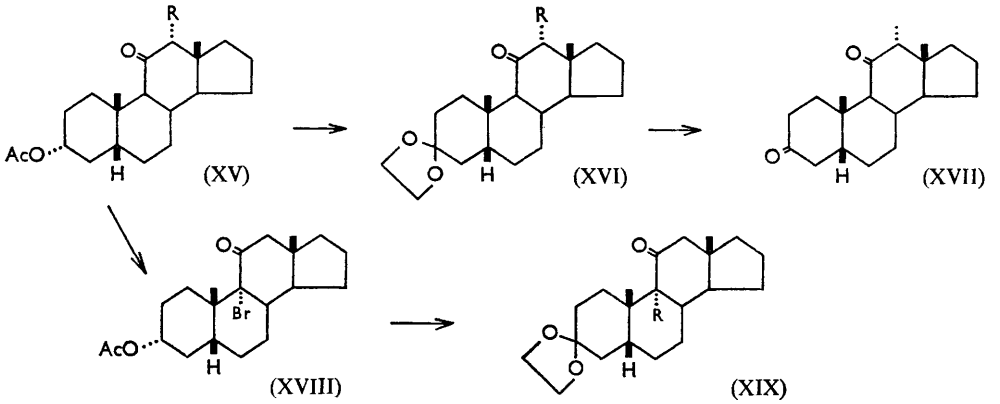
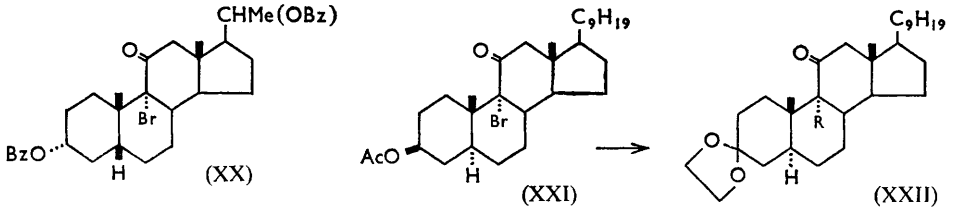
the 9(11)-enol acetate [6] and converted into the bromo-ketal (XIX; R = Br). The conditions successfully employed to methylate the 12-bromo-compounds (XV or XVI; R = Br) of the 5β-series, and the 9-bromo-compound (X; R = Br) of the 5α-series, when



applied to these 9-bromo-ketones (*i.e.*, XVIII and XIX; R = Br), gave only the parent ketones (XV; R = H and XIX; R = H, respectively). The reaction of the bromo-ketone (XVIII) was studied most thoroughly * and if any methylated product was formed the amount could not have been more than 5%. A similar observation was made with the bromo-ketone (XX); [6] the major product of an attempted methylation followed by chromic acid oxidation was 5β-pregnane-3,11,20-trione.

Since the work of Beyler, Hoffman, Sarett, and Tishler [8] had been carried out with a 9α-bromo-11-ketone containing a 5,6-ethylenic bond it was desirable, before embarking on the series of conversions (VII—XIII) described above to check that methylation by their procedure would succeed with a 9α-bromo-11-ketone in the 5α-series. Advantage was taken of the availability of suitable compounds in the ergostane series. The bromo-ketone (XXI) was converted into the bromo-ketal (XXII; R = Br); methylation [8] gave a monomethyl ketone (20% yield) to which the structure (XXII; R = Me) was assigned



on the basis of infrared spectral absorption, optical rotation, rotatory dispersion, and n.m.r. measurements. Subsequently, the acetate (XXI) was methylated under the conditions employed for the 5α-androstanone (X; R = Br); g.l.c. analysis indicated that the 9α-methyl compound was formed in about 45% yield although complete separation from 11-oxoergostanyl acetate could not be achieved.

It was concluded [8] that the first step in the methylation reaction is probably the formation of the enolate anion with loss of the C-9 bromine atom, followed by slow methylation of the resultant C-9 carbanion. Our experience shows that if the reaction mixture is worked up soon after treatment with the Grignard reagent the main product is the bromine-free parent ketone. In the 5β-androstane and 5β-pregnane series the approach

* We thank Dr. J. Smolicz for this careful experiment.

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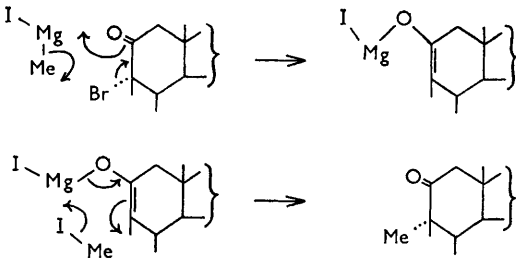

of methyl iodide molecules from the rear-side would be expected to be greatly hindered, as is that of the Grignard reagent itself.[17]

Experimental

Melting points were determined on a Kofler block and are corrected. Rotations were measured for chloroform solutions at room temperature. Infrared spectra, unless otherwise specified, were recorded for carbon disulphide, and ultraviolet absorption spectra for ethanol solutions. Optical rotatory dispersion curves were measured for 0·1% solutions in methanol and n.m.r. spectra (cf. ref. 18) for AnalaR chloroform solutions, with benzene and tetramethylsilane as external and internal standards, respectively. For g.l.c. analysis a column (4 ft. × 4 mm.) of 3% silicone E301 on Embacel, at temperatures of 190—220°, with an inlet heater at *ca.* 300° and inlet pressures of argon of 4—10 lb./sq. in. was used, in conjunction with a Pye argon β-ray ionisation detector. Retention times of the order of 10—30 min. were obtained. Deactivated alumina was prepared by treating Peter Spence Grade "H" alumina with 5% (by volume) of 10% acetic acid. Neutral activated alumina was prepared by neutralising Grade "H" alumina with ethyl acetate, and reactivating it at 250° for 24 hr. Silica gel refers to Crosfield "Sorbsil" [60—120 mesh]. Light petroleum refers to the fraction of b. p. 60—80°.

5α-*Androstane Series*

3β,20-*Diacetoxy*-5α-*pregn*-17(20)-*en*-11-*one* [10] (VIII).—To a vigorously stirred suspension of 3β-hydroxy-5α-pregnane-11,20-dione [19] (50 g.; m. p. 188—191°; $[\alpha]_D$ +109°) in carbon tetrachloride (285 c.c.) at 5°, was added perchloric acid (0·35 c.c.; 71% w/w) in acetic anhydride (83 c.c.) during 40 min., the temperature being kept below 7° throughout. After 16 hr. at 0° excess of anhydride was decomposed by vigorous stirring with water. The carbon tetrachloride solution was washed and evaporated. Crystallisation from light petroleum (b. p. 100—120°) and then from aqueous methanol yielded the enol acetate as prisms (36·5 g.), m. p. 159—161°, $[\alpha]_D$ +8° (*c* 1·79) (lit.,[10] m. p. 152—154°, $[\alpha]_D$ +7°) (Found: C, 72·1; H, 8·7. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%); $\nu_{max.}$ 1753, 1212, 1013 (enol acetate), 1738, 1237, 1024 (acetate), and 1708 cm.$^{-1}$ (ketone); $\lambda_{max.}$ 2980 Å (ε 29).

3β-*Acetoxy*-5α-*androstane*-11,17-*dione*.—Through a mixture of glacial acetic acid (50 c.c.; previously refluxed with potassium permanganate and distilled) and dichloromethane (50 c.c.) at 0°, was bubbled ozone (12·45 mmoles per hr.; 3·5%) until a constant stream of ozone was emerging (9·15 mmoles per hr.). 3β,20-Diacetoxy-5α-pregn-17(20)-en-11-one (4·9 g.) was then added and ozone was passed into the stirred solution for 5 hr. The mixture was stirred with zinc dust (6 g.) overnight at 20°, the filtered solution was washed, and the solvent was removed. Crystallisation from methanol yielded the dione (3·0 g.) as prisms, m. p. 165—166·5° (lit.,[20] m. p. 162—164°), $[\alpha]_D$ +105° (*c* 1·03) (Found: C, 73·05; H, 8·9. Calc. for $C_{21}H_{30}O_4$: C, 72·8; H, 8·75%); $\nu_{max.}$ 1743 (broad, acetate and 17-ketone), 1237, 1023 (acetate), and 1715 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α-*androstan*-11-*one* (IX).—3β-Acetoxy-5α-androstane-11,17-dione (1·5 g.) was heated with diethylene glycol (94 c.c.) and 80% hydrazine hydrate (1·5 c.c.) from 100 to

[17] Shoppee and Lock, *J.*, 1962, 3624; Kirk and Petrow, *J.*, 1961, 2091.
[18] Cox, Bishop, and Richards, *J.*, 1960, 5118.
[19] Cameron, Evans, Hamlet, Jones, and Long, *J.*, 1955, 2807.
[20] Reichstein, *Helv. Chim. Acta*, 1937, **20**, 978.

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180° during 40 min. Water and excess of hydrazine (5 c.c.) were distilled, the mixture was cooled to below 100° and after sodium hydroxide (9 g.) had been added, the temperature was raised to 155° when vigorous effervescence occurred. The mixture was eventually heated at 177—181° for 90 min., cooled, and diluted with water (500 c.c.). The crude product (1·25 g.), isolated with ether, was acetylated with acetic anhydride and pyridine at 20°, and after the usual isolation procedure the acetate was adsorbed on deactivated alumina (150 g.) from light petroleum–benzene (1 : 1). Elution with the same solvent mixture and crystallisation from methanol yielded 3β-*acetoxy*-5α-*androstan*-11-*one* (920 mg.) as prisms, m. p. 94—95°, $[\alpha]_D$ +39° (*c* 1·14) (Found: C, 76·05; H, 10·0. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%); $\nu_{max.}$ 1735, 1238, 1028 (acetate), and 1714 cm.$^{-1}$ (ketone), $\nu_{max.}$ (in CCl_4) 1738, 1368 (acetate), 1713 (ketone), 1457, and 1385 cm.$^{-1}$ (C–Me); $\lambda_{max.}$ 2980 Å (ε 27); R.D. [*M*] (5890 Å) +230°, (5000) +250°, (4000) +450°, (3100) +1650°, (2800) +927°, (2700) +1100°.

3β-*Acetoxy*-9α-*bromo*-5α-*androstan*-11-*one* (X; R = Br).—To a solution of 3β-acetoxy-5α-androstan-11-one (2·0 g.) in acetic acid (12·5 c.c.; containing 3% w/w hydrogen bromide) at 40°, in the dark and under nitrogen, was added bromine (1·01 g.; 1·05 mol.) in acetic acid (2·9 c.c.). After 5 min. 5% aqueous sodium sulphite was added; isolation *via* ether and several recrystallisations from acetone–methanol yielded 3β-*acetoxy*-9α-*bromo*-5α-*androstan*-11-*one* (1·6 g.) as prisms, m. p. 160—162°, $[\alpha]_D$ +160° (*c* 1·0) (Found: C, 60·95; H, 7·5; Br, 19·9. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·45%); $\nu_{max.}$ 1735, 1238, 1028 (acetate), 1714 (ketone), and 742 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3190 Å (ε 94) [cf. 9α-bromo-3α,20β-diacetoxy-5β-pregnan-11-one, $\lambda_{max.}$ 3200 Å (ε 100) [6]; 9α-bromo-3,3-ethylenedioxy-5β-androstan-11-one, $\lambda_{max.}$ 3190 Å (ε 97)*]; R.D. [*M*] (5890 Å) +500°, (5000) +900°, (4000) +3000°, (3450) +10,680°, (2975) −14,550°, (2870) −13,800°.

All residues from the crystallisations of the 9α-bromo-11-ketone were treated with zinc powder in acetic acid. The regenerated 3β-acetoxy-5α-androstanone was then rebrominated.

Treatment of the bromo-ketone with lithium carbonate in boiling dimethylformamide for 2 hr. gave a noncrystalline product with light absorption typical of an αβ-unsaturated 11-ketone ($\lambda_{max.}$ 2530 Å, ε 12,500).

9α-*Bromo*-5α-*androstane*-3,11-*dione*.—3β-Acetoxy-9α-bromo-5α-androstan-11-one (1·5 g.) in methanol (300 c.c.) was heated under reflux with 20% v/v aqueous sulphuric acid (15 c.c.) for 2 hr. The methanol was partially removed, the mixture was diluted with water and the crude hydroxy-ketone (1·45 g.), m. p. 96—98°, isolated with ether. A portion (1·24 g.) of this in acetone (200 c.c.) at 0° was treated with 8N-chromic acid in sulphuric acid [21] (1·38 c.c.) for 5 min. and isolation as usual gave 9α-*bromo*-5α-*androstane*-3,11-*dione* (1·03 g.) as prisms (from light petroleum, b. p. 40—60°) m. p. 115—119°, $[\alpha]_D$ +199° (*c* 0·61) (Found: C, 62·0; H, 7·2; Br, 22·35. $C_{19}H_{27}BrO_2$ requires C, 62·15; H, 7·4; Br, 21·75%); $\nu_{max.}$ 1713 (ketone) and 742 cm.$^{-1}$ (C–Br).

9α-*Bromo*-3,3-*ethylenedioxy*-5α-*androstan*-11-*one*.—A solution of 9α-bromo-5α-androstane-3,11-dione (1·02 g.), toluene-*p*-sulphonic acid (101 mg.; as monohydrate), and ethylene glycol (4 c.c.) in benzene (40 c.c.) was heated under reflux, with azeotropic removal of water, for 5 hr. Sodium hydrogen carbonate, and then water, were added to the hot solution. Isolation of the product *via* ether and crystallisation from light petroleum (b. p. 40—60°), yielded 9α-*bromo*-3,3-*ethylenedioxy*-5α-*androstan*-11-*one* (670 mg.), m. p. 185—186°, $[\alpha]_D$ +167° (*c* 0·495) (Found: C, 61·05; H, 7·45. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6%); $\nu_{max.}$ 1708 (ketone), 1130, 1078 (ketal), and 742 cm.$^{-1}$ (C–Br).

3β-*Hydroxy*-5α-*androstan*-11-*one*.—3β-Acetoxy-5α-androstan-11-one (1·26 g.) was hydrolysed in methanol–sulphuric acid in the usual manner. Crystallisation from methanol afforded 3β-*hydroxy*-5α-*androstan*-11-*one* as prisms, m. p. 161—162°, $[\alpha]_D$ +60° (*c* 0·44) (Found: C, 78·25; H, 10·5. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%); $\nu_{max.}$ (in CCl_4) 3610 (hydroxyl) and 1713 cm.$^{-1}$ (ketone).

5α-*Androstane*-3,11-*dione*.—The crude hydroxy-ketone (890 mg.) in acetone (140 c.c.) was oxidised with 8N-chromic acid [21] in the normal way to give 5α-*androstane*-3,11-*dione* (890 mg.) [prisms from light petroleum (b. p. 40—60°)], m. p. 123—124°, $[\alpha]_D$ +88° (*c* 1·01) (Found: C, 79·35; H, 9·9. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%); $\nu_{max.}$ 1714 cm.$^{-1}$ (broad, ketone).

3,3-*Ethylenedioxy*-5α-*androstan*-11-*one*.—5α-Androstane-3,11-dione (500 mg.) was heated

* See below, p. 1172.

[21] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

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under reflux with toluene-*p*-sulphonic acid (63 mg.; as monohydrate) and benzene (32 c.c.) for 5 hr., and the ketal was isolated in the usual way. 3,3-*Ethylenedioxy*-5α-*androstan*-11-*one* was obtained as prisms (485 mg.) (from light petroleum, b. p. 40—60°), m. p. 98—100°, $[\alpha]_D$ +53° (*c* 1·05) (Found: C, 75·7; H, 9·5. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%); $\nu_{max.}$ 1717 (ketone), 1100, and 1073 cm.$^{-1}$ (ketal).

3β-*Acetoxy*-9α-*methyl*-5α-*androstan*-11-*one* (X; R = Me).—3β-Acetoxy-9α-bromo-5α-androstan-11-one (0·99 g.) in tetrahydrofuran (180 c.c.; freshly distilled from lithium aluminium hydride) was added to methylmagnesium iodide [from magnesium (3·5 g.) in ether (100 c.c.) and methyl iodide (15 c.c.) in ether (120 c.c.)], which had been filtered under nitrogen through glass wool. The mixture was stirred for 15 min. at 20°, then under reflux for 45 min. and, after addition of methyl iodide (300 c.c.), under reflux for 18 hr. Aqueous ammonium chloride was added and the product (921 mg.) was isolated *via* ether and adsorbed on deactivated alumina (40 g.). Ether elution gave an oil (725 mg.) which was treated with sulphuric acid (7·5 c.c.) in refluxing methanol (150 c.c.), and then acetylated with acetic anhydride and pyridine. According to g.l.c. analysis (relative areas) the product (733 mg.) contained 3β-acetoxy-5α-androstan-11-one (50%), monomethylation product (45%) (relative retention time 1·41), and a component B (5%) (relative retention time *ca.* 2·0). The required product was further purified (to *ca.* 70%) by fractional crystallisation of the crude acetates from light petroleum (b. p. 40—60°) and adsorbed on alumina (200 : 1 ratio). Elution with light petroleum–benzene (19 : 1) afforded fractions containing successively component B, then the methylation product, and finally 3β-acetoxy-5α-androstan-11-one, the fractions being monitored by g.l.c. analysis. Recrystallisation from methanol of fractions containing more than 95% of the required product afforded 3β-*acetoxy*-9α-*methyl*-5α-*androstan*-11-*one* (450 mg.) as plates, m. p. 144—145°, $[\alpha]_D$ +87° (*c* 0·495) (Found: C, 76·0; H, 9·65. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%); $\nu_{max.}$ 1732, 1239, 1022 (acetate), 1707 (ketone), 1449, and 1382 cm.$^{-1}$ (C–Me); R.D. [*M*] (5890 Å) +450°, (5000) +850°, (4000) +1700°, (3300) +5730°, (2825) −4420°, (2700) −3300°. The n.m.r. spectrum indicated the presence of 3 tertiary methyl groups.

3β-*Hydroxy*-9α-*methyl*-5α-*androstane*.—Anhydrous hydrazine was distilled into a solution of sodium (1 g.) in diethylene glycol (50 c.c.) under nitrogen until the mixture was refluxing freely at 180° (internal temp.). 3β-Acetoxy-9α-methyl-5α-androstan-11-one (380 mg.) was added quickly to the cooled solution and refluxing was resumed at 180° with occasional addition of hydrazine. Samples (1 c.c.) were withdrawn at intervals, g.l.c. analysis revealing the rate of disappearance of the ketone; after 7 days only 10% remained. Excess of hydrazine was distilled off and the mixture was heated to 227—235° for a further 24 hr. Steroidal product was isolated with ether (g.l.c. analysis showed the presence of *ca.* 70% of the required material) and adsorbed on deactivated alumina (20 g.) from benzene. Elution with benzene gave material (123 mg.) (almost homogeneous by g.l.c. analysis) which after several wasteful crystallisations from methanol yielded 3β-*hydroxy*-9α-*methyl*-5α-*androstane* as prisms (41 mg.), m. p. 146—147° (subliming to needles at *ca.* 130°), $[\alpha]_D$ −9° (*c* 0·53) (Found: C, 82·75; H, 11·85. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%); $\nu_{max.}$ 3500 and 1037 cm.$^{-1}$ (hydroxyl).

The crystallisation residues were combined with the ether eluate (95 mg.) of the above column, and acetylated with acetic anhydride and pyridine. The crude acetate (184 mg.) was adsorbed on deactivated alumina (100 g.). Elution with light petroleum (1200 c.c.) and crystallisation from acetone–methanol yielded 3β-*acetoxy*-9α-*methyl*-5α-*androstane* (56 mg.) as plates, m. p. 95—97°, $[\alpha]_D$ −26° (*c* 0·46) (Found: C, 79·85; H, 11·05. $C_{22}H_{36}O_2$ requires C, 79·45; H, 10·9%), $\nu_{max.}$ 1724, 1240, and 1028 cm.$^{-1}$ (acetate). Total yields of up to 65% of 11-deoxygenated product have subsequently been obtained.

9α-*Methyl*-5α-*androstan*-3-*one* (XI).—3β-Hydroxy-9α-methyl-5α-androstane (200 mg.) in acetone (20 c.c.) at 0° was treated with 8N-chromic acid in sulphuric acid for 5 min. Isolation in the usual manner afford 9α-*methyl*-5α-*androstan*-3-*one* (190 mg.) as plates (from methanol), m. p. 138—140°, $[\alpha]_D$ +9° (*c* 0·51) (Found: C, 83·15; H, 11·05. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%); $\nu_{max.}$ 1710 cm.$^{-1}$ (ketone), $\nu_{max.}$ (in CCl_4) 1721 (ketone), 1455, and 1385 cm.$^{-1}$ (C–Me); R.D. [*M*] (5890 Å) −30°, (5000) +250°, (4000) +350°, (3100) +2100°, (2700) −2940°, (2650) −2830°.

9α-*Methyl*-2,2-*trimethylenedithio*-5α-*androstan*-3-*one* (XII).—9α-Methyl-5α-androstan-3-one (100 mg.) in dry benzene (1·8 c.c.) was treated with sodium hydride (22·4 mg.) and ethyl formate (0·15 c.c.). The mixture was kept under nitrogen for 40 hr. at 20° with occasional swirling. The semisolid mass was partitioned between ether and a phosphate buffer of pH 8. From the

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ether layer was obtained a pale yellow solid (107 mg.), m. p. 150—156°; $\nu_{max.}$ (in CCl_4) 1715 (ketone, trace) and 1647 cm.$^{-1}$ (conjugated ketone); $\nu_{max.}$ (in Nujol) 1705 (ketone, trace), 1644, and 1604 cm.$^{-1}$ (hydroxymethylene ketone); $\lambda_{max.}$ 2830 Å (ε 11,500).

The hydroxymethylene derivative (368 mg.; as above without purification) in absolute ethanol (12 c.c.), was heated under reflux with trimethylene ditoluene-*p*-thiosulphonate (460 mg.) and fused potassium acetate (950 mg.) under carbon dioxide for 9 hr. The solvent was removed, and the residue was partitioned between ether and water. The ether yielded a yellow solid (470 mg.) which, in benzene, was filtered through deactivated alumina (10 g.) and then adsorbed on neutral activated alumina (40 g.). Elution with light petroleum–benzene (9 : 1) afforded *9α-methyl-2,2-trimethylenedithio-5α-androstan-3-one* as prisms (210 mg.) (from ether–benzene), m. p. 174·5—176·5°, $[\alpha]_D$ +81·5° (*c* 0·515) (Found: C, 70·15; H, 8·85; S, 16·4. $C_{23}H_{36}OS_2$ requires C, 70·35; H, 9·25; S, 16·3%); $\nu_{max.}$ 1695 cm.$^{-1}$ (ketone).

4α,9α-Dimethyl-5α-androstan-3-one (XIII).—To the above dithian (94 mg.) in benzene (1·2 c.c.) was added methyl iodide (0·067 c.c.; 5 mol.) in benzene (1 c.c.), followed by potassium t-butoxide in t-butyl alcohol (1·12 c.c.; *ca.* 1·08M), at 20° and the mixture was heated under reflux for 20 min. Hydrochloric acid (2 drops) in water (10 c.c.) was added, the product was extracted with ether, and the solution washed with water, 5% sodium thiosulphate solution, water, potassium hydrogen carbonate solution, and water.

The methylated dithian in ethanol (12 c.c.) was heated under reflux with Raney nickel (1·2 g.; settled suspension) for 7 hr. The mixture was filtered, the solvent was removed, and the residue was partitioned between water and ether. The ethereal solution yielded an oil (93 mg.) which was oxidised in acetone at 0° with 8N-chromic acid in sulphuric acid. The product (79 mg.) was heated under reflux with ethanol (30 c.c.) and sulphuric acid (20%; 3 c.c.) for 2 hr. and then isolated, in the usual manner. The partially crystalline material (74 mg.) was combined with the product from a parallel series of experiments on the dithian (64 mg.) and adsorbed on neutral activated alumina (20 g.) from light petroleum. Elution with light petroleum (375 c.c.) and then with light petroleum–benzene (19 : 1; 300 c.c.) afforded oily fractions (15·5 mg.). Then 36 (25 c.c.) fractions were collected (83 mg.), their compositions were monitored by g.l.c. analysis and, apart from a few of the early ones, they contained more than 95% of the required product. Further elution gave 9α-methyl-5α-androstan-3-one (17 mg.). Crystallisation of the main bulk from acetone yielded *4α,9α-dimethyl-5α-androstan-3-one* (27 mg.) as plates, m. p. 162—163·5° (subliming to prisms from *ca.* 130°), $[\alpha]_D$ −19° (*c* 1·17) (Found: C, 83·4; H, 11·45. $C_{21}H_{34}O$ requires C, 83·4; H, 11·35%); $\nu_{max.}$ (in CCl_4) 1721 (ketone), 1457, and 1382 (C–Me), and 1352, 1316, 1168, 1142, 1118, 958, and 927 cm.$^{-1}$, corresponding exactly in relative intensity and position, *i.e.*, to within 2 cm.$^{-1}$, to the infrared absorption bands of *enantio*-4α,9α-dimethyl-5α-androstan-3-one (see following paper) run consecutively on the same paper; R.D. [*M*] (6000 Å) −30°, (5000) −30°, (4000) +30°, (3500) +150°, (3200) +1010°, (3100) +1910°, (3075) +1940°, (3050) +1910°, (3000) +1550°, (2900) −720°, (2700) −3120°, (2650) −3410°, (2625) −3540°, (2600) −2830°; g.l.c. analysis, retention times, 15·1, 15·2, and 15·35 min., cf., *enantio*-4α,9α-dimethyl-5α-androstan-3-one, retention times 15·35, 15·1, and 15·3 min. and a mixture of the two retention times 15·0, 15·3, and 15·1 min. All 9 determinations were made at the same column temperature (200°) and argon inlet pressure (7·8 lb. /sq. in), and the shapes of all the peaks were identical.

The oxime was prepared from the ketone (22 mg.) and hydroxylamine hydrochloride (25 mg.) in pyridine (2 c.c.) at 100° for 2 hr. The reaction mixture was diluted with water, and the precipitate crystallised from light petroleum to give the *oxime* (15 mg.), m. p. 215—218°, $[\alpha]_D$ −7° (*c* 0·175) [22] (Found: C, 79·75; H, 11·15. $C_{21}H_{35}NO$ requires C, 79·45; H, 11·1%); $\nu_{max.}$ 3546, 3226, 1653, and 939 cm.$^{-1}$; R.D. [*M*] (6000 Å) −240°, (5000) −230°, (4000) −580°, (3500) −780°, (3300) −930°, (3200) −1030°, (3100) −1180°.

5β-*Androstane Series*

3α-Hydroxy-5β-androstane-11,17-dione.—This was prepared following Wilson [23] from 3α-acetoxy-5β-pregnane-11,20-dione (5·8 g.) by treatment with amyl nitrite and sodium ethoxide for 7 days. The product (2·3 g.) had m. p. 181—183·5° (lit.,[23] m. p. 185—187°), $[\alpha]_D$ +115° (*c* 1·1); $\nu_{max.}$ (in Nujol) 3460, 1048 (hydroxyl), 1733, (17-ketone), and 1709 cm.$^{-1}$ (11-ketone).

[22] This and several other $[\alpha]_D$ determinations were made with the sensitive Bendix-Ericsson polarimeter (type 143A).

[23] Wilson, U.S.P. 2,515,482/1950 (*Chem. Abs.*, 1950, **44**, 9990; 1952, **47**, 12,429).

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3α-*Acetoxy*-5β-*androstan*-11-*one* (XV; R = H).—Hydrazine hydrate (8 c.c.; 85%) was added to a solution of 3α-hydroxy-5β-androstane-11,17-dione (8·0 g.) in diethylene glycol (400 c.c.). The reaction mixture was heated under reflux for 30 min. at 180°, then cooled slightly before the removal of 8 c.c. of liquid by vacuum distillation. The solution was cooled further and solid sodium hydroxide (48 g.) added quickly. The reaction mixture was heated gradually to 180° and then under reflux for 1·5 hr. Pouring into water and extraction with ether gave an oil which was treated with acetic anhydride–pyridine (1 : 1) for 15 hr. at 20°. Isolation with ether and crystallisation from acetone provided 3α-acetoxy-5β-androstan-11-one (4·6 g.) as needles, m. p. 125—127°, $[\alpha]_D$ +74° (*c* 1·1) (lit.,[24] m. p. 130°, $[\alpha]_D$ +74°); $\nu_{max.}$ 1730, 1238, 1028 (acetate), and 1704 cm.$^{-1}$ (ketone); R.D. [*M*] (3180 Å) +1800, (2800) +400°.

5β-*Androstane*-3,11-*dione*.—8N-Chromic acid (0·5 c.c.) was added to a cooled (10°) solution of 3α-hydroxy-5β-androstan-11-one (500 mg.) in acetone (70 c.c.). After being shaken for 20 min. the product was isolated with ether and adsorbed from light petroleum on deactivated alumina (50 g.). Benzene eluted crystalline material which on recrystallisation from light petroleum gave 5β-*androstane*-3,11-*dione* as prisms (257 mg.), m. p. 105—107°, $[\alpha]_D$ +73° (*c* 1·1) (Found: C, 79·0; H, 9·8. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%); $\nu_{max.}$ 1720sh (3-ketone) and 1707 cm.$^{-1}$ (11-ketone); R.D. [*M*] (3250 Å) +2000°, (2800) +400°.

3,3-*Ethylenedioxy*-5β-*androstan*-11-*one* (XVI; R = H).—Ethylene glycol (2 c.c.) was added to a solution of 5β-androstane-3,11-dione (300 mg.) and toluene-*p*-sulphonic acid (50 mg.) as monohydrate in benzene (50 c.c.). The reaction mixture was heated under reflux for 5 hr. with the azeotropic removal of water. The usual isolation gave an oil which was adsorbed on deactivated alumina (30 g.). Elution with light petroleum–benzene (3 : 7) gave 3,3-*ethylenedioxy*-5β-*androstan*-11-*one*, prisms (from aqueous methanol), m. p. 129—130°, $[\alpha]_D$ +42° (*c* 1·0) (Found: .C, 76·2; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%); $\nu_{max.}$ 1706 (ketone) and 1096 cm.$^{-1}$ (ketal); R.D. [*M*] (3250 Å) +1600°, (2820) +530°.

3α-*Acetoxy*-12α-*bromo*-5β-*androstan*-11-*one* (XV; R = Br).—A solution of 3α-acetoxy-5β-androstan-11-one (4·0 g.) in acetic acid (200 c.c.) at 50° was treated, in nitrogen in the dark, with bromine (3·24 g.) in acetic acid (5·2 c.c.) and with hydrobromic acid in acetic acid (50% w/v; 10 drops). The reaction mixture was kept at 50° for 2 hr. and the product, isolated *via* ether, was adsorbed on silica gel. Elution with light petroleum–benzene (1 : 1) gave 3α-*acetoxy*-12α-*bromo*-5β-*androstan*-11-*one* crystallising from methanol as needles (4·1 g.), m. p. 120—121°, $[\alpha]_D$ −30° (*c* 0·9) (Found: C, 61·3; H, 7·5; Br, 19·8. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·45%); $\nu_{max.}$ 1730, 1236, 1028 (acetate), 1704 (ketone), and 723 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3170 Å (ε 143); R.D. [*M*] (3430 Å) −7600°, (2950) +12,900°.

12α-*Bromo*-3α-*hydroxy*-5β-*androstan*-11-*one*.—An aqueous solution (2 c.c.) of potassium carbonate (685 mg.) was added to 3α-acetoxy-12α-bromo-5β-androstan-11-one (685 mg.) in methanol (75 c.c.). After 24 hr. at 20° the reaction mixture was diluted with water and crystallisation of the precipitate from aqueous methanol gave 12α-*bromo*-3α-*hydroxy*-5β-*androstan*-11-*one* as needles (506 mg.), m. p. 161—163°, $[\alpha]_D$ −58° (*c* 1·0) (Found: C, 61·8; H, 7·9; Br, 21·2. $C_{19}H_{29}BrO_2$ requires C, 61·8; H, 7·9; Br, 21·65%); $\nu_{max.}$ 3610, 1035 (hydroxyl), 1715 (ketone), and 723 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3190 Å (ε 142); R.D. [*M*] (3470 Å) −7500°, (2950) +12,200°.

12α-*Bromo*-5β-*androstane*-3,11-*dione*.—A solution of 12α-bromo-3α-hydroxy-5β-androstan-11-one (900 mg.) in acetone (120 c.c.) was cooled to 10°, and 8N-chromic acid (0·83 c.c.) was added. The reaction mixture was shaken for 2 min., water was added, and the product was crystallised from aqueous acetone to give 12α-*bromo*-5β-*androstane*-3,11-*dione* as plates (700 mg.), m. p. 169—172°, $[\alpha]_D$ −71° (*c* 1·0) (Found: C, 62·4; H, 7·5; Br, 21·8. $C_{19}H_{27}BrO_2$ requires C, 62·15; H, 7·4; Br, 21·75%); $\nu_{max.}$ 1724sh (3-ketone), 1718 (11-ketone), and 723 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3190 Å (ε 139); R.D. [*M*] (3400 Å) −9100°, (2900) +10,900°.

12α-*Bromo*-3,3-*ethylenedioxy*-5β-*androstan*-11-*one* (XVI; R = Br).—Ethylene glycol (2 c.c.) was added to a solution of 12α-bromo-5β-androstane-3,11-dione (800 mg.) and toluene-*p*-sulphonic acid (50 mg., as monohydrate) in benzene (65 c.c.). The solution was heated under reflux for 4 hr. with azeotropic removal of water and the product, isolated as usual, on crystallisation from methanol gave 12α-*bromo*-3,3-*ethylenedioxy*-5β-*androstan*-11-*one* as rods (780 mg.), m. p. 113—115°, $[\alpha]_D$ −53° (*c* 1·1) (Found: C, 61·2; H, 8·0; Br, 19·4. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·45%); $\nu_{max.}$ 1712 (ketone), 1098 (ketal), and 723 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3200 Å (ε 144); R.D. [*M*] (3550 Å) −10,000°, (2900) +14,200°.

[24] Velluz, Amiard, Martel, and Warnant, *Bull. Soc. chim. France*, 1957, 1484.

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3,3-*Ethylenedioxy*-12α-*methyl*-5β-*androstan*-11-*one* (XVI; R = Me).—Methyl iodide (35 c.c.) was dropped in to a stirred suspension of magnesium turnings (800 mg.) in dry ether (120 c.c.) under nitrogen. A solution of 12α-bromo-3,3-ethylenedioxy-5β-androstan-11-one (750 mg.) in freshly distilled tetrahydrofuran (45 c.c.) was added and the mixture was stirred at 20° for 15 min., then heated under reflux for 1 hr. Isolation as usual yielded an oil which was adsorbed on alumina (100 g., Grade "0"). Elution with light petroleum–benzene (3 : 7) provided crystalline material which on recrystallisation from dilute methanol gave **3,3-*ethylenedioxy*-12α-*methyl*-5β-*androstan*-11-*one*** as prisms (244 mg.) m. p. 114°, $[\alpha]_D$ +40° (*c* 0·9) (Found: C, 76·5; H, 9·85. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%); $\nu_{max.}$ 1706 (ketone) and 1096 cm.$^{-1}$ (ketal). The n.m.r. spectrum showed the expected doublet for an additional secondary C–Me group.

12α-*Methyl*-5β-*androstane*-3,11-*dione* (XVII).—(*a*) Treatment of a solution of 3,3-ethylenedioxy-12α-methyl-5β-androstan-11-one (28 mg.) in methanol (20 c.c.) with 2N-sulphuric acid (1 c.c.) for 40 min. under reflux provided crystals, which on recrystallisation from aqueous methanol gave **12α-*methyl*-5β-*androstane*-3,11-*dione*** as needles (20 mg.), m. p. 155—157°, $[\alpha]_D$ +60° (*c* 1·14) (Found: C, 79·2; H, 9·9. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%), $\nu_{max.}$ (in CCl_4) 1728 (3-ketone) and 1715 cm.$^{-1}$ (11-ketone), R.D. [*M*] (3220 Å) −500°, (2750) +3800°.

(*b*) The acetoxy-bromo-ketone (XVIII; 330 mg.) in ether (30 c.c.) was added to a mixture of methyl iodide (5·5 c.c.) and methylmagnesium iodide [from magnesium (1·67 g.) in ether (30 c.c.) and methyl iodide (6 c.c.) in ether (15 c.c.)]. The reaction mixture was stirred for 15 min. at 20° and then for 1 hr. under reflux. Decomposition with ammonium chloride solution and ether extraction yielded a gum (214 mg.) which in acetone (30 c.c.) was treated with 8N-chromic acid in sulphuric acid (0·2 c.c.) at 20° for 15 min. Isolation *via* ether gave crystals (206 mg.) which were adsorbed on deactivated alumina (10 g.) from light petroleum–benzene (19 : 1). Elution with the same solvent (425 c.c.), evaporation, crystallisation from methanol, and sublimation at 150°/0·1 mm. gave 12α-methyl-5β-androstane-3,11-dione (40 mg.) m. p. 155—157°. The infrared spectrum was identical with that of the material described above. G.l.c. retention times were also identical. Further elution gave a mixture (52 mg.) and later 5β-androstane-3,11-dione (27 mg.), m. p. and mixed m. p. 105—107°.

3α,11-*Diacetoxy*-5β-*androst*-9(11)-*ene*.—A solution of 3α-acetoxy-5β-androstan-11-one (3·0 g.) and toluene-*p*-sulphonic acid (4·5 g., as monohydrate) in acetic anhydride (450 c.c.) was refluxed for 10 hr. with slow distillation of the solvent. Acetic anhydride was removed at 20 mm. and isolation *via* ether gave an oil which was adsorbed from light petroleum on deactivated alumina (300 g.). Light petroleum–benzene (2 : 1) eluted the enol acetate mixed with varying amounts of the starting material. The fractions whose infrared spectra indicated the presence of relatively little parent ketone were seeded with pure enol acetate crystals (obtained by tedious repeated recrystallisation of impure enol acetate) and triturated with methanol. Eventually the *enol diacetate* (2·38 g.) was obtained from aqueous methanol as prisms, m. p. 99—100°, $[\alpha]_D$ +87° (*c* 2·07) (Found: C, 73·5; H, 9·15. $C_{23}H_{34}O_4$ requires C, 73·75; H, 9·15%); $\nu_{max.}$ 1748sh, 1218 (enol acetate), 1735, 1240 (acetate), and 1638 cm.$^{-1}$ [9(11)-ene].

3α-*Acetoxy*-9α-*bromo*-5β-*androstan*-11-*one* (XVIII).—Bromine (2·3 g.) in acetic acid (3·6 c.c.) was added to a solution of 3α,11-diacetoxy-5β-androst-9(11)-ene (3·5 g.) in acetic acid (100 c.c.) and pyridine (18 c.c.). The mixture was kept for 28 hr. at 30° in the dark in nitrogen. The product was isolated in the usual manner and chromatographed on silica gel (100 g.). Elution with benzene and crystallisation from aqueous methanol gave **3α-*acetoxy*-9α-*bromo*-5β-*androstan*-11-*one*** (2·0 g.) as prisms, m. p. 93—94°, $[\alpha]_D$ +186° (*c* 2·64) (Found: C, 61·2; H, 7·35; Br, 19·3. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·45%); $\nu_{max.}$ 1730, 1241 (acetate), 1715 (ketone), and 760, 741 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3200 Å (ε 91); R.D. [*M*] (3420 Å) +930°, (2950) −11,000°.

9α-*Bromo*-5β-*androstane*-3,11-*dione*.—A solution of 3α-acetoxy-9α-bromo-5β-androstan-11-one (800 mg.) in methanol (80 c.c.) was heated with 3N-sulphuric acid (8 c.c.) under reflux for 2 hr. The product, isolated *via* ether, was dissolved in acetone (80 c.c.), cooled to 10°, and treated with 8N-chromic acid (0·8 c.c.). After 2 min., isolation *via* ether and crystallisation from aqueous acetone provided **9α-*bromo*-5β-*androstane*-3,11-*dione*** as plates (620 mg.), m. p. 131—133°, $[\alpha]_D$ +90° (*c* 2·3) (Found: C, 62·0; H, 7·1; Br, 21·9. $C_{19}H_{27}BrO_2$ requires C, 62·15; H, 7·4; Br, 21·75%); $\nu_{max.}$ 1721sh (3-ketone), 1715 (11-ketone), 778, and 746 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3160 Å (ε 110); R.D. [*M*] (3400 Å) +9700°, (2970) −12,500°.

9α-*Bromo*-3,3-*ethylenedioxy*-5β-*androstan*-11-*one* (XIX; R = Br).—A solution of 9α-bromo-5β-androstane-3,11-dione (500 mg.) and toluene-*p*-sulphonic acid (50 mg., as monohydrate) in

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benzene (70 c.c.) and ethylene glycol (2 c.c.) was heated under reflux for 5 hr. with the azeotropic removal of water. Isolation *via* ether and crystallisation from methanol gave 9α-*bromo*-3,3-*ethylenedioxy*-5β-*androstan*-11-*one* (420 mg.), m. p. 97—98°, $[\alpha]_D$ +97° (*c* 0·9) (Found: C, 61·2; H, 7·9; Br, 19·3. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·45%); $\nu_{max.}$ 1715 (ketone), 1100 (ketal), and 744 cm.$^{-1}$ (C–Br); $\lambda_{max.}$ 3190 Å (ε 97).

Action of Methylmagnesium Iodide and Methyl Iodide on 9α-*Bromo*-3,3-*ethylenedioxy*-5β-*androstan*-11-*one* (XIX; R = Br).—The bromo-ketone (331 mg.) in ether (15 c.c.) was added to a mixture of methyl iodide (5 c.c.) and methylmagnesium iodide [from magnesium (421 mg.) and methyl iodide in ether (20 c.c.)]. The mixture was stirred at 20° for 1 hr. and then heated under reflux for 1 hr. Isolation as usual *via* ether gave a bromine-free oil (260 mg.), which on seeding and crystallisation from methanol yielded 3,3-ethylenedioxy-5β-androstan-11-one (146 mg.), m. p. and mixed m. p. 128—130° with an infrared spectrum indistinguishable from that of authentic material. Examination of the mother-liquors by careful chromatography failed to produce any crystalline material. Essentially similar results were obtained by using ether–tetrahydrofuran or by a similar reaction on 3α-acetoxy-9α-bromo-5β-androstan-11-one; the more vigorous conditions which succeeded with the corresponding 5α-androstan-11-one were also without effect.

Ergostane Series

3β-*Hydroxyergostan*-11-*one*.—3β-Acetoxyergostan-11-one (1·0 g.) was heated under reflux with methanolic potassium hydroxide (50 c.c.; 5%) for 2 hr. Dilution with water, isolation *via* ether, and several crystallisations from methanol gave 3β-*hydroxyergostan*-11-*one* (600 mg.) as needles, m. p. 168—169°, $[\alpha]_D$ +41° (*c* 0·8) (Found: C, 80·5; H, 11·4. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%), $\nu_{max.}$ 3550, 1035 (hydroxyl), and 1707 cm.$^{-1}$ (ketone).

9α-*Bromo*-3β-*hydroxyergostan*-11-*one*.—(*a*) 3β-Acetoxy-9α-bromoergostan-11-one [10] (470 mg.) was dissolved in methanol (100 c.c.) and treated with an aqueous solution of potassium carbonate (5 c.c.; 8%); dioxan (10 c.c.) was added and the solution was kept at 20° for 48 hr. The product (420 mg.) was isolated in the usual manner *via* ether. Several crystallisations from methanol gave 9α-*bromo*-3β-*hydroxyergostan*-11-*one* as needles (changing to blades at 153—155°), m. p. 182—183°, $[\alpha]_D$ +146° (*c* 1·53) (Found: C, 67·5; H, 9·5; Br, 16·25. $C_{28}H_{47}BrO_2$ requires C, 67·85; H, 9·55; Br, 16·15%); $\nu_{max.}$ 3510, 1032 (hydroxyl), 1708 (ketone), and 743 cm.$^{-1}$ (C–Br).

(*b*) A solution of 3β-hydroxyergostan-11-one (1·05 g.) in chloroform (25 c.c.) was treated successively, under nitrogen and in darkness, with hydrobromic acid (50% in acetic acid; 2 drops) and bromine (0·13 c.c.) in chloroform (3 c.c.), and the solution was then heated at 40° until the bromine colour disappeared (10 min.). Isolation in the usual way and several crystallisations from methanol gave the bromo-hydroxy-ketone (680 mg.), double m. p. 155—156° and 182—183°, $[\alpha]_D$ +142° (*c* 0·9), identical with the product obtained under (*a*).

9α-*Bromoergostane*-3,11-*dione*.—A solution of 9α-bromo-3β-hydroxyergostan-11-one (528 mg.) in pyridine (10 c.c.) was treated [25] with a slurry of chromium trioxide (1 g.) in pyridine (10 c.c.). The product, isolated *via* ether, after several crystallisations from methanol gave 9α-*bromoergostane*-3,11-*dione* (350 mg.) as needles, m. p. 132—134°, $[\alpha]_D$ +105° (*c* 1·74) (Found: C, 68·2; H, 9·3; Br, 15·9. $C_{28}H_{45}BrO_2$ requires C, 68·15; H, 9·2; Br, 16·2%); $\nu_{max.}$ 1707 (3- and 11-keto-peaks not resolved) and 745 cm.$^{-1}$ (C–Br). The dione was also obtained in 70—80% yield from the alcohol with 8N-chromic acid in acetone.

9α-*Bromo*-3,3-*ethylenedioxyergostan*-11-*one* (XXII; R = Br).—A solution of 9α-bromoergostane-3,11-dione (435 mg.) and toluene-*p*-sulphonic acid (60 mg., as monohydrate) in benzene (60 c.c.) and ethylene glycol (2 c.c.) was heated under reflux for 6 hr. with azeotropic removal of water. Isolation as usual and crystallisation from methanol gave 9α-*bromo*-3,3-*ethylenedioxyergostan*-11-*one* (300 mg.), m. p. 186—188°, $[\alpha]_D$ +129° (*c* 2·5) (Found: C, 66·7; H, 9·1; Br, 15·0. $C_{30}H_{49}BrO_3$ requires C, 67·0; H, 9·2; Br, 14·85%); $\nu_{max.}$ 1708 (ketone), 1095 (ketal), and 742 cm.$^{-1}$ (C–Br); R.D. [*M*] (3450 Å) +11,200°, (2900) −13,300°.

3,3-*Ethylenedioxyergostan*-11-*one* (XXII; R = H).—Ethylene glycol (20 c.c.) was added to a solution of ergostane-3,11-dione (5 g.) and toluene-*p*-sulphonic acid (200 mg., as monohydrate) in benzene (200 c.c.). The reaction mixture was refluxed for 6 hr. with the azeotropic removal of water. Isolation as usual and crystallisation from methanol gave 3,3-*ethylenedioxyergostan*-11-*one* (3·2 g.) as blades, m. p. 152—153°, $[\alpha]_D$ +23° (*c* 1·5) (Found: C, 78·4; H, 10·7.

[25] Poos Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 427.

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$C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%), $\nu_{max.}$ 1708 (ketone) and 1095 cm.$^{-1}$ (ketal); R.D. [*M*] (3180 Å) +1630°, (2800) −360°.

3,3-*Ethylenedioxy*-9α-*methylergostan*-11-*one* (XXII; R = Me).—Magnesium turnings (224 mg.) were stirred in dry ether (25 c.c.) and treated with methyl iodide until all the metal had reacted. An excess of methyl iodide (5 c.c.) and a solution of 9α-bromo-3,3-ethylenedioxyergostan-11-one (176 mg.) in tetrahydrofuran (20 c.c.; freshly distilled from lithium aluminium hydride) were then added. The reaction mixture was stirred at 20° for 30 min., then heated under reflux for 1 hr. Isolation in the normal manner gave a gum (159 mg.) which was adsorbed from light petroleum on alumina (10 g.). Elution with light petroleum–benzene (1 : 1) gave several crystalline fractions which were combined (78 mg.) and crystallised from methanol to yield **3,3-*ethylenedioxy*-9α-*methylergostan*-11-*one*** (38 mg.) as needles, m. p. 188—190°, $[\alpha]_D$ +54° (*c* 1·74) (Found: C, 79·0; H, 11·3. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%); R.D. [*M*] (3290 Å) +3150°, (2750) −1850°. N.m.r. analysis was consistent with the introduction of a new tertiary methyl group at C-9. Small differences in the C–Me region (*i.e.*, *ca.* 1380 cm.$^{-1}$) were observed in the infrared spectrum, in carbon tetrachloride, between this compound and the corresponding 9αH-compound.

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