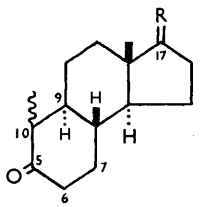
466. *Experiments on the Synthesis of Substances Related to the Sterols. Part LIV.* Degradative and Synthetical Studies on the A-Ring of Androst-4-ene-3 : 17-dione.*

By M. J. Temple Robinson.

The A-ring of androst-4-ene-3 : 17-dione (III) has been degraded through the acid (V) to des-A-androstane-5 : 17-dione (I) (a structurally but not stereochemically identical racemic compound had been prepared previously [1]). By-products in the potassium permanganate oxidation of androst-4-ene-3 : 17-dione to the acid (V) and methods for reconverting this acid into the dione (III) have been studied.

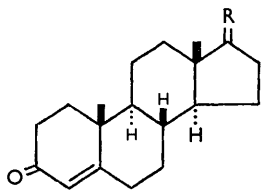
Martin and Robinson [1] obtained a mixture of stereoisomers of the diketone (I), which contains the B-, C-, and D-ring of androst-4-ene-3 : 17-dione (III), and isolated one racemate, m. p. 116—117°. An attempt to add the A-ring by condensing the diketone (I) with diethylmethyl-3-oxobutylammonium iodide gave derivatives of perhydro-1 : 2-benzofluorene [2] by reaction at position 16.† Because the overall yield of Martin and Robinson's diketone was low and the stereoisomerism of the five asymmetric centres was unknown the " natural " diketone (I) has been prepared as a potential relay by the degradation of androst-4-ene-3 : 17-dione.

The A-ring of some derivatives of cholest-4-en-3-one (IV) has been removed in one operation by oxidation, but the yields of the " Inhoffen ketone " (II) [3] were poor.[4] Further, it is now known [4] that $C_{(6)}$, as well as $C_{(16)}$, would be more reactive than $C_{(10)}$ in the diketone (I) and that the A-ring is best built up through acids such as (V) and (VI),[4] the

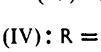


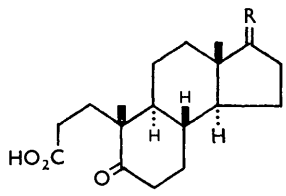
(I) : R = O

(II) : R = 

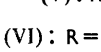


(III) : R = O

(IV) : R = 



(V) : R = O

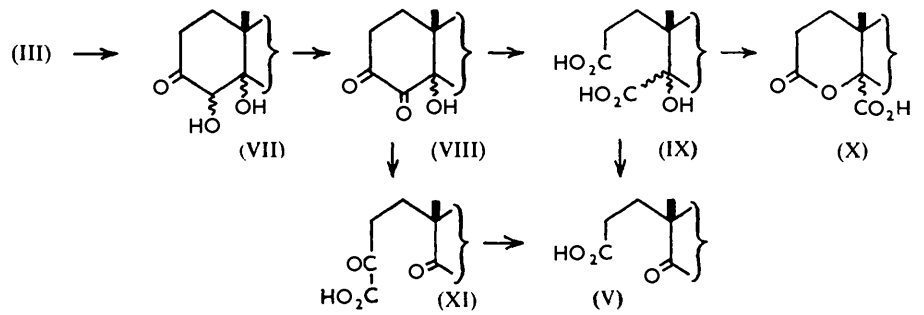
(VI) : R = 

three carbon atoms being added at $C_{(10)}$ after the more reactive positions have been blocked.[4,5] For these reasons the A-ring of androst-4-ene-3 : 17-dione was removed stepwise so that the acid (V) could be used as a relay.

* Part LIII, Cornforth, Kauder, Pike, and Robinson, *J.*, 1955, 3348. † Steroid numbering.

[1] Martin and Robinson, *J.*, 1943, 491.
[2] *Idem*, *J.*, 1949, 1866.
[3] Inhoffen and Huang-Minlon, *Ber.*, 1938, **71**, 1720.
[4] Pinder and Robinson, *J.*, 1952, 1224.
[5] Woodward, Sondheimer, Taub, Heussler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

The oxidation of androst-4-ene-3 : 17-dione (III) by potassium permanganate in acetone was studied in some detail in order to improve on yields previously obtained in similar oxidations (see, *e.g.*, Windaus [6]) and to elucidate the course of the reaction. At first this was greatly hindered by the practical difficulty of working with the poorly crystalline acid (V) and its oily methyl ester, but the ethyl ester was found to be very satisfactory. Derivatives of the acids (V) and (IX) (probably both isomers) were isolated when androst-4-ene-3 : 17-dione (III) was oxidised with the least amount of potassium permanganate required to convert it entirely into acidic compounds, but attempts to oxidise the acids (IX) to the keto-acid (V) by increasing the amount of oxidant merely increased the amount of intractable gums. Therefore, the acid (XI), though not isolated, may be the main intermediate leading to (V). The oxidation was completed by manganic acetate [7] prepared *in situ*, with care to avoid lactonising the acids (IX), and the acid (V) was converted directly into its ethyl ester in an overall yield of 50%. Lead tetra-acetate was unsuitable because the more abundant isomer of the acids (IX) formed an insoluble lead salt.



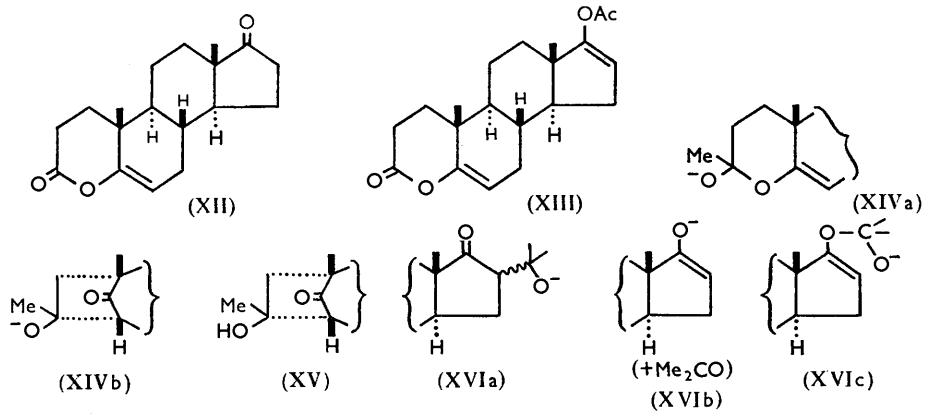
An alternative route to the acid (V) involved hydroxylation of androst-4-ene-3 : 17-dione (III) with osmium tetroxide and hydrogen peroxide [8] followed by oxidation of the diol (VII) (one isomer) with lead tetra-acetate in aqueous acetic acid.[9] Because the second reaction is very specific this method provided the first crystalline speciment of the acid (V) but the poor yield in the first stage made it impractical for larger preparations. Butenandt and Wolz [8] reported much better yields from analogous αβ-unsaturated ketones but the yields of the diol (VII) could not be improved.

The potassium permanganate oxidation provided several points of interest. The manganese oxides formed when the amount of the oxidant [less than the theoretical amount for oxidation to (IX) or (XI), let alone (V), if mainly manganese dioxide was formed] just sufficed to convert androst-4-ene-3 : 17-dione entirely into acidic products corresponded to $MnO_{1\cdot7}$ rather than to MnO_2. The manganese dioxide which is formed as an intermediate presumably contributes to the oxidation of the diol (VII) to (VIII) (although manganese dioxide of a different quality and under different conditions is stated not to oxidise adipoin [10]) and possibly (VIII) to (IX) (cf. ref. 11). One isomer of the hydroxy-dibasic acids (IX) was isolated and its structure demonstrated by relating it and its dimethyl ester to one of the lactone acids (X) (cf. refs. 6, 12). The other isomer (IX) was only detected by isolating the methyl ester of the corresponding lactone acid (X), the structure of this ester being inferred from the close similarity of its infrared spectrum (particularly the carbonyl stretching frequencies) to that of its isomer.

[6] Windaus, *Ber.*, 1906, **39**, 2008.
[7] Criegee, Kraft, and Rank, *Annalen*, 1938, **507**, 159.
[8] Butenandt and Wolz, *Ber.*, 1938, **71**, 1483.
[9] Baer, Grosheintz, and Fischer, *J. Amer. Chem. Soc.*, 1939, **61**, 2607.
[10] Highet and Wildman, *ibid.*, 1955, **77**, 4399.
[11] Sondheimer, Amendolla, and Rosenkranz, *ibid.*, 1953, **75**, 5932.
[12] Tschesche, *Annalen*, 1932, **498**, 185.

Reconversion of the acid (V) into androst-4-ene-3 : 17-dione was more complicated than the analogous change for " Windaus acid " (VI). The methods used for the latter would have caused undesirable side reactions with the 17-carbonyl group which, therefore, had to be protected. Because the enol-lactone Grignard reaction has been so successful in related series [5,13] the enol-lactone enol-acetate (XIII) appeared to be suitable. If the addition of methylmagnesium iodide to an enol-lactone gives a stable intermediate such as (XIVa) the protection is readily understood. But the first products isolated in other cases [14] have structures such as (XV) formed by rearrangement of (XIVa) to (XIVb), the driving force coming from the lower energy of the system R–C–C=O than of the system C=C–O–R. Similar rearrangements account for the good yields of 1 : 3-diols obtained from Grignard reagents and some enol esters,[14] and it has been suggested that steric hindrance in the 10β-methyl series (the natural steroid series) prevents the 5-carbonyl group from reacting.[14] Successful protection at position 17 in the case of androst-4-ene-3 : 17-dione may, therefore, depend on the low reactivity of the hindered carbonyl group in (XVIa) rather than on the formation of the enol derivatives (XVIb) or (XVIc) as was first thought.

The sodium salt of the acid (V), which was more readily obtained pure than the acid itself by hydrolysis of the ethyl ester, was converted into the enol-lactone (XII) by boiling acetic anhydride. When the acid (V) was treated with acetic anhydride and acetyl chloride,[15] acetic anhydride and catalytic amounts of sodium acetate,[5] or *iso*propenyl acetate and an acid catalyst,[16] yields of the enol-lactone were low and variable, and excessive losses resulted when removing a neutral gummy by-product, probably containing the enol-acetate (XIII). The enol-lactone (XII) with *iso*propenyl acetate and toluene-*p*-



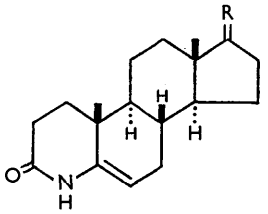
sulphonic acid gave the enol-acetate (XIII),[16] the acid being neutralised at the end of the reaction by filtering the reaction mixture through alumina. The enol-acetate was converted by methylmagnesium iodide followed by dilute alkali [13] into androst-4-ene-3 : 17-dione.

Because of the difficulties encountered during early preparations of the enol-lactone (XII) and the enol-acetate (XIII) other methods of protecting the carbonyl groups in the acid (V) by ketal formation or by reduction were tried but the following routes were unsuccessful:

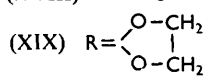
(*a*) The ethyl ester of the acid (V) with ethanolic ammonia at room temperature gave a substance thought to be the imino-lactam (XVII), probably contaminated with some of

[13] Fujimoto, *J. Amer. Chem. Soc.*, 1951, **73**, 1856.
[14] Zwahlen, Horton, and Fujimoto, *ibid.*, 1957, **79**, 3131.
[15] Turner, *ibid.*, 1950, **72**, 579.
[16] Moffett and Weisblat, *ibid.*, 1952, **74**, 2183.

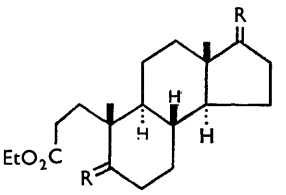
the ketone (XVIII) [the nitrogen analyses were low for (XVII)]. This gave a ketal (XIX) under the usual conditions for a ketone;[17] but when the ketal reacted with methylmagnesium iodide,[5,18] only basic tars were formed. (*b*) When benzylamine was used in the above series of reactions [5] no crystalline products were formed. (*c*) The ethyl ester of the acid (V) with ethyl orthoformate in acidified ethanol gave a substance which was not the expected bisdiethyl ketal (XX). Analytical and spectral data were later interpreted as



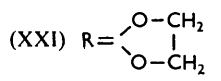
(XVII) R = NH
(XVIII) R = O



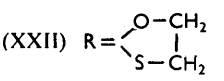
(XIX)



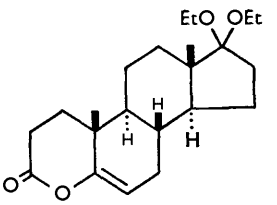
(XX)



(XXI)

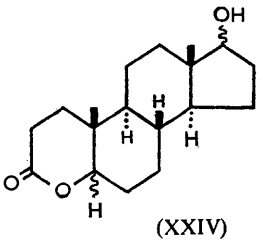


(XXII)

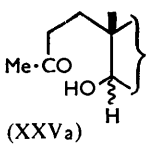


(XXIII)

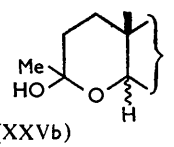
consistent with the structure (XXIII) but this conflicts with the strong positive optical rotation. It has been noted that ethyl γ-oxopimelate does not form a diethyl ketal.[19] (*d*) The ether ester of the acid (V) gave good yields of the ketals (XXI) and (XXII) by standard methods [17,20] but these ketals failed to undergo Claisen condensations in workable yields, even under forcing conditions. When the ester ketal (XX) was condensed with acetophenone and the product was treated with methylmagnesium iodide and then alkali [21] the corresponding methyl ketone was obtained in 1—2% yield. (*e*) Potassium borohydride reduced the acid (V) to a mixture of hydroxy-lactones (XXIV), which condensed with a large excess of phenyl acetate. A single isomer of the dihydroxy-ketone (XXV) was isolated but it could not be oxidised and cyclised to androst-4-ene-3 : 17-dione: this may have been due to the formation of a cyclic semiketal (XXVb) and this substance showed no infrared absorption band in the carbonyl region (1600—1800 cm.$^{-1}$); on the other hand it has been suggested that the formation of a cyclic semiketal can accelerate the oxidation of a hydroxy-ketone.[22]



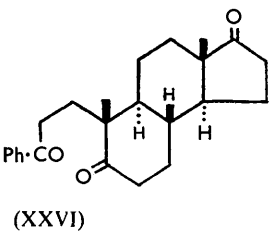
(XXIV)



(XXVa)



(XXVb)



(XXVI)

Experiments on the further degradation of the A-ring, in order to prepare the diketone (I), were based on the reported fission of several 1 : 5-dicarbonyl compounds.[23] The

[17] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[18] McKenzie, Martin, and Rule, *J.*, 1914, **105**, 1583.
[19] Lukes, Poos, and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1401.
[20] Romo, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 4961.
[21] Chaney and Astle, *J. Org. Chem.*, 1951, **16**, 57.
[22] Barton and Mayo, *J.*, 1956, 142.
[23] Achtermann, *Z. physiol. Chem.*, 1934, **225**, 141; Cornforth, Youhotsky, and Popják, *Nature*, 1954, **173**, 536; Riniker, Arigoni, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 546.

phenyl ketone (XXVI) was prepared from the enol acetate (XIII) by the action of phenylmagnesium bromide. Heating this ketone or the ethyl ester of the acid (V) at *ca.* 300° for several hours, or boiling the ketone with potassium hydroxide in ethylene glycol, gave the diketone (I) in 1—2% yield. Fortunately at this stage of the work there appeared a correction to an earlier report [15] claiming that pyrolysis of the barium salt of the " Windaus acid " (VI) led to decarboxylation. It was found that the product was the " Inhoffen ketone " (II) formed by the loss of acrylic acid.[24] When the barium salt of the acid (V) was heated at 320—330°/0·01 mm. the diketone (I) was formed in 10—20% yield. This low yield may be due to the tendency of the *cyclo*pentanone ring in (I) to undergo base-catalysed condensations more readily than the *cyclo*hexanone ring,[2] so that more side reactions are likely in the pyrolysis of the acid (V) than of the " Windaus acid " (VI). No pure specimen of Martin and Robinson's synthetic (racemic) diketone, m. p. 116—117°,[1] was available for comparison with our product (I). When a very small impure specimen of the synthetic diketone was recrystallised from methanol a substance (B) of m. p. 130—131°, was obtained, a difference which may be due to polymorphism. The structural, but not stereochemical, identity of des-A-androst-5 : 17-dione (A) and the substance (B), m. p. 130—131°, may be inferred from the absorption bands observed in CCl_4 solution (see Table) and assigned to specific groups on the basis of R. N. Jones's empirical rules.[25] α-Methylene groups next to 4-, 6-, 7-, 11-, and 12-carbonyl groups and next to 3-carbonyl groups have been associated with bands at 1438—1426 and 1426—1415 cm.$^{-1}$ respectively.[25] A 5-carbonyl group in a des-A-steroid might be expected to be analogous to a 3-carbonyl group in a steroid but the bands at 1432 cm.$^{-1}$ in (A) and

Absorption maxima (cm.$^{-1}$).

(A)	1748	1720	1454 *	1432	1408	1375 *
(B)	1747	1725	1464 1449	1434	1410	1380 1374
Group	17-CO	5-CO	$-CH_2-$ (unperturbed)	6-CH_2–	16-CH_2–	CH_3–

* Broad maximum, probably two overlapping bands.

1434 cm.$^{-1}$ in (B) may reasonably be assigned to the 6-methylene groups since the two ranges of values are so close. At frequencies below 1350 cm.$^{-1}$ the absorption spectra of (A) and (B) are distinct and in view of this difference this work was discontinued.

Experimental

Optical rotations were measured with $CHCl_3$ as solvent unless otherwise stated. Alumina used was Type H from Messrs. Peter Spence and Co., except for one sample which was acid-washed and reactivated at 200—220° for 6 hr., after it had been found to be strongly alkaline.

Specimen Oxidation of Androst-4-ene-3 : 17-dione by Potassium Permanganate in Acetone.— Powdered potassium permanganate (2·0 g.) was added slowly to a stirred solution of androst-4-ene-3 : 17-dione (1·0 g.) in acetone (30 c.c.) at 0°, and the mixture was stirred at room temperature until the supernatant solution was colourless (1—2 hr.). The precipitated manganese oxides were collected, air-dried, and then stirred with ether (100 c.c.) and N-acetic acid (50 c.c.) while 30% hydrogen peroxide was added dropwise until no solid remained. The ethereal layer was dried and evaporated and the residue was heated for 15 min. at 100°, cooled, and treated with ethereal diazomethane (from *N*-nitrosomethylurea, 1·0 g.). The resulting solution was concentrated to 5 c.c., then kept at −10° overnight, and the product (0·22 g.), m. p. 235—239°, was collected and washed with methanol. *5-Methoxycarbonyl-4-oxa-androstane-3 : 17-dione* separated from methanol in plates, m. p. 239—240°, $[\alpha]_D^{18}$ +92°, $\nu_{max.}$ 1742 and 1733 cm.$^{-1}$ (Found: C, 69·2; H, 8·3. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%). If the crude product was not esterified it partly crystallised under ether at −20°, and after three crystallisations from aqueous

[24] Turner, *J. Amer. Chem. Soc.*, 1954, **76**, 1390.
[25] Jones and Cole, *ibid.*, 1952, **74**, 5648.

acetone (1 : 1) the *lactone acid* (X) was obtained in needles (0·04 g.), m. p. 257—262° (Found: C, 68·2; H, 7·7. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·8%). This acid with diazomethane gave the methyl ester, m. p. and mixed m. p. 238—239° (after crystallisation from methanol). The ester (0·22 g.), 0·25N-barium hydroxide (10 c.c.), and methanol (10 c.c.) were boiled for 3 days. The precipitate was collected, washed with methanol, suspended in water (4 c.c.), and treated with 2N-nitric acid (1·5 c.c.). The solid dissolved quickly and the resulting solution deposited the *hydroxy-dibasic acid* (IX) in needles (0·15 g.), m. p. 196—198° [with effervescence and formation of the lactone acid (X)] (Found: C, 64·7; H, 8·1. $C_{19}H_{28}O_6$ requires C, 64·8; H, 8·0%). Diazomethane converted this acid into a *dimethyl ester* which separated from ether–light petroleum (1 : 1) in needles, m. p. 152—153° (Found: C, 66·3; H, 8·5. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5%). A solution of the dimethyl ester in methanol containing 2N-hydrochloric acid (1 drop) was heated at 50° for 2 hr. and cooled to room temperature, and the lactone ester separated in plates, m. p. and mixed m. p. 238—239°.

The residues from the preparation of the lactone ester were adsorbed on alumina (acid-washed; 30 g.). The column was washed with benzene [which eluted a substance crystallising from light petroleum in plates (*ca.* 2 mg.), m. p. 118—119°, not investigated further], and fractionally eluted with benzene–ether (9 : 1, 10 × 200 c.c.). Fractions 6 and 7 (*ca.* 0·1 g. each) partly crystallised during 2—3 weeks, and after trituration with ether (which was not discarded, see below) a *substance* (0·03 g.) was obtained which separated from acetone in needles, m. p. 209—212°, $\nu_{max.}$ 1744 and 1732 cm.$^{-1}$ (Found: C, 69·1; H, 7·9. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%). This substance is probably the $C_{(5)}$-epimer of the lactone ester rather than the methyl ester of the trioxo-acid (XI).

The ether washings from fractions 6 and 7 were evaporated, the residue in aqueous-methanolic (1 : 1) N-sodium hydroxide was boiled for 2 hr., and the resulting solution was neutralised with 2N-acetic acid, treated with semicarbazide hydrochloride, and left overnight at room temperature. The precipitate was washed with hot methanol, leaving the *bissemicarbazone* of the acid (V) as needles (0·1 g.), m. p. 270—280° (decomp.), identical (infrared spectra) with an authentic specimen (see below).

4ξ : 5ξ-*Dihydroxyandrostane*-3 : 17-*dione* (VII).—Androst-4-ene-3 : 17-dione (1·00 g.) and osmium tetroxide (0·05 g.) in ether (100 c.c.) were shaken for 5 min. with 30% hydrogen peroxide (2 c.c.) and then left for 36 hr. in the dark at room temperature. The ether was evaporated under reduced pressure, the residue was treated with water (5 c.c.), and acetone was added until the supernatant solution was clear. The solid was collected and crystallised from aqueous ethanol (1 : 2), to give the *diol* (VII) (0·18 g.), m. p. 210—216° (decomp.), which separated from ethanol in plates, m. p. 216—217·5° (decomp., rapid heating) or laths, m. p. 218—220° (decomp., rapid heating), $[\alpha]_D^{17·5}$ +86° (Found: C, 71·1; H, 9·0. $C_{19}H_{28}O_4$ requires C, 71·2; H, 9·0%). The diol and acetic anhydride in pyridine at room temperature gave a *monoacetate*, needles (from ethanol), m. p. 236—237·5° (Found: C, 70·0; H, 8·5. $C_{21}H_{30}O_3$ requires C, 69·6; H, 8·3%). The yield of the diol was not improved by longer reaction times (after about three weeks colloidal osmium was formed), or by using more osmium tetroxide, or benzene or acetone as solvent. In acetone the reaction was very slow.

10-2′-*Carboxyethyldes*-A-*androstane*-5 : 17-*dione* (V).—(*a*) The diol (VII) (0·10 g.) in acetic acid (1 c.c.) was added to water (5 c.c.) and the resulting suspension was shaken for 5 min. with lead tetra-acetate (0·45 g.), then left at room temperature for 1 hr. 2N-Sulphuric acid was added slowly until no more lead sulphate was precipitated and the filtered solution was evaporated to dryness. The residue was extracted with ether and the extract was concentrated to a syrup. When the syrup was diluted with benzene and then with sufficient light petroleum to give an opalescent solution at 30—40°, the *acid* (V), with half a molecule of benzene of crystallisation, separated in large prisms (0·085 g.), m. p. 70—75° (unchanged after recrystallisation). The acid was purified by dissolving it in ice-cold N-sodium hydrogen carbonate, extracting the turbid solution with ether until clear, and then recovering and crystallising the acid (m. p. 73—75°) (Found: C, 73·4; H, 8·3. $C_{18}H_{26}O_4,\frac{1}{2}C_6H_6$ requires C, 73·0; H, 8·4%). When the solvated acid was dried at 100°/15 mm. for 1 hr. and left under light petroleum it resolidified after 2 months and then separated from dry ether as needles, m. p. 107—109° (Found: C, 70·3; H, 8·2. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·4%). The *bissemicarbazone* (prepared in pyridine) crystallised from aqueous pyridine in needles, m. p. 270—280° (decomp.) (Found: C, 56·9; H, 7·5. $C_{20}H_{32}O_4N_6$ requires C, 57·1; H, 7·7%).

(*b*) Finely powdered potassium permanganate (24·0 g.) was added during 1½ hr. to a stirred

solution of androst-4-ene-3 : 17-dione (20·0 g., m. p. 169—170·5°) in acetone (600 c.c.) at −6° to −8°, and the mixture was then stirred for 3 hr. at 0° and at room temperature for 1 hr. The manganese oxides were collected, air-dried, and dissolved in 50% acetic acid (100 c.c.) at 30°. The resulting dark brown solution was diluted with water (150 c.c.) and stirred at 30—35° until effervescence ceased (2—3 hr.), by which time the manganese oxides had reprecipitated. Hydrogen peroxide (30%; 12—14 c.c.) was added during ½ hr. (an excess was avoided), until the manganese oxides had redissolved, whereupon powdered potassium permanganate (16 g.) was added and the mixture was stirred at 30—35° until effervescence ceased. The manganese oxides were again brought into solution by the addition of hydrogen peroxide (30%; 40—45 c.c.), and the resulting solution was evaporated at 100°/15 mm. The semisolid residue was dissolved in hot 2N-acetic acid (150 c.c.), and the cold solution was extracted with chloroform (10 × 100 c.c.). The chloroform was evaporated, leaving crude acid (V), which was either crystallised (up to 7·0 g., m. p. 60—73°) from benzene–light petroleum or used directly in the next preparation.

10-2′-*Ethoxycarbonylethyldes*-A-*androstane*-3 : 17-*dione* (*ethyl ester of the acid* V).—The acid (V) (the crude product from the previous preparation; *ca.* 22 g.) in ethanolic 1% sulphuric acid (100 c.c.) was boiled for 2 hr., and the solution was concentrated to 40 c.c. and poured with shaking into N-sodium hydrogen carbonate (200 c.c.). An oil separated which soon solidified and was crystallised from methanol, to give the *ethyl ester* of the acid (V) (11—12 g., 47—51%; m. p. 104—107°), which separated from methanol after three more crystallisations in prisms, m. p. 107·5—109°, $[\alpha]_D^{17\cdot5}$ +91° (Found: C, 71·7; H, 8·9. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%). This ester was also obtained from the purified acid (V) by esterification with 1% ethanolic sulphuric acid and by diazoethane in ether.

4-*Oxa-androst*-5-*ene*-3 : 17-*dione* (XII).—The ethyl ester of the acid (V) (3·0 g.) and sodium hydroxide (0·45 g.) in aqueous methanol (1 : 1; 10 c.c.) were boiled for 2 hr. and evaporated to dryness at 100°/15 mm. Acetic anhydride (5 c.c.) was added to the residue and the mixture was boiled for 2 hr. and again evaporated to dryness. Dry toluene (5 c.c.) was added to the residue and evaporated, and this treatment was repeated until the residue no longer smelt of acetic anhydride (three evaporations usually sufficed). The product in dry benzene was filtered through neutral alumina (4 g.), the benzene was evaporated, and the residual oil crystallised when diluted with dry ether while still warm, giving 4-*oxa-androst*-5-*ene*-3 : 17-*dione* (2 crops; 2·4 g.), m. p. 136—143°, which separated from methanol, containing pyridine (1 drop in 5 c.c.), in prisms, m. p. 144—145°, $[\alpha]_D^{18}$ −71° (Found: C, 75·2; H, 8·4. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·4%).

17-*Acetoxy*-4-*oxa-androst*-5 : 16-*dien*-3-*one* (XIII).—The enol lactone (XII) (5·00 g.), toluene-*p*-sulphonic acid (0·30 g.), and *iso*propenyl acetate (25 c.c.) were boiled so that approximately 10 c.c. evaporated during 8 hr. The residue was diluted with benzene, filtered through alumina (15 g.; the acid being thereby neutralised), and evaporated. The residual oil crystallised under ether–methanol, to give the *enol acetate* (XIII) (5·2—5·4 g.), m. p. 146—150°, which separated from benzene–light petroleum in blades, m. p. 152—154° (Found: C, 72·3; H, 7·8. $C_{20}H_{26}O_4$ requires C, 72·7; H, 8·1%). A short time after purification this compound smelt of acetic acid.

Androst-4-*ene*-3 : 17-*dione* (III).—Ethereal methylmagnesium iodide (0·21M; 22 c.c., *ca.* 3·1 mol.) was added in small drops during 30 min. to a stirred solution of the enol acetate (XXVI) (0·495 g.) in benzene (20 c.c.) and ether (30 c.c.) under dry nitrogen at −15°, the solvents having been freshly distilled from sodium hydride directly into the reaction flask. The mixture was stirred while it came slowly to room temperature during 2 hr., then washed with 2N-sulphuric acid and with water, and the solvents were evaporated. The oily residue was left for 12 hr. with sodium hydroxide (1·0 g.) in water (2 c.c.) and methanol (20 c.c.); the resulting solution was diluted with water and extracted with ether. Evaporation of the ether gave crude androst-4-ene-3 : 17-dione (0·24 g.), m. p. 164—167°. After purification by chromatography on alumina androst-4-ene-3 : 17-dione separated from methanol in prisms, m. p. and mixed m. p. 171—172·5°, $[\alpha]_D^{21}$ +182° (Found: C, 79·5; H, 9·1. Calc. for $C_{19}H_{26}O_2$: C, 79·7; H, 9·1%). The infrared spectra and *X*-ray powder photographs of the authentic and the partially synthetic specimen were identical.

Synthetic androst-4-ene-3 : 17-dione (40 mg.), toluene-*p*-sulphonic acid (50 mg.), and *iso*propenyl acetate (5 c.c.) were boiled for 12 hr. The solution was diluted with dry ether, neutralised by filtration through alumina (2 g.), and evaporated. The residual oil was diluted

with boiling methanol (2 c.c.). 3 : 17-*Diacetoxyandrost*-3 : 5 : 16-*triene* crystallised in needles, m. p. 137—138°, undepressed by an authentic specimen similarly prepared (Found: C, 74·2; H, 8·1. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·1%).

17-*Imino*-4-*aza*-*androst*-5-*en*-3-*one* (?) (XVII).—The ethyl ester of the acid (V) (2·0 g.) in ethanol (20 c.c.) was saturated with ammonia at 0° and the mixture was set aside at room temperature for 2 days. The imine (?) (XVII) was washed with ethanol and formed prisms, decomp. *ca.* 330° before and after crystallisation from ethanol (Found: C, 75·4; H, 8·6; N, 8·6. Calc. for $C_{18}H_{25}O_2N$: C, 75·3; H, 8·8; N, 4·8. Calc. for $C_{18}H_{26}ON_2$: C, 75·5; H, 9·1; N, 9·5%).

17-*Ethylenedioxy*-4-*aza*-*androst*-5-*en*-3-*one* (?) (XIX).—The imine (XVII) (0·30 g.), ethylene glycol (freshly distilled; 1·0 c.c.), and toluene-*p*-sulphonic acid (0·2 g.) were stirred for 2 hr. with slowly distilling benzene (volume maintained at *ca.* 20 c.c. while 200 c.c. distilled). The cooled residue was washed with N-sodium hydrogen carbonate and concentrated to 5 c.c. and cooled. The *ethylene ketal* (XIX) was collected and crystallised from benzene in plates (0·25 g.), m. p. 270—272° (Found: C, 72·4, 72·3; H, 9·0, 8·9; N, 4·3, 4·3. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·8; N, 4·2%).

Reaction between the Ethyl Ester of the Acid (V) *and Ethyl Orthoformate.*—The ethyl ester of the acid (V) (0·50 g.), toluene-*p*-sulphonic acid (0·05 g.), ethyl orthoformate (1 c.c.), and ethanol (3 c.c.) were left at 30° for 12 hr. The resulting solution was shaken with benzene and N-sodium hydrogen carbonate, and the benzene layer was washed several times with water, dried, diluted with light petroleum, and filtered through neutral alumina (20 g.). The column was eluted with benzene which was evaporated and the residual oil crystallised under methanol, giving the *ketal* (?) (XXIII) in plates, m. p. 97—99°, $[\alpha]_D^{19}$ +49° (in EtOH) (Found: C, 72·9, 72·8; H, 9·6, 9·4. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·4%).

5 : 17-*Bisethylenedioxy*-10-(2-*ethoxycarbonylethyl*)-*des*-A-*androstane* (XXI).—The ethyl ester of the acid (V) (3·00 g.), ethylene glycol (5 c.c.), and toluene-*p*-sulphonic acid (0·10 g.) were stirred for 6 hr. with slowly distilling benzene (volume maintained at *ca.* 50 c.c. while 1 l. distilled). The cooled solution was washed with N-sodium hydrogen carbonate and evaporated, leaving an oil which crystallised under methanol to give the *ketal* (XXI) (3·00 g.). This separated from methanol in needles, m. p. 104—105·5°, $[\alpha]_D^{18}$ 0° (Found: C, 68·1; H, 9·2. $C_{24}H_{38}O_6$ requires C, 68·2; H, 9·1%).

5 : 17-*Bis*(*oxyethylenethio*)-10-(2-*ethoxycarbonylethyl*)-*des*-A-*androstane* (XXII).—Finely powdered 1 : 1 zinc chloride–sodium sulphate (5·0 g.) was added to the ethyl ester of the acid (V) (1·0 g.) and 2-mercaptoethanol (2 c.c.) in dry dioxan (5 c.c.). The semi-solid mass was left overnight, diluted with chloroform, and washed successively with water, 2N-sodium hydroxide (50 c.c.), and water. The chloroform was evaporated and the remaining syrup, when diluted with methanol, crystallised, giving the *ketal* (XXII) (0·88 g.), m. p. 100—110°, which, after purification by chromatography, separated from ethanol in needles, m. p. 113—115°, $[\alpha]_D^{18}$ 0° (Found: C, 63·2; H, 8·4. $C_{24}H_{38}O_4S_2$ requires C, 63·4; H, 8·4%).

17ξ-*Hydroxy*-4-*oxa*-*androstan*-3-*one* (XXIV, probably a mixture of isomers epimeric at positions 5 and 17).—The ethyl ester of the acid (V) (1·0 g.) and potassium hydroxide (0·4 g.) in methanol (10 c.c.) were boiled for 2 hr., cooled, and treated with potassium borohydride (0·2 g.) in water (1 c.c.). After being kept overnight at room temperature the solution was concentrated until crystallisation began, diluted with water (10 c.c.), and acidified with 12N-hydrochloric acid. The product was isolated with chloroform and crystallised from ether at 0°, to give the *hydroxy-lactone* (XXIV) (0·62 g.) as prisms, m. p. 143—168°, and needles, m. p. 118—159°, which were not separated (Found: C, 73·9; H, 9·8. $C_{18}H_{28}O_3$ requires C, 73·9; H, 9·6%).

5ξ : 17ξ-*Dihydroxy*-4 : 5-seco*androstan*-3-*one* (XXV, probably one isomer in the semiketal form XXVb).—The hydroxy-lactone (XXIV) (0·59 g.) and phenyl acetate (freshly distilled; 0·25 c.c.) were added to potassium (1·1 g.) dissolved in *tert.*-butyl alcohol (25 c.c.). Phenyl acetate (4·5 c.c., in 18 equal portions) was added at half-hourly intervals to the boiling solution, and boiling was then continued overnight. After water (10 c.c.) had been added, the butyl alcohol was slowly evaporated under reduced pressure and the precipitate was collected, boiled for 1 hr. with 2N-potassium hydroxide (10 c.c.), washed with water, and dried *in vacuo*. The solvated *ketone* (XXV) separated from methanol in prisms (0·18 g.), m. p. 171—172°, which were dried at room temperature (Found: C, 70·7; H, 10·3. $C_{19}H_{32}O_3,CH_4O$ requires C, 70·5; H, 10·7%). The methanol of crystallisation was readily removed in part at 100°/15 mm., but some remained even after 2 hr. at 140°/15 mm. and the substance became gummy when heated

longer (Found, after drying at 140°/15 mm.: C, 73·5; H, 10·3. Calc. for $C_{19}H_{32}O_3$: C, 74·2; H, 10·4%). This compound did not show an absorption band in the region 1650—1800 cm.$^{-1}$ and was assumed to exist in a lactol form.

10-(3-*Oxo*-3-*phenylpropyl*)-*des*-A-*androstane*-5 : 17-*dione* (XXVI).—Ethereal phenylmagnesium bromide (0·33M; 60 c.c.) was added in small drops during ½ hr. to a stirred solution of the enol lactone (XIII) (1·98 g.) in benzene (30 c.c.) and ether (50 c.c.) at −15° under dry nitrogen. The mixture was stirred for 1 hr. at −10°, washed with 2N-sulphuric acid (20 c.c.) and water, and evaporated. The residual oil crystallised under ether–methanol, to give the *phenyl ketone* (XXVI) (0·75 g.), m. p. 135—140° (a further 0·25 g., making a total yield of 45%, was isolated from the mother-liquors by chromatography), which separated from methanol in plates, m. p. 141—143°, $[\alpha]_D^{21}$ +110° (Found: C, 78·4; H, 8·3. $C_{24}H_{30}O_3$ requires C, 78·7; H, 8·2%).

Des-A-*androstane*-5 : 17-*dione* (I).—(*a*) The phenyl ketone (XXVI) (0·25 g.) was heated at 280—300°/15 mm. and then distilled at *ca.* 350°/10 mm. Volatile compounds were removed from the yellow distillate by steam-distillation and the dried residue was adsorbed on alumina. Elution with benzene–light petroleum (1 : 1) gave the *ketone* (I) which separated from light petroleum in prisms (5 mg.), m. p. 115—120°, undepressed by the specimen prepared as below.

(*b*) Pyrolysis of the barium salt of the acid (V) (prepared from the ethyl ester and barium hydroxide) at 320—340°/0·01 mm. in batches (1 g. or less) gave the *ketone* (I) which, after purification by chromatography, separated from light petroleum in prisms (10—20%), m. p. 119·5—120·5°, $[\alpha]_D^{21}$ +89° (Found: C, 76·7; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). This ketone was also obtained in very low yields (<1%) by pyrolysis of the ethyl ester of the acid (V) and by the action of potassium hydroxide in ethylene glycol on the phenyl ketone (XXVII) at 200°.

The ketone (I), in carbon tetrachloride, had absorption bands with $\nu_{max.}$ 1748, 1720, 1454, 1442, 1432, 1408, 1375, 1357, 1350, 1312, 1279, 1156, 1121, 1094, 1070, 1047, 955, 919, and 902 cm.$^{-1}$. After crystallisation from methanol Martin and Robinson's diketone, m. p. 130—131°, in carbon tetrachloride, had absorption bands at 1747, 1725, 1464, 1449, 1434, 1410, 1380, 1374, 1352, 1305, 1278, 1231, 1184, 1155, 1140, 1086, 1041, 1034, 942, and 933 cm.$^{-1}$.

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