521. *An Approach to the Partial Synthesis of Aldosterone from Steroids lacking Substitution at* C_{18}.

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3β-Acetoxyandrostane-11 : 17-dione, conveniently available by degradation of hecogenin, has been converted, by fission and subsequent reclosure of the 13—17 bond, and by other appropriate manipulations, into 18-benzylidene-3β-hydroxy-14-*iso* : 17-*iso*-*allo*pregnane-11 : 20-dione. Reduction of the 11-carbonyl group of the latter to 11β-hydroxyl, followed by ozonolytic cleavage of the benzylidene group, affords the masked aldehyde system characteristic of aldosterone.

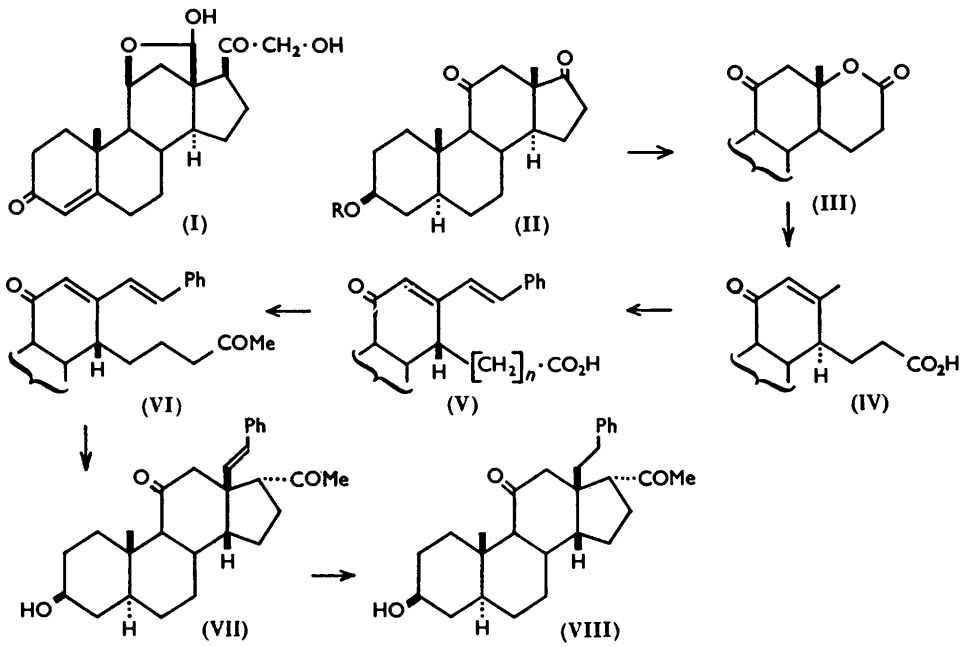
Simpson, Tait, Wettstein, Neher, von Euw, Schindler, and Reichstein [1] have shown that aldosterone has the constitution and stereochemistry depicted in (I). In view of the minute amounts of the hormone available from natural sources its partial or total synthesis is of some importance. Indeed a total synthesis has recently been reported,[2] based upon the fundamental work of Sarett and his collaborators.[3] The power of modern methods of total steroid synthesis [3, 4] is such that the total synthesis of aldosterone may be easier than a partial synthesis from a steroid *lacking* an oxygenated or other functional group at position 18. There is, of course, also the possibility of partial synthesis from one of the few steroids, for example, conessine,[5] bearing a substituent at position 18.[6]

Some preliminary experiments on the opening of ring D of the steroid nucleus to permit modification of the 18-methyl group have appeared,[7, 8] but there is no published work on the introduction of the masked aldehyde (acetal) system of aldosterone (I) or on the reclosure of ring D. We have found a solution to the first of these problems and a possible, but laborious, solution to the second. Our starting point for the partial synthesis of aldosterone was to be an intermediate (or suitable derivative) available from the commercial process for the conversion of hecogenin into cortisone.[9]

The first series of experiments was based on 3β-acetoxyandrostane-11 : 17-dione [10] (II; R = Ac). Treatment with peracetic acid gave the lactone (III; R = Ac) which with dilute ethanolic potassium hydroxide furnished the unsaturated ketone (IV; R = H). The preferential fission of the ketone (II; R = Ac) at the 13—17 bond is in accord with prior knowledge.[7, 11] Reaction of the ketone (IV; R = H) with benzaldehyde in ethanolic hydrogen chloride followed by mild basic hydrolysis of the ethyl ester thus formed gave the benzylidene-acid (V; $n = 2$; R = H). This was homologated by the Arndt–Eistert procedure [12] to the acid (V; $n = 3$; R = H). The latter, on treatment with oxalyl chloride,[13] diazomethane, and then hydriodic acid [14] afforded the oily methyl ketone

[1] Simpson, Tait, Wettstein, Neher, von Euw, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 1163, 1200.
[2] Schmidlin, Anner, Billeter, and Wettstein, *Experientia*, 1955, **11**, 365; Vischer, Schmidlin, and Wettstein, *ibid.*, 1956, **12**, 50.
[3] Sarett *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 4974; 1953, **75**, 422; and later papers.
[4] Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361; Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223; Stork, Loewenthal, and Mukharji, *ibid.*, 1956, **78**, 501; W. S. Johnson *et al.*, *ibid.*, p. 6278 and following papers; Wilds, Ralls, Tyner, Daniels, Kraychy, and Harnik, *ibid.*, 1953, **75**, 4878.
[5] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115; and earlier papers.
[6] Cf. also Lábler, Černy, and Šorm, *Chem. and Ind.*, 1955, 1119; Uffer, *Helv. Chim. Acta*, 1956, **39**, 1834.
[7] Wendler, Taub, and Slates, *J. Amer. Chem. Soc.*, 1955, **77**, 3559.
[8] Heusser, Wohlfahrt, Müller, and Anliker, *Helv. Chim. Acta*, 1955, **38**, 1399; Anliker, Müller, Wohlfahrt, and Heusser, *ibid.*, p. 1404.
[9] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356; Chapman, Elks, Phillips, and Wyman, *ibid.*, p. 4344; and earlier papers there cited.
[10] von Euw and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 988.
[11] Murray, Johnson, Petersen, and Ott, *J. Amer. Chem. Soc.*, 1956, **78**, 981.
[12] Cf. Newman and Beal, *ibid.*, 1950, **72**, 5163.
[13] Shunk and Wilds, *ibid.*, 1948, **70**, 2427.
[14] Wolfrom and Brown, *ibid.*, 1943, **65**, 1516.

(VI; R = H). Without purification this compound was cyclised with mild base at room temperature to give 18-benzylidene-3β-hydroxy-14-*iso* : 17-*iso-allo*pregnane-11 : 20-dione (VII). This showed infrared bands at 3350 (OH), 1700 (11- and 20-ketones) and at 1630, 1600, 1585, 1494, 994, 747, and 694 cm.$^{-1}$ (*trans*-benzylidene).[15] It was further characterised by hydrogenation to the dihydro-derivative (VIII). Proof of the constitution and stereochemistry of (VII) is given later.

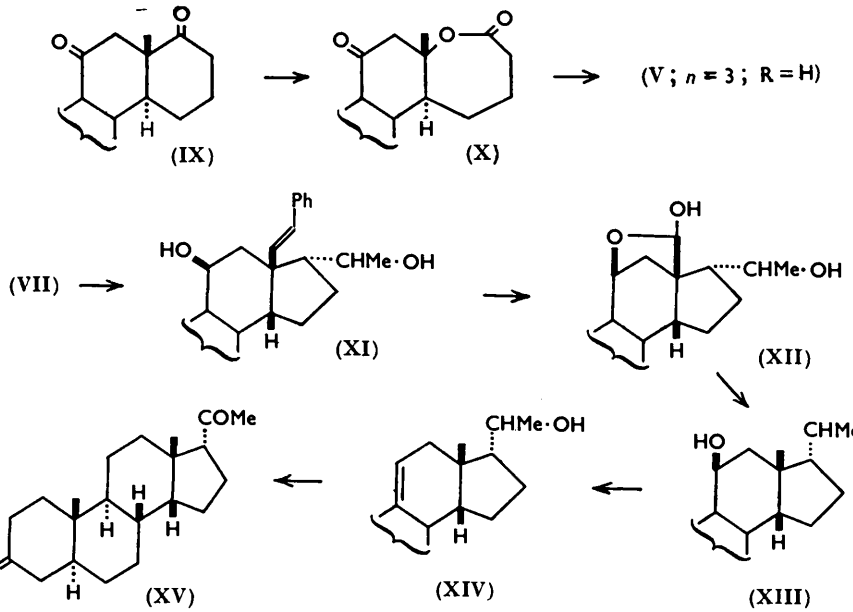


Since the yield in the homologation was unsatisfactory an alternative method for preparation of the acid (V; $n = 3$; R = H) was sought. The starting diketone (II; R = Ac) was converted into the cyanohydrin (or mixture of stereoisomeric cyanohydrins) and then, by hydrogenation and treatment with nitrous acid,[16] transformed into the D-homo-diketone (IX; R = Ac). Although this diketone did not react readily with peracetic acid, it was smoothly converted into the desired lactone (X; R = Ac) with trifluoroperacetic acid.[17] On treatment with benzaldehyde, etc., as before the lactone (X; R = Ac) gave the desired benzylidene-acid (V; $n = 3$; R = H) in a yield of 20—25% based on (IX; R = Ac). This procedure was, therefore, the method of choice for the preparation of the derivative (VII).

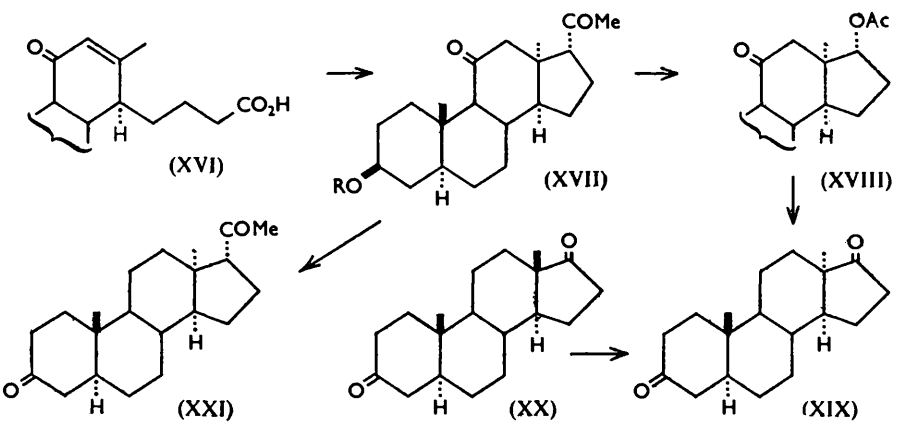
The constitution and stereochemistry of the benzylidene derivative (VII) were established as follows. Reduction with lithium aluminium hydride gave a triol (XI; R = H) which retained its benzylidene group as shown by the ultraviolet and infrared spectra [bands at 3350 (OH) and 1640, 1600, 1580, 1494, 998, 784, and 696 cm.$^{-1}$ (*trans*-benzylidene group)] and by ozonolysis under controlled conditions to give the masked aldehyde system (*no* carbonyl infrared absorption), typical (see above) of aldosterone, as in (XII; R = H). On Wolff-Kishner reduction this acetal afforded a new triol (XIII; R = H), characterised as its diacetate. The 11β-hydroxyl group was conveniently removed by catalytic hydrogenation in acetic acid over platinum in the presence of a trace of perchloric acid. The

[15] Cf. Sheppard and Simpson, *Quart. Rev.*, 1952, **6**, 1; A.P.I. Infra-red Spectrograms, No. 330.
[16] Goldberg *et al.*, *Helv. Chim. Acta*, 1940, **23**, 376, 840; 1941, **24**, 478, 295E; 1942, **25**, 1553, 1556; 1943, **26**, 1142.
[17] Sager and Duckworth, *J. Amer. Chem. Soc.*, 1955, **77**, 188; Emmons and Ferris, *ibid.*, 1953, **75**, 4623.

first step must be elimination of the 11β-hydroxyl group, to give (XIV; R = H), followed by further hydrogenation. The hydrogenation product (probably partially acetylated) was saponified and the resulting diol oxidised to the corresponding 3 : 20-dione. The latter was shown to be identical with an authentic specimen of 14-*iso* : 17-*iso-allo*pregnane-3 : 20-dione [18] (XV) kindly supplied by Professor T. Reichstein.



In order to examine the effect of the C_{14} configuration on the course of the cyclisation, the lactone (X; R = Ac) was treated under mild basic conditions to furnish the oily acid (XVI; R = H). The latter, when converted into the methyl ketone and cyclised with base as before, gave, after acetylation, a new diketone shown by the evidence that follows



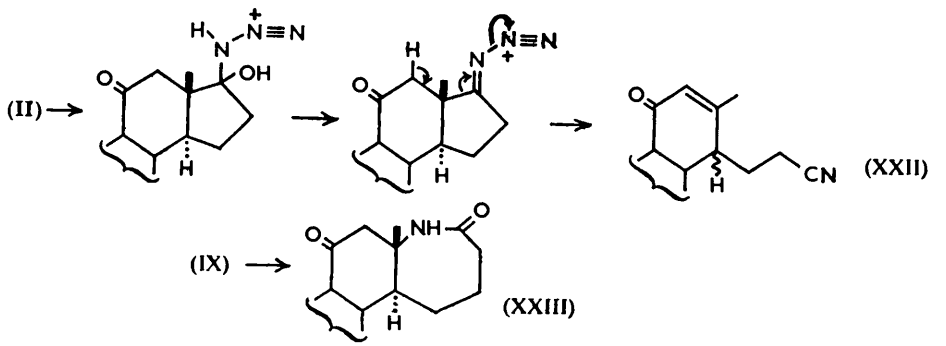
to be 3β-acetoxy-13-*iso* : 17-*iso-allo*pregnane-11 : 20-dione (XVII; R = Ac). The compound was further characterised by hydrolysis followed by oxidation to 13-*iso* : 17-*iso-allo*pregnane-3 : 11 : 20-trione. Treatment of the acetoxy-diketone (XVII; R = Ac)

[18] See Shoppee, *Helv. Chim. Acta*, 1944, **27**, 246; Press and Reichstein, *ibid.*, 1947, **30**, 2124.

with trifluoroperacetic acid gave the diacetate (XVIII; R = Ac). On reduction with lithium aluminium hydride, hydrogenation in the presence of perchloric acid, and further processing as in the case above, 13-*iso*androstane-3 : 17-dione [19] (XIX) resulted. Owing to incomplete removal of the 11β-oxygen function in this particular example some 13-*iso*-androstane-3 : 11 : 17-trione was also isolated. The authentic specimen of diketone (XIX) was obtained by irradiation of androstane-3 : 17-dione (XX) with ultraviolet light.[19,20] The configuration at C_{17} in (XVII; R = Ac) is not established directly by these experiments. However, if we accept a three-chair conformation for rings A, B, and C, then the more stable configuration of the side chain of (XVII; R = Ac), which would surely be the configuration produced from its mode of genesis, would be 17α, as already written. The acetoxy-dione (XVII) was also subjected to the procedure for the removal of the 11-oxygen function (see above). This gave a new diketone, 13-*iso*-*allo*pregnane-3 : 20-dione (XXI) showing a single infrared carbonyl frequency at 1700 cm.$^{-1}$.

The results obtained on the stereochemistry of the cyclisation process become rational if the cyclisation is controlled by the configuration at C_{14}. This would require that the 14-side-chain of (V; $n = 2$ or 3; R = H) is more stable in the quasiaxial than in the quasiequatorial configuration.[21,22] This is conceivable since the quasiequatorial 14-side-chain is hindered by the 7—8 bond, such hindrance not obtaining in its quasiaxial analogue.

Some investigation was made on the cleavage of the 13—17 bond through the Schmidt reaction.[23] 3β-Acetoxyandrostane-11 : 17-dione (II; R = Ac), under the usual Schmidt conditions, afforded mainly the unsaturated nitrile (XXII; R = Ac), presumably by the mechanism indicated. The Schmidt reaction on 3β-acetoxy-D-homoandrostane-11 : 17*a*-dione (IX; R = Ac), in contrast, gave the desired lactam (XXIII; R = Ac). On treatment with sodium acetate and acetic anhydride followed by benzaldehyde and ethanolic hydrogen chloride in the usual way (see above), this furnished the known benzylidene-acid (V; $n = 3$; R = H) although in poor yield. This confirms that the lactam is produced by rupture of the 13—17 bond.[8] Some further transformation products involving Schmidt reactions are recorded in the Experimental section.



Experimental

$[\alpha]_D$ are in $CHCl_3$ unless stated otherwise; ultraviolet absorption spectra refer to EtOH solutions. Infrared spectra were kindly determined by Dr. G. Eglinton and his colleagues, for Nujol suspensions unless specified to the contrary. The alumina for chromatography was

[19] Billeter and Miescher, *Helv. Chim. Acta.*, 1951, **34**, 2053.
[20] Butenandt *et al.*, *Ber.*, 1941, **74**, 1308; 1942, **75**, 1931; 1944, **77**, 392, 394.
[21] Cf. Barton, *J.*, 1953, 1027.
[22] Cf. Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21.
[23] Wolff, "Organic Reactions," Vol. III, p. 307; Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 431: and many earlier papers.

Brockmann Grade III. Light petroleum refers to the fraction of b. p. 40—60° unless stated otherwise.

3β-*Acetoxy*-13-*hydroxy*-11-*oxo*-13(17)-seco*androstan*-17-*oic Lactone* (III; R = Ac).—3β-Acetoxyandrostane-11 : 17-dione, m. p. 162—163°, $[\alpha]_D$ +95° (*c* 1·16 in dioxan) (2·0 g.), in "AnalaR" acetic acid (10 ml.) was treated with peracetic acid (4·0 g.) in the same solvent (20 ml.) containing toluene-*p*-sulphonic acid (20 mg.) at 7—10° for 120 hr. (negative test with ethanolic 2 : 4-dinitrophenylhydrazine reagent). Cautious addition of water gave the *lactone* (III; R = Ac) (1·10 g.), m. p. (needles from aqueous methanol) 218—219°, $[\alpha]_D$ −22° (*c* 1·81) (Found: C, 69·6; H, 8·3. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%). Further dilution gave additional lactone (420 mg.).

3β-*Hydroxy*-11-*oxo*-13(17)-seco*androst*-12-*ene*-17-*carboxylic Acid* (IV; R = H).—The above-mentioned lactone (1·07 g.) in ethanol (49 ml.) was treated with potassium hydroxide (800 mg.) in ethanol (200 ml.), and the appearance of a max. at 239 mμ followed spectrophotometrically (ε constant at 10,300 after 45 min.). The acidic *product* (1·0 g.) gave, on crystallisation from ether, needles, m. p. 155°, $[\alpha]_D$ −4° (*c* 2·01; 1·76), $\lambda_{max.}$ 239 mμ (ε 13,600) (Found: C, 71·05; H, 8·75. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

This acid (260 mg.) in ethanolic hydrogen chloride (25 ml.; 40% w/w) containing benzaldehyde (250 mg.; redistilled) was left at 20°, the appearance of a max. at 320 mμ being followed spectrophotometrically (ε constant at 29,000 after 16 hr.). Addition of water (cooling), extraction into ether, and washing with saturated sodium hydrogen sulphite solution gave the oily ethyl ester. Treated with potassium hydroxide (1·0 g.) in ethanol (50 ml.) containing water (1·0 ml.) at room temperature for 16 hr., this furnished 18-*benzylidene*-3β-*hydroxy*-11-*oxo*-13(17)-seco*androst*-12-*ene*-17-*carboxylic acid* (V; *n* = 2; R = H) (130 mg.), m. p. (from methanol) 237—238°, $[\alpha]_D$ +320° (*c* 1·25 in pyridine), $\lambda_{max.}$ 240 (ε 10,600), 325 mμ (ε 34,200) (Found: C, 76·4; H, 8·3. $C_{26}H_{32}O_4$ requires C, 76·45; H, 7·9%). The neutral fraction (40 mg.), on rehydrolysis, gave further acid (25 mg.).

18-*Benzylidene*-3β-*hydroxy*-11-*oxo*-13(17)-seco*androst*-12-*en*-17-*ylacetic Acid* (V; *n* = 3; R = H).—The acid described in the preceding paragraph (1·64 g.) in dry benzene (7·0 ml.) was treated with oxalyl chloride (3·0 g.) in benzene (3·0 ml.) at room temperature for 16 hr. Removal of the solvent *in vacuo* gave an oil. This in benzene (7·0 ml.) was added dropwise to diazomethane (2·0 g.) in ether (200 ml.) at 5°. After 45 min. the solvent was removed *in vacuo* at <40° to give the desired diazo-ketone (1·5 g.). Without further purification this ketone, in methanol (50 ml.), was kept at 46—48° during the addition with stirring of silver benzoate–triethylamine catalyst [12] (2·5 ml. added in five portions during 15 min.). The mixture was refluxed for 5 min., filtered, and evaporated *in vacuo*. The residue was extracted into benzene and washed with sodium hydrogen carbonate solution and with water, and the solution evaporated. The resultant oil was chromatographed over silica gel to give, on elution with benzene–ether (1 : 1), an oil (200 mg.) which on hydrolysis (50 ml. of 2% ethanolic potassium hydroxide at 20° for 16 hr.) and chromatography of the acidic fraction over silica [elution with benzene–acetone (9 : 1)] gave the homologous *acid* (V; *n* = 3; R = H) (175 mg.), prisms (from methanol), m. p. 233—234°, $[\alpha]_D$ +301° (*c* 0·82 in pyridine), $\lambda_{max.}$ 238 (ε 14,000), $\lambda_{max.}$ 325 mμ (ε 35,200) (Found: C, 77·0; H, 7·75. $C_{27}H_{34}O_4$ requires C, 76·75; H, 8·1%).

3β-*Hydroxy*-18-*benzylidene*-14-iso : 17-iso-allo*pregnane*-11 : 20-*dione* (VII).—The above-mentioned acid (1·0 g.) was finely powdered and suspended in dry benzene (5·0 ml.) Oxalyl chloride (1·0 g.) was added and the mixture left until all had dissolved (3—40 hr. depending on the state of subdivision of the acid). Removal of the solvent *in vacuo*, dissolution in benzene (5·0 ml.), and addition to diazomethane (2·0 g.) in ether (150 ml.) at 0—5°, storage for 2 hr., and then removal of the excess of ethereal diazomethane at <40°, gave an oily diazo-ketone. This was taken up in chloroform and shaken with 55% aqueous hydriodic acid solution (1·0 ml.) for 5 min., to furnish an oily methyl ketone. The latter (1·0 g.) in benzene (3·0 ml.) was treated with 0·2N-ethanolic potassium hydroxide (100 ml.) at room temperature for 16 hr. under nitrogen {$[\alpha]_D$ constant at +57° (*c* 1·0), replacement of max. at 235 and 325 mμ by a band at 255 mμ (ε 12,000)} to give 18-*benzylidene*-3β-*hydroxy*-14-iso : 17-iso-allo*pregnane*-11 : 20-*dione* (VII). Purified by chromatography over silica gel in benzene–ether (9 : 1) and sublimation at 160°/10^{-5} mm. this (250 mg.) formed needles (from ether), m. p. 194—195°, $[\alpha]_D$ −26° (*c* 0·84), $\lambda_{max.}$ 255 mμ (ε 20,900), inflex. at 284 and 293 mμ (ε 2600 and 1800 respectively) (Found: C, 80·05; H, 8·4. $C_{28}H_{36}O_3$ requires C, 79·95; H, 8·65%). On hydrogenation (62 mg.) over 10% palladized charcoal (20 mg.) in ethyl acetate (5·0 ml.) for 24 hr. (0·96 mol. absorbed), this

furnished 18-*benzyl*-3β-*hydroxy*-14-iso : 17-iso-allo*pregnane*-11 : 20-*dione* (VIII), plates (from ether), m. p. 193—194°, $[\alpha]_D$ 0° (*c* 1·00), no styryl absorption in the ultraviolet region (Found : C, 79·6; H, 8·9. $C_{28}H_{38}O_3$ requires C, 79·6; H, 9·05%).

3β-*Acetoxy*-D-*homoandrostane*-11 : 17a-*dione* (IX; R = Ac).—3β-Acetoxyandrostane-11 : 17-dione (5·5 g.) in absolute ethanol (138 ml.) was treated with " AnalaR " potassium cyanide (33 g.) and kept at 0—5° with efficient stirring and addition during 1 hr. of " AnalaR " acetic acid (35·75 ml.). The resultant paste was stirred for a further 1½ hr. and poured into water (1 l.). The precipitate of mixed cyanohydrins, m. p. 103—106°, $[\alpha]_D$ −6° (*c* 2·3), was filtered after 30 min. and dried (5·8 g.) over phosphoric oxide *in vacuo* for 24 hr. at not more than room temperature. This material (5·8 g.) in " AnalaR " acetic acid (160 ml.) was hydrogenated over platinum (2·0 g.) (2 mols. uptake in 40 min.). The catalyst was removed by filtration, and the solution concentrated *in vacuo* on the steam-bath to 25 ml. and then diluted with water to 250 ml. Care must be taken during the concentration of the acetic acid solution that the temperature does not rise too high and that the heating is not too prolonged. In one experiment (with Dr. M. Martin-Smith) the primary amino-group was acetylated during the evaporation, to afford 17ξ-*acetamidomethyl*-3β-*acetoxy*-17ξ-*hydroxyandrostan*-11-*one*, plates (from methanol), m. p. 258—260°, $[\alpha]_D$ +10° (*c* 2·28), infrared max. at 3305 (NH), 3270 (OH), 1720 and 1242 (acetate), 1700 (11-ketone), and 1640 and 1547 cm.$^{-1}$ (CO·NH) (Found : C, 68·7; H, 8·9; N, 3·35; Ac, 20·5. $C_{24}H_{37}O_5N$ requires C, 69·45; H, 8·8; N, 3·55; Ac, 20·3%). The amine solution (see above) was treated at 0—5° with 10% sodium nitrite solution (36 ml.) at the same temperature for 3 hr. Extraction with chloroform and chromatography over alumina (100 g.) gave, on elution with benzene, 3β-*acetoxy*-D-*homoandrostane*-11 : 17a-*dione* (IX; R = Ac) (4·24 g.), prisms [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 185—186°, $[\alpha]_D$ −29° (*c* 1·79) (Found : C, 73·55; H, 8·75. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

3β-*Acetoxy*-13-*hydroxy*-11-*oxo*-13(17a)-seco-D-*homoandrostan*-17-*oic Lactone* (X; R = Ac).—3β-Acetoxy-D-homoandrostane-11 : 17*a*-dione (1·05 g.) in methylene dichloride (10 ml.) containing toluene-*p*-sulphonic acid (10 mg.) was treated with stirring with trifluoroperacetic acid (715 mg., 2 equiv.) in the same solvent (5 ml.) during 10 min. at <5°. The stoppered reaction flask was stored at 20° in the dark for 70 min. (1 equiv. consumed). The solution was diluted with chloroform (25 ml.) and washed very rapidly with water (50 ml.), saturated sodium hydrogen carbonate (50 ml.) and water (50 ml.). Trituration of the oily product with ether afforded the *lactone* (X; R = Ac) (500 mg.), needles (from ether), m. p. 182—183°, $[\alpha]_D$ −66° (*c* 1·05) (Found : C, 70·8; H, 8·5. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·6%). For routine preparations the total crude lactone (see above) was suitable for the conversion described in the sequel.

This lactone was treated with benzaldehyde as in the procedure described above. The acidic product, chromatographed over silica [elution with benzene–acetone (9 : 1)] gave 18-benzylidene-3β-hydroxy-11-oxo-13(17)-*seco*androst-12-ene-17-ylacetic acid (see above), identified by m. p., mixed m. p., rotation, and infrared spectrum. The overall yield from 3β-acetoxy-D-homoandrostane-11 : 17*a*-dione was 20—25%.

18-*Benzylidene*-14-iso : 17-iso-allo*pregnane*-3β : 11β : 20ξ-*triol* (XI; R = H).—18-Benzylidene-3β-hydroxy-14-*iso* : 17-*iso-allo*pregnane-11 : 20-dione (see above) (400 mg.) was extracted with dry ether from a Soxhlet thimble into lithium aluminium hydride (400 mg.) in the same solvent (150 ml.). Decomposition of the excess of reductant with ethyl acetate and isolation in the usual way afforded 18-*benzylidene*-14-iso : 17-iso-allo*pregnane*-3β : 11β : 20ξ-*triol* (XI; R = H) (300 mg.), prisms (from ethyl acetate), m. p. 237—238°, $[\alpha]_D$ +59° (*c* 1·50), +58° (*c* 1·00), $\lambda_{max.}$ 255 mμ (ε 20,800) (Found : C, 79·05; H, 9·05. $C_{28}H_{40}O_3$ requires C, 79·2; H, 9·5%).

3β : 11β : 20ξ-*Trihydroxy*-14-iso : 17-iso-allo*pregnan*-18-*al* (cf. XII; R = H).—The benzylidene-triol described above (101 mg.) in methylene dichloride (100 ml.) was ozonised at −60° until the styrene absorption band at 255 mμ had been replaced by a band of lower intensity at 245 mμ (ε 11,000) (spectrophotometric control by removal of aliquot parts). The solution was stirred with zinc dust (500 mg.; freshly activated with acetic acid) and 80% acetic acid (5 ml.) whilst the temperature rose from −60° to +20° (2 hr.). Crystallisation of the product from chloroform furnished the *product* (cf. XII; R = H), needles, m. p. 208—210°, $[\alpha]_D$ +106° (*c* 1·30 in MeOH), no ultraviolet absorption, no infrared carbonyl absorption (Found : C, 72·2; H, 9·65. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·8%).

This masked aldehyde (150 mg.) was added to a mixture of sodium ethoxide (300 mg.) in absolute ethanol (3 ml.) and anhydrous hydrazine (1·5 ml.) and heated at 180° for 16 hr.

Isolation of the product in the usual way afforded 14-iso : 17-iso-allo*pregnane*-3β : 11β : 20ξ-*triol* (XII; R = H) (140 mg.), prisms (from ethyl acetate), m. p. 202—203°, $[\alpha]_D$ +59° (*c* 0·73) (Found: C, 75·15; H, 10·8. $C_{21}H_{36}O_3$ requires C, 74·95; H, 10·8%). Treatment with pyridine–acetic anhydride overnight at room temperature gave the 3β : 20ξ-*diacetate*, needles (from methanol), m. p. 181—184°, $[\alpha]_D$ +45° (*c* 0·70) (Found: C, 71·75; H, 9·35. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%).

14-*iso* : 17-*iso-allo*Pregnane-3β : 11β : 20ξ-triol (see above) (140 mg.) in " AnalaR " acetic acid (20 ml.) containing 71% aqueous perchloric acid (0·2 ml.) was hydrogenated over pre-reduced platinum catalyst (70 mg.) for 24 hr. (absorption of 1 mol. of hydrogen). The product was hydrolysed by refluxing 5% methanolic potassium hydroxide (25 ml.), to give 14-*iso* : 17-*iso-allo*pregnane-3β : 20ξ-diol (125 mg.), needles (from methanol), m. p. 163—164°, $[\alpha]_D$ +43° (*c* 2·30). The diol (125 mg.) in " AnalaR " acetic acid (2 ml.) was treated with chromium trioxide (99·0 mg.) in the same solvent (6 ml.) for 16 hr. at room temperature. The product was chromatographed over alumina (grade 3; 3 g.). Elution with light petroleum (b. p. 60—80°)–benzene (9 : 1) gave 14-*iso* : 17-*iso-allo*pregnane-3 : 20-dione (XV) (48 mg.), needles (from light petroleum), m. p. 139—141°, $[\alpha]_D$ +39° (*c* 1·10), identified by m. p., mixed m. p., rotation, and infrared spectrum (KCl disc). The authentic specimen had m. p. 137—139°, $[\alpha]_D$ +40°.

Action of Base on 3β-*Acetoxy*-13-*hydroxy*-11-*oxo*-13(17a)-seco-D-*androstan*-17-*oic Lactone*.—The lactone (1·95 g.) in 5% ethanolic potassium hydroxide solution (100 ml.) was refluxed under nitrogen for 1 hr. Separation into acid and neutral fractions gave in the former an acidic oil (1·80 g.), showing $\lambda_{max.}$ 237 mμ (ε 12,600). This acid was transformed, without isolation of intermediates, into the corresponding methyl ketone and then cyclised (spectrophotometric control) by the processes already described. The cyclised diketone was acetylated (1·10 g.) and then chromatographed over alumina. Elution with benzene afforded 3β-*acetoxy*-13-iso : 17-iso-allo*pregnane*-11 : 20-*dione* (XVII; R = Ac) (200 mg.), needles [from light petroleum (b. p. 60—80°)], m. p. 121—122°, $[\alpha]_D$ −182° (*c* 1·10) (Found: C, 73·8; H, 8·8. $C_{23}H_{34}O_4$ requires C, 73·75; H, 9·15%). This acetoxy-dione (300 mg.) was hydrolysed with 5% methanolic potassium hydroxide for 3 hr. on the steam-bath, and the resultant 3β-hydroxy-compound (200 mg.) in " AnalaR " acetic acid (10 ml.) oxidised by chromium trioxide (200 mg.) overnight at room temperature, to give 13-iso : 17-iso-allo*pregnane*-3 : 11 : 20-*trione* (150 mg.), needles (from ethyl acetate–light petroleum), m. p. 140°, $[\alpha]_D$ −165° (*c* 0·85) (Found: C, 76·5; H, 9·25. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%).

3β-Acetoxy-13-*iso* : 17-*iso-allo*pregnane-11 : 20-dione (300 mg.) in dry ether (20 ml.) was reduced with lithium aluminium hydride (300 mg.) in the same solvent (180 ml.) under reflux overnight. The product (260 mg.) in " AnalaR " acetic acid (20 ml.) containing 72% perchloric acid (0·2 ml.) was hydrogenated over pre-reduced platinum catalyst (130 mg.) for 24 hr. (1 mol. uptake). The product was hydrolysed with methanolic potassium hydroxide, and the resultant diol (230 mg.) oxidised with chromium trioxide (200 mg.) in " AnalaR " acetic acid (15 ml.) for 16 hr. at room temperature. The oily dione (100 mg.) was chromatographed over alumina in carbon tetrachloride, to give 13-iso : 17-iso-allo*pregnane*-3 : 20-*dione*, needles (from light petroleum), m. p. 147—148°, $[\alpha]_D$ −61° (*c* 0·75) (Found: C, 79·6; H, 10·2. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

3β-Acetoxy-13-*iso* : 17-*iso-allo*pregnane-11 : 20-dione (240 mg.) in methylene dichloride (4 ml.) was treated with trifluoroperacetic acid (150 mg.) in the same solvent (1·0 ml.) for 1·5 hr. at room temperature to furnish 3β : 17α-*diacetoxy*-13-iso*androstan*-11-*one* (XVIII; R = Ac) (200 mg.). On purification by chromatography over alumina elution with benzene–light petroleum mixtures, this (130 mg.) formed needles (from light petroleum), m. p. 123°, $[\alpha]_D$ −125° (*c* 1·10) (Found: C, 70·5; H, 8·95. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). This diacetate (300 mg.) was reduced with lithium aluminium hydride, hydrogenated, and oxidised as described above. The product was chromatographed over alumina in carbon tetrachloride. Elution with that solvent gave 13-*iso*androstane-3 : 17-dione (XIX) (30 mg.), needles (from light petroleum), m. p. 165—167°, $[\alpha]_D$ −74° (*c* 0·38), identical (m. p., mixed m. p., rotation, and infrared spectrum) with an authentic specimen (see below). Development of the chromatogram with benzene–light petroleum (1 : 1) gave 13-iso*androstane*-3 : 11 : 17-*trione* (77 mg.), needles or prisms (from ether–light petroleum), m. p. 174—175°, $[\alpha]_D$ −160° (*c* 2·00) (Found: C, 75·4; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%).

The authentic specimen of 13-*iso*androstane-3 : 17-dione was obtained by the following

procedure.[19, 20] Androstane-3 : 17-dione (XX) (495 mg.) in benzene (30 ml.) was irradiated in a silica tube with ultraviolet light for 23 hr. (rotational change from +104° to +16°). Chromatography over alumina and elution with carbon tetrachloride gave authentic 13-*iso*-androstane-3 : 17-dione, m. p. 167—168°, $[\alpha]_D$ −76° (*c* 0·63) (Found : C, 79·3; H, 9·4. Calc. for $C_{19}H_{28}O_2$: C, 79·1; H, 9·8%). Billeter and Miescher [19] reported m. p. 165—166°, $[\alpha]_D$ −58° (*c* 0·60).

Bromination of 3β-*Acetoxy*-D-*homoandrostane*-11 : 17a-*dione*.—The diketone (1·0 g.) in " AnalaR " acetic acid (22 ml.) containing hydrogen bromide (50% in acetic acid; 5 drops) was treated with bromine (446 mg.) in the same solvent (18·7 ml.) for 1 min. (discharge of colour). Crystallisation of the product from ethyl acetate–light petroleum furnished 3β-*acetoxy*-17α-*bromo*-D-*homoandrostane*-11 : 17a-*dione* (975 mg.), needles, m. p. 225—227° (decomp.), $[\alpha]_D$ +24° (*c* 2·00), infrared max. at 1735 (acetate), 1725 (equatorial α-bromo-ketone), and 1710 cm.$^{-1}$ (11-ketone) (Found : C, 60·4; H, 7·3; Br, 18·2. $C_{22}H_{31}O_4Br$ requires C, 60·15; H, 7·1; Br, 18·15%). This bromo-ketone was recovered unchanged after treatment with trifluoroperacetic acid.

The bromo-ketone (800 mg.) was refluxed with collidine (20 ml.) for 15 min. Filtration of the product in benzene solution through alumina gave 3β-*acetoxy*-D-*homoandrost*-16-*ene*-11 : 17a-*dione* (300 mg.), needles (from ether), m. p. 170—172°, $[\alpha]_D$ −32° (*c* 2·30), $\lambda_{max.}$ 225 mμ (ε 8200) (Found : C, 73·9; H, 8·15. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·45%). Treatment with pyridine–hydroxylamine hydrochloride overnight at room temperature furnished the 17a-*monoxime*, m. p. (from aqueous methanol) 237—239°, $[\alpha]_D$ −166° (*c* 1·12 in pyridine), $\lambda_{max.}$ 236 mμ (ε 8400) (Found : C, 70·9; H, 8·3; N, 3·95. $C_{22}H_{31}O_4N$ requires C, 70·75; H, 8·35; N, 3·75%).

Bromination of 3β-*Acetoxyandrostane*-11 : 17-*dione*.—The diketone (1·0 g.) in " AnalaR " acetic acid (20 ml.) containing hydrogen bromide (50% in acetic acid; 5 drops) was treated with bromine (463 mg.) in the same solvent (13·1 ml.) for 1 hr. The product, after crystallisation from ethyl acetate, was a mixture of mono- and di-bromide. Further fractionation gave 3β-*acetoxy*-16ξ-*bromoandrostane*-11 : 17-*dione*, plates (from ethyl acetate), m. p. 183—185°, $[\alpha]_D$ +125° (*c* 1·06), infrared max. at 1730 (acetate and *cyclo*pentanone) and 1705 cm.$^{-1}$ (11-ketone) (Found : C, 58·9; H, 6·65. $C_{21}H_{29}O_4Br$ requires C, 59·3; H, 6·85%). This bromo-ketone was recovered unchanged after treatment with trifluoroperacetic acid.

Schmidt Reaction on 3β-*Acetoxyandrostane*-11 : 17-*dione*.—The diketone (344 mg.) in chloroform (7·0 ml.) and " AnalaR " concentrated sulphuric acid (2·0 ml.) was treated, at 0° with stirring, with sodium azide (97 mg.) portionwise. The stirring was continued for 30 min. Chromatography of the product over alumina (6 g.) and elution with benzene gave 3β-*acetoxy*-11-*oxo*-13(17)-seco*androst*-12-*ene*-17-*nitrile* (XXII; R = Ac), needles, m. p. 138° or 155—157°, $[\alpha]_D$ −55° (*c* 1·07), $\lambda_{max.}$ 234, 311—315 (ε 7200 and 27 respectively) (Found : C, 73·25; H, 8·1; N, 3·85. $C_{21}H_{29}O_3N$ requires C, 73·45; H, 8·5; N, 4·1%). Elution with benzene–methanol (4 : 1) gave a small quantity (20 mg.) of a lactam, m. p. 305—307° (sublimes), which was not investigated.

3β-*Acetoxy*-17b-*aza*-D-*bishomoandrostane*-11 : 17a-*dione*.—3β-Acetoxy-11 : 17*a*-dioxo-D-homoandrostane (720 mg.) in chloroform (14 ml.) and " AnalaR " concentrated sulphuric acid (4·0 ml.) was treated at 0—5° with sodium azide (200 mg.) in small portions. Working up after 30 min. gave 3β-*acetoxy*-17b-*aza*-D-*bishomoandrostane*-11 : 17a-*dione* (XXIII), plates (from methanol), m. p. 278—279°, $[\alpha]_D$ −77° (*c* 1·01), infrared max. at 1727 (acetate), 1706 (11-ketone), and 1667 cm.$^{-1}$ (lactam) (Found : C, 70·05; H, 8·5; N, 3·95. $C_{22}H_{33}O_4N$ requires C, 70·35; H, 8·85; N, 3·75%). The lactam (1·0 g.) was refluxed for 5 hr. with acetic anhydride (50 ml.) and fused sodium acetate (3·0 g.). Separation into acid and neutral fractions gave, in the former, an oil (396 mg.), $\lambda_{max.}$ 237 mμ (ε 5100), and, in the latter, a product (600 mg.), $\lambda_{max.}$ 237 mμ (ε 6400). The crude acid fraction was treated with benzaldehyde and further processed as above, to give 18-benzylidene-3β-hydroxy-11-oxo-13(17)-*seco*androst-12-en-17-ylacetic acid, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +294° (*c* 0·37 in pyridine)}, and infrared spectrum.

3β-*Acetoxy*-17α-*bromo*-17b-*aza*-D-*bishomoandrostane*-11 : 17a-*dione*.—The appropriate 17α-bromo-dione (see above) (3·1 g.) in chloroform (60 ml.) and " AnalaR " concentrated sulphuric acid (16·8 ml.) was treated with sodium azide (730 mg.) as in the cognate preparation reported above. Crystallisation from ethyl acetate gave 3β-*acetoxy*-17α-*bromo*-17b-*aza*-D-*bishomoandrostane*-11 : 17a-*dione* (3·0 g.), prisms, m. p. 183—185°, $[\alpha]_D$ −12° (*c* 1·09) (Found : C, 58·15; H, 6·8; N, 3·45; Br, 17·9. $C_{22}H_{32}O_4NBr$ requires C, 58·1; H, 7·1; N, 3·1; Br, 17·6%). This

bromo-lactam (560 mg.) was refluxed with collidine for 15 min., to furnish, on chromatography over alumina and elution with ether–methanol (9 : 1), 3β-*acetoxy*-17b-*aza*-D-*bishomoandrost*-16-*ene*-11 : 17a-*dione*, prisms (from ethyl acetate), m. p. 262°, $[\alpha]_D$ −95° (*c* 0·92); in the ultraviolet absorption spectrum a shoulder was found at 230—240 mμ (ε 3000),[24] infrared max. at 1725 (acetate), 1711 (11-ketone), and 1675 (lactam) cm.$^{-1}$ (Found: C, 70·7; H, 8·6; N, 4·1. $C_{22}H_{31}O_4N$ requires C, 70·75; H, 8·4; N, 3·75%).

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[24] Cf. Edwards and Singh, *Canad. J. Chem.*, 1954, **32**, 683.