355. *Aza-steroids. Part IX.* Approaches to the Partial Synthesis of* 11-*Azaprogesterone*

By C. W. Shoppee and L. N. Mander

The preparation of 11α,12α-dihydroxy-5β-pregnane-3,20-dione, methyl 3α,20β-diacetoxy-9-oxo-9,11-seco-11-nor-5β-pregnan-12-oate, and methyl 3α,9β,20β-triacetoxy-9,11-seco-5β-pregnan-11-oate is described, and an account is given of some of their reactions.

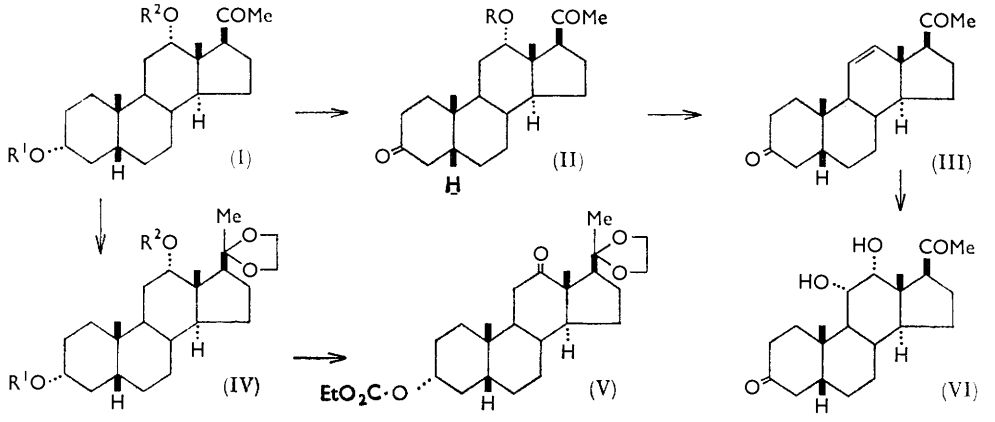
Various methods based on the Beckmann, Hofmann, and Curtius rearrangements, and on the cyclisation of A-seco-steroid acids have successfully been used for the preparation of 3- and 4-aza-steroids.[1] Continuing interest in the field, as shown by the preparation of 2-,[2] 3-,[2] 4-,[2] and 5-aza-A-nor-B-homo-steroids,[3] 6-azaequilenin,[4] 6-aza-,[5] 9-aza-C-homo,[6] 11a-aza-C-homo-,[7] and 12a-aza-C-homo-steroids,[8] prompts us to describe the preparation of some C-seco-pregnanes for use as intermediates in the partial synthesis of 11-azaprogesterone.

Our initial approach required a suitable 11,12-disubstituted 5β-pregnane. 3α,12α-Diacetoxy-5β-pregnan-20-one [9,10] (I; $R^1 = R^2 = Ac$) was hydrolysed with potassium carbonate to the 12α-monoacetate [10] (I; $R^1 = H$, $R^2 = Ac$), which was smoothly oxidised by the Jones reagent to 12α-acetoxy-5β-pregnane-3,20-dione [10,11] (II; R = Ac). This was hydrolysed by potassium hydroxide to 12α-hydroxy-5β-pregnane-3,20-dione [11] (II; R = H), which, as the 12α-toluene-*p*-sulphonate (II; R = Ts), gave 5β-pregn-11-ene-3,20-dione [12,13] (III) on treatment with alkaline aluminium oxide.

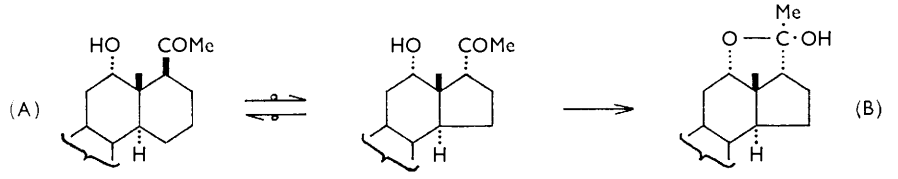
It has been found [14] that the presence of a 12α-hydroxyl group may facilitate inversion

* Part VIII, Shoppee, Akhtar, and Lack, *J.*, 1964, 3392.

[1] Shoppee and Krüger, *J.*, 1961, 3641; Shoppee, Killick, and Krüger, *J.*, 1962, 2275.
[2] Patel, *Diss. Abs.*, 1963, **24**, 986; Havranek, *ibid.*, p. 1409.
[3] Rodenwald and Wicha, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1963, **11**, 437.
[4] Huisman, Speckamp, de Koning, and Pandit, *Tetrahedron Letters*, 1964, 1275.
[5] Knof, *Annalen*, 1964, **670**, 88.
[6] Zderic and Iriarte, *J. Org. Chem.*, 1962, **27**, 1756.
[7] Zderic, Carpio, Limon, and Ruiz, *J. Org. Chem.*, 1961, **26**, 2842.
[8] Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454; 1960, **82**, 3992.
[9] Hoehn and Mason, *J. Amer. Chem. Soc.*, 1938, **60**, 1493.
[10] Reichstein and von Arx, *Helv. Chim. Acta*, 1940, **23**, 747.
[11] Cf. Shoppee and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 351; Bockmühl, Ehrhart, Ruschig, and Aumüller, Amer. Patent, 2,142,170/1938 (*Chem. Zentr.*, 1939, **110**, 2, 170).
[12] Hegner and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 721.
[13] Just and C. R. Engel, *J. Org. Chem.*, 1958, **23**, 12.
[14] Tschesche, Brügmann, Marquandt, and Machleidt, *Annalen*, 1961, **648**, 185.



of a 14α,17β-20-oxopregnane in the presence of hydroxide ions to a 14α,17α-20-oxopregnane by formation from the latter of a 12α,20-cyclohemiacetal:



Inversion of configuration at position 17 could occur in the alkaline hydrolysis of (II; R = Ac) to (II; R = H). Such inversion is associated with a very large increase in lævorotation $\Delta[M_D] = -538°$,[15] but this is not observed:

Compound	(I: R^1 = H, R^2 = Ac)	(II: R = Ac)	(II: R = H)	(III)
$[M]_D$	~+600	~+600	+448	+286
$\Delta[M]_D$	—	—	−152	−162

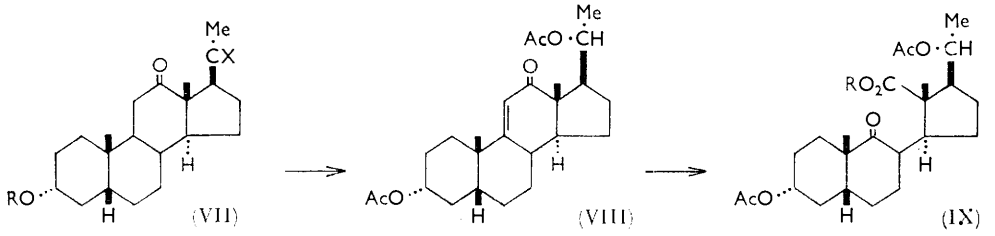
Moreover, an attempt was made using the compound (II; R = H) to effect the change (A) ⟶ (B) using the conditions of Tschesche *et al.*,[14] but the substance was recovered unaltered. Further, the nuclear magnetic resonance (n.m.r.) spectrum of (III), the dehydration product of (II; R = H), is not only consistent with the presence of a 17β-acetyl side-chain but excludes the presence of a 17α-acetyl side-chain.

Oxidation of compound (III) or its 3,20-bisketal with potassium permanganate in acetone gave only intractable oils; ozonolysis, followed by treatment with alkaline hydrogen peroxide, yielded a considerable acidic fraction, but neither a crystalline 11,12-seco-11,12-dioic acid nor a homogeneous dimethyl ester could be isolated. Hydroxylation of (III) with osmium tetroxide gave a crystalline osmate ester in moderate yield, but conversion of this by sodium hydrogen sulphite to 11α,12α-dihydroxy-5β-pregnane-3,20-dione (VI) proceeded in such poor yield (17%) that the planned cleavage with lead tetra-acetate [7] to the 11,12-seco-11,12-dialdehyde and the required 11,12-seco-11,12-dioic acid was abandoned.

Alternatively, an attempt was made to use the method of Gallagher and his co-workers [16] to prepare an 11ξ-hydroxy-5β-pregnan-12-one as precursor of the desired 11,12-seco-11,12-dioic acid. 3α,12α-Dihydroxy-5β-pregnan-20-one (I; $R^1 = R^2 = H$) with ethylene glycol and toluene-*p*-sulphonic acid in refluxing benzene gave only a 35% yield of the 20-ketal (IV; $R^1 = R^2 = H$); the major product appeared to be a substituted 5β-pregnane dimer, which

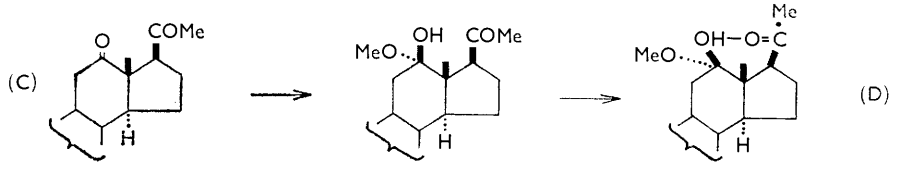
[15] Shoppee, *J.*, 1949, 1617.
[16] Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 495, 511; Gallagher and Hollander, *ibid.*, p. 533; Borgstrom and Gallagher, *ibid.*, 1949, **177**, 951.

is under investigation. Similar treatment of the 3α,12α-diacetate (I; $R^1 = R^2 = Ac$), however, gave the 20-ketal (IV; $R^1 = R^2 = Ac$) in quantitative yield; in the absence of benzene the yield was only 80%. The 20-ketal (IV; $R^1 = R^2 = Ac$) was readily hydrolysed by ethanolic sodium hydroxide to the required 20-ketal (IV; $R^1 = R^2 = H$); it seems improbable that this procedure can have led to inversion at C-17, (A) ⟶ (B), although the molecular rotation difference between the diacetate and the diol, $\Delta[M_D]$ −340°, is rather large. The 20-ketal (IV; $R^1 = R^2 = H$) with ethyl chloroformate–pyridine



yielded the 3α-ester (IV; $R^1 = CO_2Et$, $R^2 = H$), which by oxidation with chromium trioxide–pyridine gave 3α-ethoxycarbonyloxy-5β-pregnane-12,20-dione 20-monoketal (V). With 1·3 mol. of bromine the product (V) yielded, not an 11-monobromide,[17] but a dibromo-compound, whose infrared-spectral properties were in agreement with those expected for the 11α,17α- or 11α,21-dibromo-derivative [Δν +20 cm.$^{-1}$]. Selenium dioxide and lead tetra-acetate oxidation, necessarily carried out in neutral media, of (V) were unsuccessful, and attempted hydroxymethylation resulted only in hydrolysis of the ester group.

Treatment of 3α,12α-dihydroxy-5β-pregnan-20-one (I; $R^1 = R^2 = H$) with ethyl chloroformate–pyridine gave the 3α-ester (I; $R^1 = CO_2Et$, $R^2 = H$), which by oxidation with the Jones reagent[18] yielded 3α-ethoxycarbonyloxy-5β-pregnane-12,20-dione (VII; $R = CO_2Et$, X = O). It has been observed[19,20] that 12,20-dioxopregnanes in the presence of methanol may give 12-hemiacetals, which are stabilised by hydrogen bonding with the 20-carbonyl group (C) ⟶ (D), and characterised by the appearance of an intense infrared band at 3340 cm.$^{-1}$, corresponding to an intramolecularly bonded hydroxyl group, disappearance of the stretching frequency, $\nu_{max.}$ 1710—1706 cm.$^{-1}$, of the 12-carbonyl group, and a bathochromic shift of ~15 cm.$^{-1}$ of the stretching frequency, $\nu_{max.}$ 1710—1700 cm.$^{-1}$, of the 20-carbonyl group:



The 12,20-diketone (VII; $R = CO_2Et$, X = O), although recrystallised from methanol, did not undergo the transformation (C) ⟶ (D); it gave correct analytical figures, and its infrared spectrum showed both the 12- and the 20-carbonyl stretching frequencies, $\nu_{max.}$ 1708, 1702 cm.$^{-1}$, respectively, but no hydroxyl band in the 3350 cm.$^{-1}$ region. Although 5β-pregnane-3,12,20-trione with ethylene glycol and toluene-*p*-sulphonic acid yielded the 3,12-bisketal ($\nu_{max.}$ 1702, 1350 cm.$^{-1}$; optical rotatory dispersion curve characteristic of a pregnan-20-one), similar treatment of the 12,20-dione (VII; $R = CO_2Et$,

[17] Seebeck and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 536.
[18] Bowden, Heilbron, E. R. H. Jones, and Weedon, *J.*, 1946, 39; Bowers, Halsall, E. R. H. Jones, and Lemin, *J.*, 1953, 2548; Djerassi, R. R. Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.
[19] Cameron, Evans, Hamlet, Hunt, P. G. Jones, and Long, *J.*, 1955, 2807.
[20] Wall and Serota, *Tetrahedron*, 1960, **10**, 238.

X = O) furnished the 12,20-bisketal. However, exchange with 2-ethyl-2-methyl-1,3-dioxolan afforded the 12-monoketal in excellent yield; this, by reduction with sodium borohydride in refluxing methanol, gave, with simultaneous hydrolysis of the 3α-ethoxycarbonyloxy-group, and after removal of the 12-ketal grouping with toluene-*p*-sulphonic acid in acetone, 3α,20β-dihydroxy-5β-pregnan-12-one (VII; R = H, X = H,OH). 20-Oxopregnanes by reduction with sodium borohydride [21] or with lithium aluminium hydride [22] give predominantly or exclusively the 20β-ols as the result of sterically controlled asymmetric induction.[23] Oxygen functions in the neighbourhood of the 20-carbonyl group may influence its orientation,[24,25] and so alter the proportions of the epimeric 20-ols produced; it seems improbable that the 12-ketal grouping can act in this way, and sodium borohydride, unlike lithium aluminium hydride, does not form a complex [26] with a carbonyl group prior to its reduction. We therefore formulate our reduction product as the 12α,20β-diol (VII; R = H, X = H,OH). The 3α,20β-diacetate (VII; R = Ac, X = H,OAc) by oxidation with selenium dioxide [27] gave 3α,20β-diacetoxy-5β-pregn-9(11)-en-12-one (VIII) in 57% overall yield from the starting material (I; $R^1 = R^2 = H$). Ozonolysis of (VIII) gave the desired 9-oxo-11,12-seco-11-nor-5β-pregnan-12-oic acid (IX; R = H), characterised as the methyl ester (IX; R = Me), but only in 4% yield and this approach had to be abandoned. During these experiments, Engel and Herculak [28] reported a similar preparation of the methyl ester (IX; R = Me) in which they encountered very poor yields, although Engel *et al.*[29] recorded the similar preparation of the 5α-oxo-acid analogous to (IX; R = H) in 65% yield.

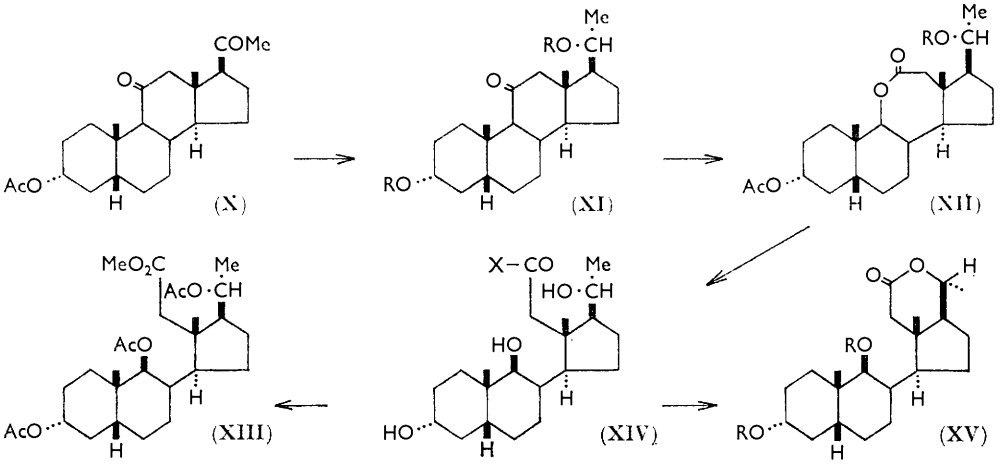
Another approach required a suitable 5β-pregnan-11-one. 3α-Acetoxy-5β-pregnan-11,20-dione (X) was reduced with sodium borohydride in methanol with concomitant hydrolysis of the 3α-acetyl group to 3α,20β-dihydroxy-5β-pregnan-11-one (XI; R = H). It has been shown [21] that 11,20-dioxopregnanes, by reduction with sodium borohydride in methanol, give stereospecifically the 11-oxo-20β-ols; an oxygen function at C-11, unlike one at C-12,[24,25] is thus too remote from the 20-carbonyl group to affect the stereochemical course of reduction. The 3α,20β-diacetate (XI; R = Ac) was not attacked by *m*-chloroperbenzoic acid or by permaleic acid, but use of trifluoroperacetic acid gave the c-homo-9 ⟶ 11-lactone (XII; R = Ac) in excellent yield. In the initial preparations of this lactone, disodium hydrogen phosphate was used as a buffer [30] to prevent transesterification of the acetate groups and the yield of lactone was variable, whilst if an excess of the buffer was used, no reaction occurred; in the absence of the buffer, the lactone was formed in 80% yield with a negligible amount (2—4%) of transesterification. Alkaline hydrolysis of the lactone (XII; R = Ac) followed by acidification with 2N-acetic acid at 0° gave 3α,9β,20β-trihydroxy-9,11-seco-5β-pregnan-11-oic acid (XIV; X = OH), which was characterised as the methyl ester triacetate (XIII). Acidification of the alkaline hydrolysis solution with a slight excess of dilute hydrochloric acid gave the 3α,9β-dihydroxy-11 ⟶ 20-lactone (XV; R = H), which was characterised as the diacetate (XV; R = Ac). This diacetate was also obtained when the sodium salt (XIV; X = ONa) of the trihydroxy-acid was treated with acetic anhydride–pyridine at 20°.

Prolonged refluxing of the methyl ester triacetate (XIII) or the corresponding trihydroxy-ester (XIV; X = MeO) with hydrazine hydrate in ethanol gave the non-crystalline hydrazide (XIV; $X = NH{\cdot}NH_2$), $\nu_{max.}$ 1690, 1640 cm.$^{-1}$; the material was soluble in 2N-hydrochloric acid, but attempts to obtain a crystalline hydrochloride, hydrobromide, or

[21] Norymberski and Woods, *J.*, 1955, 3426.
[22] Klyne and Miller, *J.*, 1950, 1972.
[23] Cram and Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828; Cram and Greene, *ibid.*, 1953, **75**, 6005.
[24] Just and Nagarajan, *Canad. J. Chem.*, 1961, **39**, 548.
[25] Heusler and Wettstein, *Helv. Chim. Acta*, 1962, **45**, 347.
[26] Wheeler and Huffman, *Experientia*, 1960, **16**, 516.
[27] McKenzie, Mattox, L. L. Engel, and Kendall, *J. Biol. Chem.*, 1948, **173**, 271.
[28] C. R. Engel and Herculak, *Canad. J. Chem.*, 1959, **37**, 2031.
[29] C. R. Engel, Rakhit, and Herculak, *Canad. J. Chem.*, 1962, **40**, 921.
[30] Emmons and Pagano, *J. Amer. Chem. Soc.*, 1955, **77**, 89; Emmons and Lucas, *ibid.*, p. 2287.

perchlorate were unsuccessful. The hydrazide by treatment with nitrous acid yielded the azide, (XIV; X = N_3), m. p. 57—60° (decomp.). When the diazotisation was carried out in a two-phase system, and the dry benzene solution of the azide heated, instead of the expected isocyanate a mixture of the 3α,20β-dihydroxy-C-homo-11 ⟶ 9-lactone (XII; R = H) (5%) and the 3α,9β-dihydroxy-11 ⟶ 20-lactone (XV; R = H) (90%) was formed. It appears that proximity of the 20β-hydroxyl group to the 11-carbonyl group leads preferentially to S_N2 substitution at C-11 with loss of azide ion: N_3–CO OH–CMe.

An attempt to prepare the amide from the methyl ester triacetate (XIII) by treatment with liquid ammonia for 16 hr. was unsuccessful; use of a solution of ammonia (*d* 0·880) in



ethanol gave mainly the acid (XIV; X = OH) together with a small amount (10%) of material, $\nu_{max.}$ 1690, 1620 cm.$^{-1}$, assumed to be the desired amide (XIV; X = NH_2) but insufficient for further experimentation.

The degradation of the 3α,9β,20β-trihydroxy-acid (XIV; X = OH) and subsequent reconstitution of ring C to give 11-azapregnanes is being investigated.

Experimental

For general directions see *J.*, 1959, 345; $[\alpha]_D$'s refer to chloroform solutions at room temperature. Infrared spectra were recorded in Nujol mulls, unless otherwise specified, on Perkin-Elmer Infracord 137 and 221 instruments. Nuclear magnetic resonance spectra were determined on a Varian D.P. 60 instrument at 60 Mc./sec., with deuterochloroform as solvent and tetramethylsilane as internal reference; the charts were calibrated by the audio side-band technique. Spence type H alumina was used for chromatography; deactivated alumina was prepared by treatment with ethyl acetate for 3 days, washing with methanol, water, and again methanol, then drying at 100°. Samples for analysis were dried at 70°/0·5 mm. for 4 hr.

12α-Acetoxy-3α-hydroxy-5β-pregnan-20-one (I; R^1 = H, R^2 = Ac).—A solution of 3α,12α-diacetoxy-5β-pregnan-20-one (350 mg.) in chloroform (0·5 ml.) was treated with a 2% solution of potassium carbonate in 90% methanol (20 ml.) at 20° for 12 hr. Dilution with water gave the 12α-monoacetate (240 mg.), m. p. 204—206°, $[\alpha]_D$ +160° (*c* 0·9) (lit.,[10] m. p. 208—210°, $[\alpha]_D$ +157°), $\nu_{max.}$ 1730, 1696 cm.$^{-1}$ (Found: C, 73·2; H, 9·8. Calc. for $C_{23}H_{36}O_4$: C, 73·4; H, 9·6%), after crystallisation from aqueous methanol.

12α-Acetoxy-5β-pregnane-3,20-dione (II; R = Ac).—12α-Acetoxy-3α-hydroxy-5β-pregnan-20-one (210 mg.), dissolved in acetone (20 ml.), was treated dropwise with Jones reagent[18] (0·2 ml.), kept at 20° for 5 min., and diluted with water. Extraction with ether (2 × 100 ml.) and the usual working up gave the 12α-acetoxy-3,20-dione (160 mg.), as the polymorph, m. p. 121—123°, $[\alpha]_D$ +154° (*c* 1·2) (lit.,[10] m. p. 121—122°; [11] m. p. 132—135°; [12] m. p. 130—131°,

[α] +159°), $\nu_{max.}$ 1735, 1712, 1702 cm.$^{-1}$ (Found: C, 73·5; H, 9·3. Calc. for $C_{33}H_{34}O_4$: C, 73·8; H, 9·2%) after crystallisation from ether–hexane.

12α-*Hydroxy*-5β-*pregnane*-3,20-*dione* (II; R = H).—The foregoing acetate (140 mg.) was refluxed with 5% methanolic potassium hydroxide (10 ml.) for 3 hr., the solution cooled, and diluted with water (10 ml.). The crystalline precipitate was collected and recrystallised from aqueous methanol to yield the 12α-hydroxy-3,20-dione (110 mg.), m. p. 179—183°, $[\alpha]_D$ +135° (*c* 1·0) (lit.,[11] m. p. 182—184°, $[\alpha]_D$ +135°), $\nu_{max.}$ 3550, 1705, 1698 cm.$^{-1}$ (Found: C, 75·5; H, 9·9. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·7%). The 12α-toluene-*p*-sulphonate was obtained by treatment of the compound (480 mg.) with toluene-*p*-sulphonyl chloride (500 mg.) in pyridine (10 ml.) at 0° and keeping at 30° for 6 days; the usual isolation procedure, chromatography on deactivated alumina with elution by ether–benzene (1 : 1), and recrystallisation from ether–hexane gave colourless needles (380 mg.), m. p. 120—125°.

5β-*Pregn*-11-*ene*-3,20-*dione* (III).—12α-Toluene-*p*-sulphonoxy-5β-pregnane-3,20-dione (380 mg.) was absorbed on basic alumina in benzene and left overnight. Elution with ether gave 5β-pregn-11-ene-3,20-dione, m. p. 132—134°, $[\alpha]_D$ +89° (*c* 0·8) (lit.,[12] m. p. 132—133°, $[\alpha]_D$ +85°; [13] m. p. 133—134°, $[\alpha]_D$ +91°), $\nu_{max.}$ 1712, 1705 cm.$^{-1}$ (Found: C, 79·8; H, 9·3. Calc. for $C_{21}H_{30}O_2$: C, 80·2; H, 9·6%); n.m.r. spectrum: quaternary 13-methyl group allylic to the 11,12-double bond as a 3-proton singlet at τ 9·04, superimposed on the quaternary 10-methyl group as a 3-proton singlet at τ 9·04 (cf. 5β-cholestane, τ 9·10), H-11 τ 4·03 ($J_{11,12}$ = 11 c./sec., $J_{9,11}$ = 3 c./sec.), H-12 τ 4·49 ($J_{11,12}$ = 11 c./sec., $J_{9,12}$ = 1·8 c./sec.). The 3,20-bisketal prepared in the usual way, did not crystallise, although the product showed no infrared carbonyl absorption peaks, and by hydrolysis with toluene-*p*-sulphonic acid in acetone at 20° overnight quantitatively regenerated the parent dione.

11α,12α-*Dihydroxy*-5β-*pregnane*-3,20-*dione* (VI).—5β-Pregn-11-ene-3,20-dione (200 mg.) was treated with osmium tetroxide (200 mg.) in ether (30 ml.) at 20° for 3 days. Hydrogen sulphide was passed through the solution for 0·5 hr., ether (100 ml.) added, and the solution well washed with water. The ethereal solution was filtered through alumina, the residual material eluted with chloroform, and the solvents evaporated to give the 11α,12α-osmate ester (120 mg.) as black lustrous prisms, m. p. 178—183°. The ester, dissolved in ethanol–pyridine (1 : 2; 15 ml.), was heated with a solution of sodium hydrogen sulphite (0·9 g.) in water (15 ml.) at 90° for 6 hr. Extraction with chloroform and the usual working up gave 11α,12α-*dihydroxy*-5β-*pregnane*-3,20-*dione* (45 mg.), m. p. 242—245°, $[\alpha]_D$ +62° (*c* 0·4), $\nu_{max.}$ 3500—3300, 1705, 1692 cm.$^{-1}$ (Found: C, 72·4; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%).

3α,12α-*Diacetoxy*-20,20-*ethylenedioxy*-5β-*pregnane* (IV; $R^1 = R^2$ = Ac).—3α,12α-Diacetoxy-5β-pregnan-20-one (1·4 g.), toluene-*p*-sulphonic acid (70 mg.), ethylene glycol (2 ml.), and benzene (70 ml.) were refluxed in a Dean–Stark water separator for 7 hr. The cooled mixture was treated with excess of sodium hydrogen carbonate and worked up in the usual way to give 3α,12α-*diacetoxy*-20,20-*ethylenedioxy*-5β-*pregnane* (1·6 g.), m. p. 144—145°, $[\alpha]_D$ +104° (*c* 0·6), $\nu_{max.}$ 1735, 1730 cm.$^{-1}$ (Found: C, 70·1; H, 9·1. $C_{27}H_{42}O_6$ requires C, 70·1; H, 9·2%). Hydrolysis with 5% methanolic potassium hydroxide under reflux, dilution to incipient turbidity, and cooling yielded 20,20-*ethylenedioxy*-3α,12α-*dihydroxy*-5β-*pregnane* (IV; $R^1 = R^2$ = H), m. p. 85—90° and 158—159°, $[\alpha]_D$ +37° (*c* 1·6), $\nu_{max.}$ 3400—3300 cm.$^{-1}$ (Found: C, 72·8; H, 10·1. $C_{23}H_{38}O_4$ requires C, 73·0; H, 10·3%), after recrystallisation from aqueous methanol.

20,20-*Ethylenedioxy*-3α-*ethoxycarbonyloxy*-12α-*hydroxy*-5β-*pregnane* (IV; $R^1 = CO_2Et$, R^2 = H).—The 3α,12α-dihydroxy-20-ketal (IV; $R^1 = R^2$ = H) (100 mg.) dissolved in pyridine (10 ml.), was treated dropwise with ethyl chloroformate (0·5 ml.) at 20° and the mixture kept at 20° for 20 hr. Dilution with water, ether extraction, and the usual working up, followed by chromatography on alumina and elution with ether–hexane (1 : 1) gave the *ester* (80 mg.), m. p. 124—128°, $[\alpha]_D$ +58° (*c* 0·4), $\nu_{max.}$ 3600, 1747 (EtO·CO·O) cm.$^{-1}$ (Found: C, 69·4; H, 9·5. $C_{26}H_{42}O_6$ requires C, 69·3; H, 9·4%), after recrystallisation from ether–hexane.

20,20-*Ethylenedioxy*-3α-*ethoxycarbonyloxy*-5β-*pregnan*-12-*one* (V).—The 12α-ol (IV; R_1 = CO_2Et, R^2 = H) (100 mg.), dissolved in pyridine (10 ml.) was treated with an excess of chromium trioxide–pyridine complex at 20° for 2 hr. Water was added, and the product extracted with ether; the ethereal extract was worked up in the usual way, and pyridine removed by co-distillation with ethanol *in vacuo*. Crystallisation from ether–hexane gave the *oxo-ester* (95 mg.), m. p. 204—205°, $[\alpha]_D$ +99° (*c* 0·6), $\nu_{max.}$ 1742 (EtO·CO·O), 1710 cm.$^{-1}$ (12-CO) (Found: C, 70·0; H, 8·9. $C_{26}H_{40}O_6$ requires C, 69·6; H, 8·9%).

11α,21-(or 11α,17α)-*Dibromo*-20,20-*ethylenedioxy*-3α-*ethoxycarbonyloxy*-5β-*pregnan*-12-*one*.—

The 12-ketone (V) (38 mg.), in benzene (6 ml.) was treated dropwise with a solution of bromine (20 mg.; 1·3 mol.) in benzene at 20° during 0·5 hr. The solvent was removed *in vacuo*, and the residue recrystallised from ether–hexane to give the *dibromo-compound* (18 mg.), m. p. 185—187°, $\nu_{max.}$ 1740 (EtO·CO·O), 1730 cm.$^{-1}$ (CHBr·CO) (Found: C, 51·6; H, 6·4. $C_{26}H_{38}Br_2O_6$ requires C, 51·6; H, 6·4. $C_{26}H_{38}Br_2O_6$ requires C, 51·5; H, 6·3%). Numerous other experiments conducted in chloroform, ether, or acetic acid gave only the same dibromide.

3,3:12,12-*Bisethylenedioxy*-5β-*pregnan*-12-*one*.—5β-Pregnane-3,12,20-trione[10] (100 mg.), toluene-*p*-sulphonic acid (5 mg.), ethylene glycol (1 ml.), and benzene (70 ml.) were refluxed together in a Dean–Stark water separator for 4 hr. to afford, after the usual isolation procedure, the 3,3:12,12-*bisethylenedioxy-derivative* (76 mg.), m. p. 160—162°, $[\alpha]_D$ +121° (*c* 2·0), $\nu_{max.}$ 1700 (20-CO), 1350 cm.$^{-1}$ (COMe) (Found: C, 71·6; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%), after recrystallisation from aqueous methanol containing a trace of pyridine.

3α-*Ethoxycarbonyloxy*-12α-*hydroxy*-5β-*pregnan*-20-*one* (I; $R^1 = CO_2Et$, $R^2 = H$).—3α,12α-Dihydroxy-5β-pregnan-20-one (I; $R^1 = R^2 = H$) (2 g.), dissolved in pyridine (10 ml.), was treated dropwise with ethyl chloroformate (1 ml.), and the mixture kept at 20° for 40 hr. Dilution with water and the usual working up gave the *oxo-ester* (1·9 g.), m. p. 140—142°, $[\alpha]_D$ +116° (*c* 1·0), $\nu_{max.}$ 3450 (OH), 1730 (EtO·CO·O), 1695 cm.$^{-1}$ (20-CO) (Found: C, 70·7; H, 9·6. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·4%), after recrystallisation from aqueous methanol.

3α-*Ethoxycarbonyloxy*-5β-*pregnane*-12,20-*dione* (VII; R = CO_2Et, X = O).—The above 12α-ol (320 mg.), dissolved in acetone, was treated dropwise with the Jones reagent[18] (0·4 ml.), the mixture diluted with water, and extracted with ether. The usual working up gave the *dione* (300 mg.), m. p. 135—136°, $[\alpha]_D$ +180° (*c* 1·5), $\nu_{max.}$ 1742 (EtO·CO·O), 1708 (12-CO), 1702 cm.$^{-1}$ (20-CO) (Found: C, 71·6; H, 8·8. $C_{24}H_{36}O_5$ requires C, 71·3; H, 9·0%), after crystallisation from aqueous methanol. The 12,12:20,20-*bisethylenedioxy-derivative* (85 mg.) was produced by heating the 12,20-dione (100 mg.), toluene-*p*-sulphonic acid (5 mg.), ethylene glycol (1 ml.), and benzene (80 ml.) under reflux in a Dean–Stark water separator for 4 hr., and had m. p. 153—154°, $[\alpha]_D$ +84° (*c* 1·2), $\nu_{max.}$ 1735 cm.$^{-1}$ (EtO·CO·O) (Found: C, 67·9; H, 8·9. $C_{28}H_{44}O_7$ requires C, 68·3; H, 9·0%), after crystallisation from aqueous methanol containing a trace of pyridine. The 12,12-ethylenedioxy-derivative was obtained by refluxing (air-condenser) the 12,20-dione (70 mg.) and toluene-*p*-sulphonic acid (5 mg.) in 2-ethyl-2-methyl-1,3-dioxolan (7 ml.) for 4 hr.; evaporation *in vacuo* and recrystallisation of the residue from aqueous methanol containing a trace of pyridine gave the 12,12-*ethylenedioxy-derivative* (64 mg.), m. p. 187—189°, $[\alpha]_D$ +144° (*c* 0·5), $\nu_{max.}$ 1740 (EtO·CO·O), 1699 cm.$^{-1}$ (20-CO) (Found: C, 70·0; H, 9·0. $C_{26}H_{40}O_6$ requires C, 69·6; H, 9·0%).

3α,20β-*Dihydroxy*-5β-*pregnan*-12-*one* (VII; R = H, X = H,OH).—The above 12,12-ethylenedioxy-derivative (78 mg.) was refluxed with sodium borohydride (50 mg.) in methanol for 1 hr., the solution cooled, diluted with water, and extracted with chloroform. The usual isolation procedure gave 12,12-*ethylenedioxy*-3α,20β-*dihydroxy*-5β-*pregnane* (60 mg.), m. p. 159—160°, $[\alpha]_D$ +54° (*c* 0·7), $\nu_{max.}$ 3450, 3400 cm.$^{-1}$ (OH) (Found: C, 73·0; H, 10·4. $C_{23}H_{38}O_4$ requires C, 73·0; H, 10·3%), after crystallisation from ether–hexane. The ketal (100 mg.) and toluene-*p*-sulphonic acid (5 mg.) were refluxed in acetone (100 ml.) for 4 hr. Evaporation *in vacuo* and recrystallisation of the residue from acetone–hexane yielded 3α,20β-*dihydroxy*-5β-*pregnan*-12-*one* (86 mg.), m. p. 200° with transformation of plates to needles, m. p. 223—225°, $\nu_{max.}$ 3400—3300 (OH), 1690 cm.$^{-1}$ (12-CO) (Found: C, 75·1; H, 10·3. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·3%). The *diacetate*, obtained with acetic anhydride–pyridine at 90° for 4 hr., had m. p. 139—140°, $[\alpha]_D$ +96° (*c* 0·8), $\nu_{max.}$ 1735 (OAc), 1702 cm.$^{-1}$ (12-CO) (Found: C, 71·4; H, 8·9. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%), after crystallisation from hexane.

3α,20β-*Diacetoxy*-5β-*pregn*-9(11)-*en*-12-*one* (VIII).—A solution of 3α,20β-diacetoxy-5β-pregnan-12-one (VII; R = Ac, X = H,Ac) (100 mg.) in acetic acid (15 ml.) was refluxed with selenium dioxide (300 mg., freshly sublimed) and 48% hydrobromic acid (0·02 ml.), under nitrogen for 23 hr. The cooled mixture was filtered, diluted with hexane (100 ml.), and washed well with water, 2N-sodium hydroxide, and water. The dried solution was concentrated and chromatographed on alumina (3 g.) in hexane; elution with ether–hexane (1 : 5) gave 3α,20β-*diacetoxy*-5β-*pregn*-9(11)-*en*-20-*one* (76 mg.), m. p. 180—184°, $\nu_{max.}$ 241 mμ (log ε 4·12), $\nu_{max.}$ (CCl_4) 1727 (Ac), 1684 cm.$^{-1}$ (C=C·CO), $\nu_{max.}$ 1727, 1721, 1670, 1597 cm.$^{-1}$ (Found: C, 71·8; H, 9·0. $C_{25}H_{36}O_3$ requires C, 72·1; H, 8·7%) after recrystallisation from hexane.

Methyl 3α,20β-*Diacetoxy*-9-*oxo*-9,11-*seco*-11-*nor*-5β-*pregnan*-12-*oate* (IX; R = Me).—3α,20β-Diacetoxy-5β-pregn-9(11)-en-20-one (VIII) (1·5 g.), dissolved in acetic acid–ethyl acetate (1 : 1;

60 ml.), was treated with ozonised oxygen (6% ozone; 100 ml./min.) at 0° for 10 hr.; hydrogen peroxide (10 ml.; 30 vol.) was then added, and the mixture kept at 20° overnight. The neutral fraction, after reacetylation with acetic anhydride–pyridine at 20° for 16 hr. and chromatography on alumina, yielded starting material (270 mg.). The acidic fraction was esterified with ethereal diazomethane, and the crude methyl ester treated with acetic anhydride–pyridine at 20° for 20 hr. The product was chromatographed on alumina in hexane; elution with ether–hexane (2 : 3) gave methyl 3α,20β-diacetoxy-9-oxo-9(11)-seco-11-nor-5β-pregnan-12-oate (56 mg.), m. p. 123—125°, $[\alpha]_D$ +27° (*c* 0·7) (lit.,[28] m. p. 126—127°, $[\alpha]_D$ +30°), $\nu_{max.}$ 1735—1720 (ester CO's), 1700 cm.$^{-1}$ (9-CO) (Found: C, 67·0; H, 8·7. Calc. for $C_{25}H_{38}O_7$: C, 66·6; H, 8·5%), after crystallisation from ether–hexane.

3α,20β-*Diacetoxy*-5β-*pregnan*-11-*one* (XI; R = Ac).—3α-Acetoxy-5β-pregnane-11,20-dione (X) (5 g.), dissolved in ethanol (100 ml.), was treated with sodium borohydride (2·5 g.) added gradually at 20° during 6 hr. The usual isolation procedure gave the crystalline 3α,20β-diol, which was acetylated with acetic anhydride–pyridine at 20° for 30 hr. The resultant product was chromatographed on deactivated alumina in hexane; elution with hexane gave 3α,20β-*diacetoxy*-5β-*pregnan*-11-*one* (4·2 g.), m. p. 158—160°, $[\alpha]_D$ +85° (*c* 1·2), $\nu_{max.}$ 1735 (OAc), 1708 cm.$^{-1}$ (11-CO) (Found: C, 71·9; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%), after recrystallisation from ether–hexane.

3α,20β-*Diacetoxy*-9β-*hydroxy*-9,11-*seco*-5β-*pregnan*-11-*oic Acid* 11 ⟶ 9β-*Lactone* (XII; R = Ac).—Trifluoroacetic anhydride (5·1 ml.) was added dropwise to a suspension of hydrogen peroxide (87%; 0·8 ml.) in methylene chloride; this solution was added to 3α,20β-diacetoxy-5β-pregnan-11-one (XI; R = Ac) (0·6 g.) in methylene chloride (30 ml.), and the mixture refluxed for 5 hr. After cooling and dilution with water, the product was extracted with benzene, and worked up in the usual way; repeated recrystallisation from benzene–hexane gave the *lactone* (XII; R = Ac) (0·4 g.), m. p. 210—212°, $[\alpha]_D$ +77° (*c* 1·2), $\nu_{max.}$ 1740—1720 cm.$^{-1}$ (Found: C, 69·3; H, 9·1. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

Methyl 3α,9β,20β-*Triacetoxy*-9,11-*seco*-5β-*pregnan*-11-*oate* (XIII).—The lactone (XII; R = Ac) (200 mg.) was refluxed with 5% ethanolic sodium hydroxide (20 ml.) for 3 hr. The solution was cooled to 0°, acidified to pH 5 with a minimum of ice-cold 10% acetic acid, and extracted with chloroform (5 × 100 ml.). Evaporation of the dried extract *in vacuo* gave the acid (XIV; X = OH) as a colourless glass, which was dissolved in methanol (2 ml.) and treated with a slight excess of ethereal diazomethane. The solvents were removed under reduced pressure and the methyl ester acetylated with acetic anhydride–pyridine at 20° for 20 hr.; the mixture was diluted with ice–water, and the precipitate collected, roughly dried, and recrystallised from aqueous methanol to give *methyl* 3α,9β,20β-*triacetoxy*-9,11-*seco*-5β-*pregnan*-11-*oate* (140 mg.), m. p. 132—137°, [α] +50° (*c* 0·9), $\nu_{max.}$ 1740—1720 cm.$^{-1}$ (Found: C, 66·2; H, 8·5. $C_{28}H_{44}O_8$ requires C, 66·1; H, 8·7%).

3α,9β,20β-*Trihydroxy*-9,11-*seco*-5β-*pregnan*-11-*oic Acid* 11 ⟶ 20β-*Lactone* (XV; R = H).—The 3α,20β-diacetoxy-11 ⟶ 9β-lactone (200 mg.) was hydrolysed as above; the cooled hydrolysate was acidified with 2N-hydrochloric acid and kept at 20° for 5 hr. The product was extracted with chloroform (4 × 100 ml.) and worked up in the usual way to give the 3α,9β,20β-*trihydroxy*-11 ⟶ 20β-*lactone* (XV; R = H), m. p. 232—234°, $[\alpha]_D$ +57° (*c* 0·8), $\nu_{max.}$ 3500—3400 (OH), 1740 cm.$^{-1}$ (δ-lactone) (Found: C, 71·7; H, 9·6. $C_{21}H_{35}O_4$ requires C, 72·0; H, 9·8%). The 3α,9β-*diacetate* was prepared (*a*) directly by use of acetic anhydride–pyridine at 20° for 16 hr., (*b*) by similar acetylation of the sodium salt (XIV; X = ONa), and had m. p. 214—216°, $\nu_{max.}$ 1740—1720 cm.$^{-1}$ (Found: C, 69·1; H, 8·5. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

3α,9β,20β-*Trihydroxy*-9,11-*seco*-5β-*pregnan*-11-*oic Acid Azide* (XIV; X = N_3).—A solution of methyl 3α,9β,20β-triacetoxy-9,11-seco-5β-pregnan-11-oate (XIII) (300 mg.) in ethanol (10 ml.) was treated with hydrazine hydrate (10 ml.) and the mixture refluxed for 30 hr.; ethanol was removed by distillation and the residue heated at 110° for 30 min. Dilution with water, extraction with chloroform (5 × 20 ml.), and the usual working up gave the 3α,9β,20β-trihydroxy-hydrazide (XIV; X = NH·NH_2) (240 mg.) as a colourless glass, $\nu_{max.}$ 1690, 1640 cm.$^{-1}$ [–CO(NH)–] but no acetate absorption.

(*a*) The hydrazide (XIV; X = NH·NH_2) (100 mg.), dissolved in ice-cold N-hydrochloric acid (10 ml.), was treated dropwise with an excess of 0·1N-sodium nitrite; the flocculent precipitate was filtered off and washed thoroughly with water. No attempt was made to recrystallise the azide (XIV; X = N_3), which had m. p. 57—60° (decomp. >48°), $\nu_{max.}$ 2150 cm.$^{-1}$ (N_3).

(*b*) The hydrazide (XIV; X = $NH{\cdot}NH_2$) (100 mg.), dissolved in ice-cold N-hydrochloric acid (10 ml.) was added to a stirred mixture of ether–benzene (1 : 1; 50 ml.) and followed dropwise by an excess of 0·1N-sodium nitrite. The organic layer was worked up in the usual manner, and by complete evaporation in a vacuum at 20° gave the azide (XIV; X = N_3) $\nu_{max.}$ ($CHCl_3$) 2160 $cm.^{-1}$ (N_3).

Attempted Curtius Rearrangement of the Azide (XIV; X = N_3).—A solution of the azide (120 mg.) in benzene was heated at 80° for 0·25 hr. and the solvent completely removed *in vacuo*; the residue had no infrared absorption at or near 2200 $cm.^{-1}$ but showed a very strong band at 1710 $cm.^{-1}$ (in $CHCl_3$). The material was acetylated with acetic anhydride–pyridine at 100° for 1 hr., and after working up in the usual fashion, the product was crystallised from ether–hexane to give the 11 ⟶ 20β-lactone 3α,9β-diacetate (XV; R = Ac) (102 mg.), m. p. and mixed m. p. 214—216°; from the mother-liquor the c-homo-11 ⟶ 9-lactone 3α,20β-diacetate (XII; R = Ac) (5 mg.), m. p. and mixed m. p. 210°, was isolated.

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