Unsaturated Steroids. Part 9.[1] Synthesis of Some Aromatic Ring c Steroids

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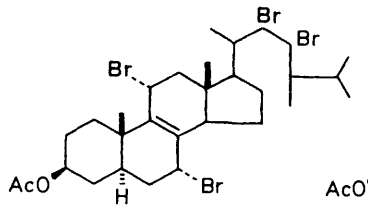
7α,11α,22α,23α-Tetrabromo-5α-ergost-8-en-3β-yl acetate (1) has been aromatised to 22α,23α-dibromo-12-methyl-18-nor-5α-ergosta-8,11,13-trien-3β-yl acetate (2) in solution by using an acidic catalyst. Stepwise removal of the side-chain from 12-methyl-18-nor-5α-ergosta-8,11,13,22-tetraen-3β-yl acetate (5) afforded successively the C-22 aldehyde (6), the C-20 ketone (8), and 3β-hydroxy-12-methyl-18-nor-5α-androsta-8,11,13-trien-17-one (18) Associated derivatives are described; certain reaction mechanisms have been clarified.

In contrast to aromatic ring A steroids, aromatic ring C steroids are not easily accessible. One of the few routes to aromatic ring C derivatives from readily available steroids is that of Stevenson *et al.*,[2] who demonstrated that the major product (*ca.* 45%) from the action of bromine on 3β-acetoxy-5α-ergosta-7,22-diene was the tetrabromo-derivative (1). Passage of (1) through Woelm alumina gave (2), the structure and absolute



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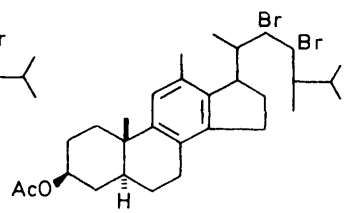

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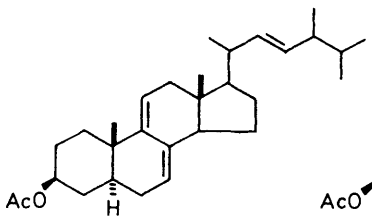

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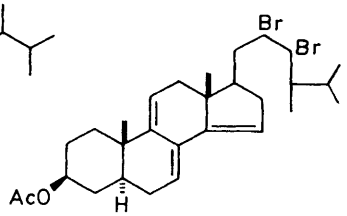


(4)

stereochemistry of which were defined by *X*-ray crystallography.[3] The technical difficulties of this process are considerable: the products are frequently extremely difficult to crystallise; the bromo-derivative (1) is unstable and the yield variable; and the aromatisation step is critically dependent upon the type and quality of the alumina (ref. 2 and our own observations that *e.g.* Spence type H alumina does not cause aromatisation). We now report an improved method for this aromatisation reaction, clarification of the relevant reaction mechanisms, and the preparation of various derivatives of (2).

Thus, our initial investigations of the bromination of 3β-acetoxy-5α-ergosta-7,22-diene indicated the deleterious effect of acetic acid upon the bromo-derivative (1). This was confirmed in pilot experiments and a major modification of earlier processes[2,4] has produced a method amenable to large-scale manipulation and which gives, reproducibly, *ca.* 55% yields of (1).

The configuration of (1) at C-7 and C-11 has not been assigned previously, but general principles combined with the fact that (1) is obtained by the addition[4] of bromine to 3β-acetoxy-5α-ergosta-7,11,22-triene (3) strongly indicate that the halogens have the α-configuration.

During our initial investigations we observed that the stability of the tetrabromide (1) is extremely dependent on the solvent. Thus decomposition with evolution of hydrogen bromide occurs rapidly at room temperature (within ½ h) in chloroform or methylene chloride; conversely the compound is stable in benzene and dioxan, *i.e.* a solvent of high dielectric constant promotes decomposition. A selection of our experiments from a more systematic investigation of this phenomenon is recorded in Table 1, which indicates that (i) [experiments (a) and (b)] the rate of thermal decomposition is temperature dependent, (ii) [experiments (d)—(f)] dehydrobromination is accelerated by acidic catalysts, (iii) the initial product from dehydrobromination is the 7,9(11),14-triene[2] (4), and (iv) [experiments (d)—(g)] a dark green colour is produced in those experiments which result in aromatisation. This colouration is remarkably similar to that produced in the Tortelli–Jaffé test[5] for steroids containing a double bond which is, or which may become, tetrasubstituted. The overall conclusion from these experiments is that the primary product of the

Table 1 †

Decomposition of the tetrabromide (1)

Expt.	Solvent	Reagent	Time (h)	Major product	Yield (%)
(a)	Xylene		0.5	(4)	50
(b)	Benzene		2.5	(4)	50
(c)	Benzene	K_2CO_3	2.0	(4)	70
(d)	Xylene	TsOH cat.	0.25	(4) ‡	60
(e)	Xylene	TsOH 2M	0.25	(2)	60
(f)	Benzene	TsOH cat.	0.5	(4) ‡	60
(g)	Benzene	TsOH 2M	0.5	(2)	80

† Abbreviations: cat., catalytic quantity; 2M, 2 mol of TsOH to 1 mol of (1). ‡ Total product contained 10% of the ring C aromatic compound (2). In these cases the quoted yield refers to the recovery of (4).

[1] Part 8, R. Ahmad, D. Hands, S. L. Leung, J. M. Midgley, H. Safwat, and W. B. Whalley, preceding paper.

[2] C. F. Hammer, D. S. Savage, J. B. Thomson, and R. Stevenson, *Tetrahedron Letters*, 1963, 1261.

[3] T. M. Margulis, C. F. Hammer, and R. Stevenson, *J. Chem. Soc.*, 1964, 4396.

[4] R. C. Anderson, R. Stevenson, and F. S. Spring, *J. Chem. Soc.*, 1952, 2901.

[5] M. Tortelli and E. Jaffé, *Chem.-Ztg.*, 1915, **39**, 14; I. M. Heilbron and F. S. Spring, *Biochem. J.*, 1930, **24**, 133.

thermal decomposition of the tetrabromide (1), in a solvent which does not promote ionisation of C–Br bonds, is the 7,9(11),14-triene (4).

The novel and significant observation that the conversion (1) ⟶ (2) occurs with an acidic catalyst in solution has been applied to achieve this conversion in high, reproducible yield. The mechanism may be as follows: the tetrabromo-steroid (1), which possesses two allylic, readily ionisable C–Br bonds, may be represented as RHBr, which when heated in solution exists in equilibrium with bromide ion and the corresponding carbocation:

$$RHBr \rightleftharpoons RH^+ + Br^-$$

In the presence of a strong acid, toluene-*p*-sulphonic acid, the bromide ion forms hydrogen bromide, which is expelled from the boiling solution; the toluene-*p*-sulphonate anion then captures the equivalent proton from the carbocation RH^+, thus forming a new double bond in the steroid.

Although it is not valid to assume from the results in Table 1 that the conversion (1) ⟶ (2) proceeds by way of the triene (4), this possibility is compatible with the observations that (i) treatment of the triene (4) with acid yields (80%) the aromatic steroid (2), and (ii) when the tetrabromide (1) is treated with 1 mol. equiv. of toluene-*p*-sulphonic acid in boiling benzene (reaction monitored by n.m.r.) the initial product is the triene (4). Hence the aromatisation, under our conditions, of the tetrabromide (1) to yield (2) proceeds through the triene (4).

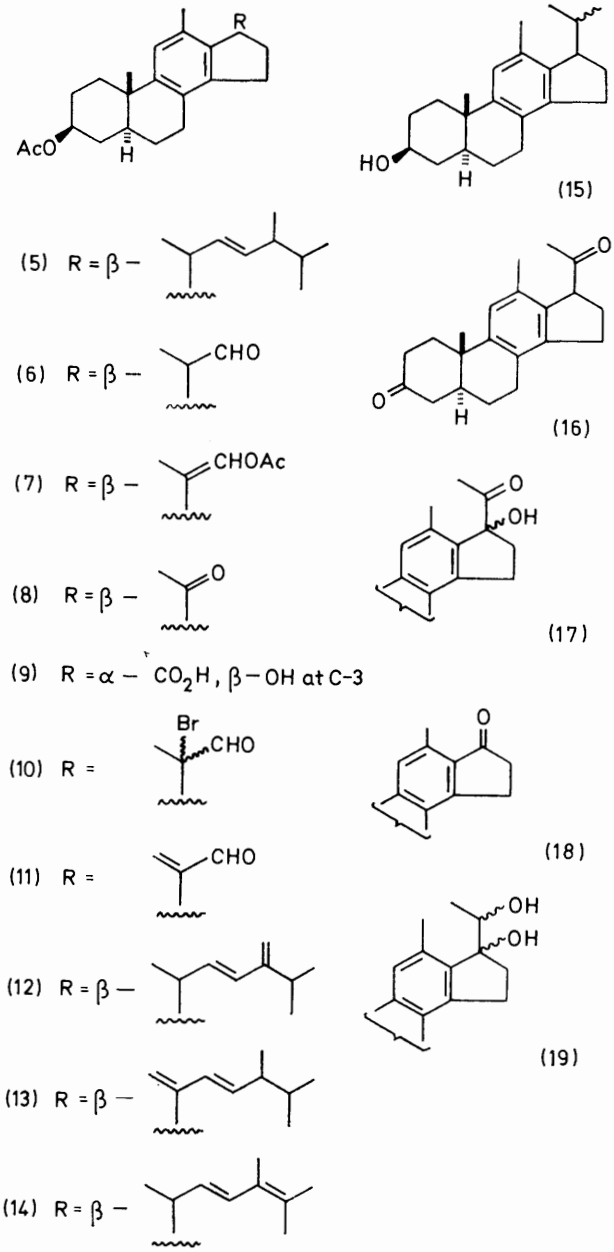
In derivatives of type (2) there is considerable steric interference between the C-12 methyl group and the 17β-substituent, with a consequent tendency for the larger group at C-17 to assume the α-configuration (*cf.* *e.g.* ref. 6). Consequently, when our process, using toluene-*p*-sulphonic acid, was applied to the aromatisation of (1) on a substantial scale we were not surprised that (2) was accompanied by the 17α-epimer. The extent of this epimerisation could be estimated from a comparison of the n.m.r. spectra of the derivatives (2), (5), and (6) (Table 2) and of the corresponding 17α-derivatives (recorded as τ values).

TABLE 2

N.m.r. data (τ values)

17β-Compounds	22-, 23-H	22-H	21-H_3	12-CH_3
(2)	5.49		9.13	7.72
(5)	5.03		9.35	7.72
(6)		0.53	9.86	7.67
17α-Compounds corresponding to				
(2)	5.55		9.19	7.70
(5)	4.60		9.41	7.74
(6)		0.16	9.15	7.75

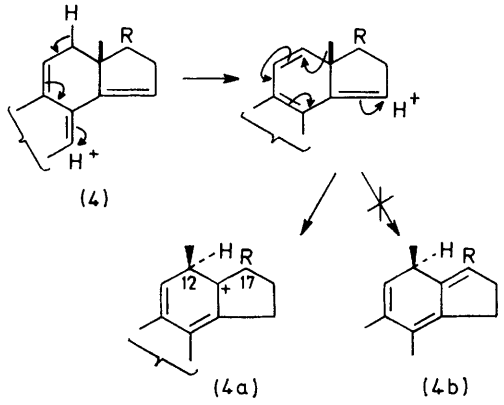
It was subsequently observed that the extent of epimerisation depended upon the concentration of toluene-*p*-sulphonic acid, so that 5 mol. equiv. gave a conversion of 80% of (1) into (2), with no detectable (n.m.r.) inversion at C-17. This observation may be understood from the following considerations. The aromatisation of the triene (4) may be formulated as in the Scheme, in which the cation (4a) has a discrete existence. Models indicate little difference in the relief of steric strain when either the C-12 or the C-17 proton



is eliminated. It may be assumed that a 4 molar excess of protons, made available from the almost completely ionised toluene-*p*-sulphonic acid, suppresses the ease of elimination of a proton from C-12 and C-17. Hence stabilisation of the carbocation (4a) proceeds essentially under thermodynamic control to yield (2) rather than under kinetic control to yield the thermodynamically less stable triene (4b), thereby preserving the β-stereochemistry of the side-chain at C-17.

[6] J. Meney, Y-Ho Kim, R. Stevenson, and T. N. Margulis, *Tetrahedron*, 1973, **29**, 21.

The derivative (2) is very difficult to crystallise and therefore was debrominated directly to the 22-ene (5), which was then converted by ozonolysis into the



SCHEME

aldehyde (6), a crystalline solid, previously obtained [7] as a gum from the 22,23-dihydroxy-derivative of (5). The corresponding enol acetate (7) was non-crystalline; ozonolysis gave the crystalline 3β-acetoxy-12-methyl-18-nor-5α-pregna-8,11,13-trien-20-one (8). This substance is characterised by the ease of isomerisation to the 17α-derivative, particularly with base, because of the 1,3-coplanar interaction of the CH_3CO residue and the *C*-methyl group at C-12. Thus treatment of (8) under the conditions of the iodoform reaction gave the 17-carboxylic acid (9), in which the carboxy-residue probably has the α-configuration. This assignment is in agreement with the lack of anti-inflammatory activity exhibited by this phenylacetic acid.[8]

In order to avoid epimerisation at C-17 during hydrolysis of the 3β-acetate (8), the ketone (8) was treated with lithium aluminium hydride to form the 3β,21ξ-diol (15). Oxidation of this in a two-phase system gave the 3,20-dione (16).

Oxidation of the C-20 ketone (8) with oxygen in the presence of potassium t-butoxide [9] followed by treatment of the resultant hydroperoxide (not isolated) with zinc–acetic acid gave a mixture of 3β-hydroxy-12-methyl-18-nor-5α-androsta-8,11,13-trien-17-one (18) and 3β,17ξ-dihydroxy-12-methyl-18-nor-5α-pregna-8,11,13-trien-20-one (17). Reduction of (17) with lithium aluminium hydride gave 12-methyl-18-nor-5α-androsta-8,11,13-trien-3β,17ξ,21ξ-triol (19). Oxidation of (19) or of (17) with lead tetra-acetate gave the 17-ketone (18).

In a search for an alternative route from the C-20 ketone (8) to the C-17 ketone (18), the ketone (8) was treated with methylmagnesium iodide to give the corresponding tertiary alcohol, which was very resistant to dehydration. Bromination of the C-22 aldehyde (6) readily gave the unstable bromo-derivative (10); dehydrobromination by 1,5-diazabicyclo[4.3.0]non-5-ene formed 12-methyl-22-formyl-18-nor-5α-pregna-8,11,13,-20-tetraen-3β-yl acetate (11), rather than the conjugated 17(20)-ene. In each case product development to yield a double bond in this position would bring the C-17 substituent close to the C-12 methyl group.

Previously we have shown [10] that dehydrobromination of 22,23-dibromo-5β-ergostane and cognate derivatives forms almost exclusively the 22,24(28)-dienes of type (12). Application of this process to (2) gave a non-crystalline, inseparable mixture of dienes, thought to consist of (12), (13), and (14) on the basis of the n.m.r. spectra (*cf.* ref. 11) and the formation from the mixed dienes on ozonolysis of (i) formaldehyde, (ii) (—)-α-methylisovaleraldehyde, (iii) the aldehyde (6), and (iv) acetone (all isolated and identified as their 2,4-dinitrophenylhydrazones).

5α-Cholest-7-en-3β-ol had been converted into 12-methyl-18-nor-5α-cholesta-8,11,13-trien-3β-yl acetate by a process similar to that used for the ergosterol analogue.

EXPERIMENTAL

Optical rotations are recorded for solutions in chloroform, and u.v. spectra for solutions in ethanol; ^{1}H n.m.r. spectra (60 MHz) are recorded for solutions in deuteriochloroform.

7α,11α,22α,23α-*Tetrabromo*-5α-*ergost*-8-*en*-3β-*yl Acetate* (1)—A solution of 5,6-dihydroergosteryl acetate (20 g) in warm ether (800 ml) was cooled *rapidly*, with *rapid* stirring, to −70 °C to ensure a finely divided suspension of steroid; acetic acid (25 ml) was then added, followed by bromine (3 ml), and vigorous stirring was continued. The mixture was maintained at −70 °C for 1 h, then the volume was reduced *in vacuo*, below 0 °C, to 400 ml. The solid product was collected and washed with cold (−5 °C) light petroleum (b.p. 40—60 °C) and dried over solid potassium hydroxide to yield 7α,11α,22α,23α-tetrabromo-5α-ergost-8-en-3β-yl acetate (20 g, 52%), which formed needles, m.p. 138° (lit.,[2] 130°) (from benzene); $[\alpha]_D^{22}$ +245° (*c* 1.5) [lit.,[2] +205° (in CCl_4)].

22α,23α-*Dibromo*-5α-*ergosta*-7,9(11),14-*trien*-3β-*yl Acetate* (4).—A solution of the tetrabromo-derivative (1) (1 g) in benzene (30 ml) was refluxed during 2.5 h with potassium carbonate (5 g). Purification of the product from acetone–methanol gave the title compound (0.52 g) in needles, m.p. 130° (lit.,[2] 128—131°); $[\alpha]_D^{22}$ −87° (*c* 1.1) (lit.,[2] −88°); τ 7.9 (3 H, s, $OCOCH_3$), 5.3 (1 H, m, H-3), and 4.5, 4.2, and 3.9 (m, H-7, -11, and -15); $\lambda_{max.}$ 228 (log ε 3.99), 236 (4.01), and 268 nm (3.96) (Found: C, 60.2; H, 7.4%; M^+, 596. Calc. for $C_{30}H_{44}Br_2O_2$: C, 60.4; H, 7.4%; *M*, 596).

22α,23α-*Dibromo*-12-*methyl*-18-*nor*-5α-*ergosta*-8,11,13-*trien*-3β-*yl Acetate* (2).—(*a*) Percolation of a solution in benzene (10 ml) of the tetrabromide (1) (2 g) through Woelm acidic alumina (activity I) (30 g) gave the aromatic steroid (2) in needles (0.6 g), m.p. 137° (from acetone–methanol) (lit.,[6] m.p. 136—137.5°); $[\alpha]_D^{22}$ −4° (*c* 1.6) (lit.,[7] −4°) (M^+, 596. $C_{30}H_{44}Br_2O_2$ requires *M*, 596).

(*b*) A solution of toluene-*p*-sulphonic acid (62 g) in benzene (800 ml) was refluxed in a Dean–Stark apparatus until removal of water was complete. The solution was

[7] C. F. Hammer, D. S. Savage, J. B. Thomson, and R. Stevenson, *Tetrahedron*, 1964, **20**, 929.
[8] We are indebted to Organon Ltd. for this information.
[9] D. H. R. Barton, G. Mellows, D. A. Widdowson, and J. J. Wright, *J. Chem. Soc.* (*C*), 1971, 1142.
[10] A. B. Garry, J. M. Midgley, W. B. Whalley, and B. J. Wilkins, *J.C.S. Chem. Comm.*, 1972, 167.
[11] U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 1969, **25**, 691, 2023.

then cooled to below the b.p. and 7α,11α,22α,23α-tetrabromo-5α-ergost-8-en-3β-yl acetate (50 g) was added in small portions so that frothing was not too vigorous. The mixture acquired a dark green fluorescence and copious evolution of hydrogen bromide occurred. When all the tetrabromide had been added, the mixture was refluxed for ½ h, cooled, washed with water, dried, and evaporated to yield 22α,23α-dibromo-12-methyl-18-nor-5α-ergosta-8,11,13-trien-3β-yl acetate (35 g), identical with that obtained by method (*a*).

(*c*) A solution of 22α,23α-dibromo-5α-ergosta-7,9(11),14-trien-3β-yl acetate (4) (1 g) and toluene-*p*-sulphonic acid (0.2 g) was refluxed during ½ h, to yield the aromatic steroid (2) (0.8 g), identical with that produced by methods (*a*) and (*b*).

(*d*) A suspension of the tetrabromo-derivative (1) (16.7 g) in acetic acid (300 ml) was warmed at 100 °C during 45 min. The resultant solution was poured onto ice and the product extracted with ether to yield the aromatic steroid (2) as a non-crystalline gum (13.6 g) containing (n.m.r.) the 17α-epimer. Chromatography on silica from benzene and elution with benzene–ether (95 : 5) gave the triene (2) (10.5 g).

3β-*Acetoxy*-12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*triene*-20α-*carbaldehyde* (6).—Ozonolysis of 12-methyl-18-nor-5α-ergosta-8,11,13,22-tetraen-3β-yl acetate (21 g) in dichloromethane–methanol–pyridine (50 : 50 : 1; 50 ml) was carried out at −70 °C and monitored by t.l.c. When reaction was complete, the excess of ozone was removed by a stream of nitrogen and the ozonide was decomposed by addition of trimethyl phosphite (at −70 °C). Chromatography on silica from benzene, followed by elution with benzene–ether (19 : 1) gave the *aldehyde* (6) (16.5 g) in plates, m.p. 141° (from ether–methanol); $[\alpha]_D^{18}$ +99° (*c* 0.8); $\nu_{max.}$ 1 720 cm^{-1} (C=O); τ 0.52 (1 H, d, *J* 1.5 Hz, CHO), 3.03 (1 H, s, H-11), 5.23 (1 H, m, H-3), 7.65 (3 H, s, 12-Me), and 7.94 (3 H, s, $OCOCH_3$) (Found: C, 78.0; H, 8.9%; M^+, 368. $C_{24}H_{32}O_3$ requires C, 78.2; H, 8.8%; *M*, 368).

The 2,4-*dinitrophenylhydrazone* formed yellow needles, m.p. 108—110° (from dioxan–water), containing 1 mol of dioxan of crystallisation; $[\alpha]_D^{20}$ +129° (*c* 0.52); $\lambda_{max.}$ 206 (log ε 4.68) and 358 nm (4.36) [Found: C, 64.3; H, 6.7; N, 8.7%; M^+, 548. $C_{30}H_{36}N_4O_6$,$C_4H_8O_2$ requires C, 64.1; H, 7.0; N, 8.8%; *M* (loss of dioxan), 548].

Deacetylation of this derivative at room temperature, during 4 h with methanolic sodium methoxide, gave the 2,4-dinitrophenylhydrazone in yellow needles, m.p. 196—198° (from ethanol) (Found: C, 66.3; H, 6.7; N, 11.0. Calc. for $C_{28}H_{34}N_4O_5$: C, 66.4; H, 6.8; N, 11.1%) (lit.,[7] m.p. 194—197°). Reduction of a solution of the aldehyde (6) (1 g) in ethanol (25 ml) during 1 h, with sodium borohydride (1 g) gave 20α-*hydroxymethyl*-12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-3β-*yl acetate* (0.8 g) in prisms, m.p. 162—164° (from ether); $[\alpha]_D^{20}$ +60° (*c* 1.3) (Found: C, 78.0; H, 9.3%; M^+, 370. $C_{24}H_{34}O_3$ requires C, 77.8; H, 9.3%; *M*, 370).

3β-*Acetoxy*-12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-20-*one* (8).—A solution of the aldehyde (6) (1 g), potassium acetate (1 g), and acetic anhydride (5 ml) was refluxed for 6 h. The resultant enol acetate was ozonised as previously in dichloromethane–methanol–pyridine (70 ml) to yield 3β-*acetoxy*-12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-20-*one* (0.6 g), which separated from aqueous methanol in plates, m.p. 153°; $[\alpha]_D^{23}$ −42° (*c* 1.1); $\lambda_{max.}$ 206 (log ε 4.54) and 269 nm (2.96); $\nu_{max.}$ 1 725 (acetate C=O) and 1 705 cm^{-1} (C=O); τ 3.07 (1 H, s, H-11), 5.23 (1 H, m, H-3), 5.95 (1 H, t, H-17), 7.83 (3 H, s, 13-Me), 7.93 (3 H, s, $OCOCH_3$), and 7.95 (3 H, s, 20-Me) (Found: C, 78.2; H, 8.3%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354). The *oxime* formed needles, m.p. 157° (from aqueous ethanol) (Found: C, 74.5; H, 8.5; N, 3.5. $C_{23}H_{31}NO_3$ requires C, 74.8; H, 8.5; N, 3.8%). Treatment of the acetate (8) (0.2 g) in ether (5 ml) with methylmagnesium iodide gave 12,20-*dimethyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-3β,20-*diol* (0.15 g) in stout prisms, m.p. 147° [from ether–light petroleum (b.p. 40—60 °C)]; $[\alpha]_D^{20}$ +61° (*c* 0.1) (Found: C, 79.4; H, 9.6. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%).

3β-*Hydroxy*-12-*methyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-17α-*carboxylic Acid* (9).—A solution of sodium hypobromite [prepared from sodium hydroxide (1.5 g), water (12.5 ml), dioxan (8.5 ml), and bromine (1.5 g) at 0 °C] was added dropwise (stir) to a solution of the ketone (8) (1 g) in dioxan (40 ml) and water (10 ml) at 0 °C. After 4 h the acidic product was isolated and purified from acetone–light petroleum (b.p. 40—60 °C) to yield the *acid* (9) (0.4 g) in needles, m.p. 260°; $[\alpha]_D^{20}$ +28.2° (*c* 1.1) (Found: C, 76.1; H, 8.5%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

12-*Methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-3,20-*dione* (16).—A solution of the ketone (8) (0.2 g) in ether (20 ml) was reduced with lithium aluminium hydride (0.05 g). The resultant mixture of 3β,20α- and 3β,20β-diols was dissolved in benzene (20 ml) and the solution stirred for 4 days with a solution of chromic oxide (0.1 g) in concentrated sulphuric acid (5 ml) and water (20 ml). Purification of the product from acetone–light petroleum (b.p. 40—60 °C) gave the *dione* (0.13 g) in needles, m.p. 122—124°; $[\alpha]_D^{19}$ +22° (*c* 1.3); $\nu_{max.}$ 1 720 cm^{-1} (C=O); τ 8.00 (3 H, s, 20-Me) (Found: C, 81.1; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310).

3β-*Hydroxy*-12-*methyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-17-*one* (18).—A solution of 3β-acetoxy-12-methyl-18-nor-5α-pregna-8,11,13-trien-20-one (0.5 g) in t-butyl alcohol (50 ml) containing dissolved potassium (0.5 g) was shaken in oxygen until 1 mol. equiv. (40 ml) of gas had been absorbed. The mixture was then stirred with zinc (1 g) and acetic acid (10 ml) for 2 h. After removal of the zinc the filtrate was diluted with water and the product extracted with ethyl acetate to yield a mixture which was purified by t.l.c. on silica [ethyl acetate–light petroleum (b.p. 40—60 °C)] to yield (a) 3β-*hydroxy*-12-*methyl*-18-*nor*-5α-*androsta*-8,11,13-*trien*-17-*one* (18) (R_F 0.45), which formed needles, m.p. 214—215° (from ethyl acetate); $[\alpha]_D^{20}$ +85° (*c* 0.33); $\nu_{max.}$ 3 530—3 450 (OH) and 1 695 cm^{-1} (C=O) (Found: C, 80.2; H, 8.3%; M^+, 284. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%; *M*, 284). The *acetate* formed needles, m.p. 231—232° (from methanol–ether); $[\alpha]_D^{20}$ +108° (*c* 0.27); $\nu_{max.}$ 1 730 (ester C=O) and 1 700 cm^{-1} (C=O); τ 8.86 (3 H, s, 10-Me), 7.88 (1 H, s, OH, exchangeable with D_2O), and 7.42 (3 H, s, $ArCH_3$) (Found: C, 77.1; H, 7.8%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326); and (b) 3β,17ξ-*dihydroxy*-12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-20-*one* (17) (R_F 0.51) in plates, m.p. 229—231° (from acetone); $[\alpha]_D^{20}$ −84° (*c* 0.27); $\nu_{max.}$ 1 705 cm^{-1} (C=O); τ 8.95 (3 H, s, 10-Me), 7.95 (6 H, s, 21-methyl and $ArCH_3$), and 7.88 and 5.33 (2 H, s, OH exchangeable with D_2O) (Found: C, 76.9; H, 8.3%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328). Reduction of this diol (100 mg) with lithium aluminium hydride gave 12-*methyl*-18-*nor*-5α-*pregna*-8,11,13-*trien*-3β,17ξ,20ξ-*triol* (19) in plates, m.p.

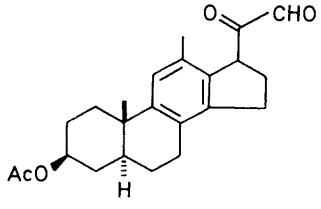
190—192° (from acetone–methanol); $[\alpha]_D^{20}$ +36° (*c* 0.11) (Found: M^+, 330.2197. $C_{21}H_{30}O_3$ requires *M*, 330.2195). Oxidation of (17) or (19) (0.2 g) at 70 °C in acetic acid (10 ml) with lead tetra-acetate gave 3β-hydroxy-12-methyl-18-nor-5α-androsta-8,11,13-trien-17-one (0.1 g), identical with the previously prepared specimen.

12-Methyl-18-nor-5α-androsta-8,11,13-triene-3,17-dione.—Oxidation of the alcohol from (18) (0.1 g) in acetone (10 ml) with an excess of Jones reagent during 15 min gave *12-methyl-18-nor-5α-androsta-8,11,13-triene-3,17-dione* (0.06 g) in plates, m.p. 183° (from acetone–methanol); $[\alpha]_D^{20}$ +134° (*c* 0.2); $\nu_{max.}$ 1 705 (six-membered ring C=O) and 1 690 cm^{-1} (five-membered ring C=O) (Found: C, 81.1; H, 7.4%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%; *M*, 282).

20α-Formyl-12-methyl-18-nor-5α-pregna-8,11,13,20-tetraen-3β-yl Acetate (11).—A solution of the aldehyde (6) (0.5 g) in acetic acid (20 ml) was treated, dropwise, during 10 min, with a solution of bromine (0.25 g) in benzene (20 ml). The unpurified bromo-derivative (10) was immediately treated with 1,5-diazabicyclo[4.3.0]non-5-ene (0.5 g) at the b.p. during 2 h, to yield the *aldehyde* (11) in prisms, m.p. 122° (from aqueous methanol); $[\alpha]_D^{20}$ +115° (*c* 0.12); $\lambda_{max.}$ 218 nm; $\nu_{max.}$ 1 723 (ester C=O) and 1 685 cm^{-1} (C=C–CHO); τ 7.98 (6 H, s, CH_3COO and 12-Me), 5.7 (1 H, m, H-17), 5.2 (1 H, m, H-3), and 4.40 and 4.07 (2 H, s, $C=CH_2$) (Found: C, 78.4; H, 8.3%; M^+, 366. $C_{24}H_{30}O_3$ requires C, 78.7; H, 8.3%; *M*, 366).

Dehydrobromination of 22,23-Dibromo-12-methyl-18-nor-5α-ergosta-8,11,13-trien-3β-yl Acetate.—A solution of this acetate (10 g) in toluene (150 ml) containing 1,5-diazabicyclo[4.3.0]non-5-ene (6.5 ml) was refluxed during 12 h to yield the non-crystalline mixture of dienes (7.5 g); τ 3.10 (1 H, s, ArH), 4.04—4.86 (m, H-22 and -23), 5.15 (1 H, m, H-3), 5.28 (H-21 and -28), 7.70 (3 H, s, 10-Me), and 7.97 (3 H, s, CH_3CO_2) (Found: C, 83.0; H, 9.8. Calc. for $C_{30}H_{42}O_2$: C, 82.9; H, 9.7%).

This mixture was ozonised as follows. (*a*) The mixture (0.1 g) in dichloromethane was oxidised and the products were chromatographed: the slowest moving fraction (12 mg) on silica, eluted with benzene, had M^+ 368.1990. The aldehyde (20) requires *M* 368.1987.



(20)

(*b*) Ozonolysis of the mixture (0.5 g) followed by conversion of the products into the 2,4-dinitrophenylhydrazones gave a mixture of derivatives which was separated by p.l.c. on silica with benzene as eluant. Fraction A (10 mg) had R_F 0.80, and crystallised from aqueous methanol to yield the 2,4-dinitrophenylhydrazone of (−)-α-methylisovaleraldehyde; m.p. 119—121°; mixed m.p. with authentic specimen 119—121°; $[\alpha]_D^{20}$ −31° (*c* 0.1) (lit.,[12] −37°); the n.m.r. and mass spectra were identical with those from an authentic sample. Fraction B (42 mg) (R_F 0.57) was further separated by benzene–light petroleum (b.p. 40—60 °C)–pyridine (40 : 58 : 2) to yield the 2,4-dinitrophenylhydrazones of formaldehyde (R_F 0.51) and acetone (R_F 0.66), identical with authentic specimens. Fraction C (72 mg) (remaining on base line) was rechromatographed on silica, with benzene–ether (85 : 15), to yield the 2,4-dinitrophenylhydrazone of 20α-formyl-12-methyl-18-norpregna-8,11,13-trien-3β-yl acetate (6) (51 mg), m.p. 108—110°, identical (m.p., mixed m.p., and n.m.r., u.v., and mass spectra) with an authentic sample.

12-Methyl-18-nor-5α-cholesta-8,11,13-trien-3β-yl Acetate.—Bromination of 5α-cholest-7-en-3β-ol (10 g) by essentially the process employed for ergosterol gave a non-crystalline product (10 g) which was aromatised directly by exposure to Woelm alumina. The aromatic steroid was purified by chromatography on silica from light petroleum (b.p. 40—60 °C) followed by elution with light petroleum (b.p. 40—60 °C)–benzene (9 : 1). *12-Methyl-18-nor-5α-cholesta-8,11,13-trien-3β-yl acetate* (5.4 g) was a gum which resisted all attempts to form crystals; it ran as one spot on t.l.c.; $[\alpha]_D^{21}$ +12.6° (*c* 3.1); $\nu_{max.}$ 1 730 cm^{-1} (acetate C=O); $\lambda_{max.}$ (cyclohexane) 205 (log ε 4.67) and 225 nm (4.07); τ 7.73 (3 H, s, 12-Me), 7.95 (3 H, s, $OCOCH_3$), and 8.86 (3 H, s, 10-Me) (Found: C, 82.0; H, 10.1%; M^+, 424.3336. $C_{29}H_{44}O_2$ requires C, 82.0; H, 10.4%; *M*, 424.3341).

Hydrolysis of this acetate with methanolic potassium hydroxide gave *12-methyl-18-nor-5α-cholesta-8,11,13-trien-3β-ol* as a non-crystallisable gum; $[\alpha]_D^{20}$ +50.7° (*c* 2.9) (Found: C, 84.0; H, 11.0%; M^+, 382. $C_{27}H_{42}O$ requires C, 84.8; H, 11.1%; *M*, 382).

The 3,5-dinitrobenzoate was ' incipiently ' crystalline and was converted into the 1 : 1 derivative with 1-aminonaphthalene. This *complex* formed deep red needles, m.p. 140° [from light petroleum (b.p. 100—110 °C)]; $[\alpha]_D^{18}$ +25.6° (*c* 0.5) [Found: C, 73.4; H, 7.4; N, 5.8%; M^+, 576. $C_{44}H_{53}N_3O_6$ requires C, 73.4; H, 7.4; N, 5.8%; *M* for $C_{34}H_{44}N_2O_6$ (complex minus 1-aminonaphthalene), 576].

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