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MODIFIED STEROID HORMONES—XLI[1]

REARRANGEMENT OF 3β-ACETOXY-4aα-HYDROXY-5β-METHYL-A-HOMO-B-NOR STEROIDS INTO NORMAL STEROIDS OF THE 6-METHYLENE-5β-H SERIES

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Abstract—Methods are described for effecting the molecular rearrangement of 3β-acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-nor steroids into corresponding normal structures of the 6-methylene-5β-H series. NMR spectral data lead to the assignment of the α-configuration to the 4a-hydroxyl group present in the initial steroidal A-homo-B-nor types.

THE isomerization of 5α,6α-epoxy-6β-methyl steroids of the spirostane and androstane series into 5β-methyl-A-homo-B-nor-4a-ketones (I; R = :O)—a novel transformation which has since been extended to certain pregnane derivatives,[3] was described in 1960.[2] We now report upon a hitherto unrecorded rearrangement of A-homo-B-nor structures into compounds having the normal perhydrocyclopentenophenanthrene skeleton.

Dehydration of 3β-acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-nor spirostane[2] (Ia; R = α-OH) (*vide infra* for configuration at C_{4a}) by treatment with thionyl chloride in pyridine at 0° gave a mixture from which three entities were isolated. The compound obtained in predominant amount, by direct crystallization of the total reaction product, has been assigned the constitution 3β-acetoxy-6-methylene-5β,25D-spirostane (IIa; R = β-OAc) on the basis of evidence presented herein. Mother-liquor material on chromatography afforded small quantities of 6-methyl diosgenin acetate[4] (IVa) and a third compound which we regard as 3β-acetoxy-6-methyl-5β,25D-spirost-6-ene (Va).

Alkaline hydrolysis of the 3β-acetate (IIa; R = β-OAc) gave the corresponding alcohol (IIa; R = β-OH), which was oxidized to the 3-ketone (IIa; R = :O). The IR spectra of these compounds show pronounced bands at 1650–1645 cm^{-1}, which, together with considerable increases of intensity of the sapogenin band at 896 cm^{-1}, point to the presence of an exocyclic methylene group.[5] The presence of this grouping is confirmed by the existence of a 2-proton singlet at 5·35τ (half-intensity band width of 8 c/s) in the NMR proton resonance spectra of compounds IIa (R = β-OAc and R = :O). Analysis of the ORD curve (*vide infra*) of the last compound

[1] Part XL, M. G. Lester, V. Petrow and O. Stephenson, *Tetrahedron* **21**, 1761 (1965).
[2] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4657 (1960).
[3] J. P. Dusza, J. P. Joseph and S. Bernstein, *J. Org. Chem.* **28**, 92, (1963).
[4] D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).
[5] M. Günthard and L. Ruzicka, *Helv. Chim. Acta* **32**, 2125 (1949).

provides evidence for assigning the β-configuration to the 5-H atom. Isomerization of this ketone (IIa; R = :O) was effected by treatment with warm formic acid to give the known 6α-methyl-25D-spirost-4-en-3-one[6] (IIIa); the 3β-acetate (IIa; R = β-OAc) was isomerized by toluene-*p*-sulphonic acid in acetic acid to 6-methyldiosgenin acetate[4] (IVa).

Further chemical evidence supporting the foregoing 6-methylene-5β-H formulations was obtained by hydroxylation, with osmic acid, of 3β-acetoxy-6-methylene-5β,25D-spirostane (IIa; R = β-OAc), followed by cleavage of the resulting diol with sodium metaperiodate under essentially neutral conditions to give 3β-acetoxy-5β,25D-spirostan-6-one. This compound differs from the known 3β-acetoxy-5α,25D-spirostan-6-one[4] into which it was isomerized by treatment with alkali followed by acetylation.

The third dehydration product arising from 3β-acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norspirostane (*vide supra*) is assigned the constitution 3β-acetoxy-6-methyl-5β,25D-spirost-6-ene (Va) as (i) the IR spectrum shows a low-intensity band at 1664 cm^{-1} (a trisubstituted ethylenic linkage[7]) and (ii) the NMR spectrum reveals an unresolved multiplet at 4·9τ (half-height band width *circa* 7 c/s) of one-proton intensity, and a band at 8·4τ consistent with the presence of the —C(CH_3)=CH— system. Alkaline saponification of the minor product (Va) followed by oxidation of the resulting (not characterized) alcohol was accompanied by rearrangement of the double bond to give the 6-methylene-3-ketone (IIa; R = :O).

3β,17β-Diacetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norandrostane (Ib; R = α-OH), prepared from 3β-acetoxy-5β-methyl-A-homo-B-nor-androstane-4a,17-dione,[8] was similarly dehydrated with thionyl chloride–pyridine to give an amorphous product from which, after alkaline hydrolysis, crystalline 6-methylene-5β-androstane-3β,17β-diol (IIb; R = β-OH) was isolated. The presence of an exocyclic methylene group in this compound and in its amorphous diacetate precursor is evidenced by IR absorption bands at 1645 and 890 cm^{-1}. The diol (IIb; R = β-OH) significantly differs from 6-methylene-5α-androstane-3β,17β-diol, prepared from 3β,17β-diacetoxy-5α-androstan-6-one[8] and methylenetriphenylphosphorane, an observation supporting the 5β-H-configuration assigned to it. Further evidence for this configuration follows from the non-identity of the 6-methylene-5β-androstane-3,17-dione obtained by oxidation of the diol (IIb; R = β-OH), with the 6-methylene-5α-androstane-3,17-dione similarly derived from 6-methylene-5α-androstane-3β,17β-diol. Both isomeric 6-methylene-3,17-diones were converted by warm formic acid into the known 6α-methylandrost-4-ene-3,17-dione.[9]

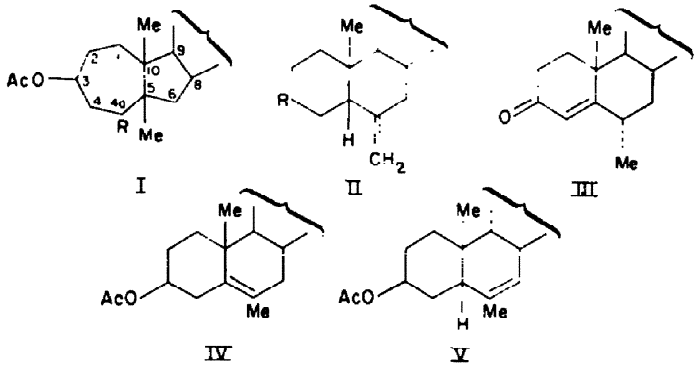
Extension of this novel dehydration reaction to a simple pregnan-20-one derivative necessitated the preparation of 3β-acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norpregnan-20-one (Ic; R = α-OH). 3β-Acetoxy-6-methylpregn-5-en-20-one[4] was oxidized with peracetic acid to give the corresponding 5α,6α-epoxide, which underwent rearrangement on treatment with boron trifluoride etherate, affording 3β-acetoxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (Ic; R = :O). The hindered 4a-oxo

[6] U.S. Pat. 2,875,198.

[7] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *J. Chem. Soc.* 2402 (1951).

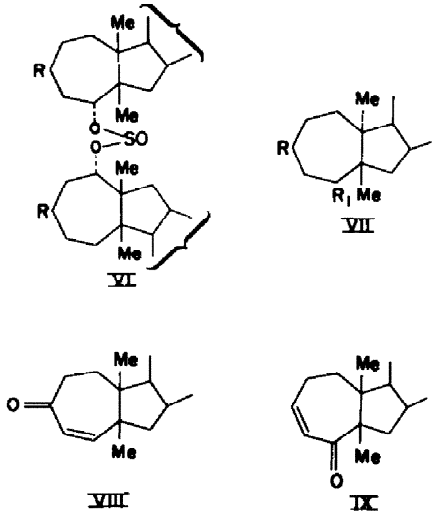
[8] H. B. MacPhillamy and C. R. Scholz, *J. Amer. Chem. Soc.* 74, 5512 (1952); V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4105 (1957).

[9] M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).



(a) 25D – Spirostane series
(b) 17β – Acetoxy(hydroxy) androstane series
(c) Pregnan – 20 – one series

group of this dione proved less reactive than the 20-oxo function, and permitted the formation, by reaction of the compound with semicarbazide, of 3β-acetoxy-5β-methyl-4a-oxo-A-homo-B-norpregnane-20-semicarbazone. Reduction of this derivative with lithium borohydride in boiling tetrahydrofuran gave the corresponding 3β,4aα-diol-20-semicarbazone, from which 3β,4aα-dihydroxy-5β-methyl-A-homo-B-norpregnan-20-one was obtained by hydrolysis with hot aqueous pyruvic acid.[10] Acetylation of the last compound at 0° furnished the required 3β-acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norpregnan-20-one (Ic; R = α-OH), the constitution of which follows from (i) its oxidation to the parent 4a-ketone (Ic; R = :O), and (ii) the formation of a 3β,4aα-diacetate (Ic; R = α-OAc) on vigorous acetylation.



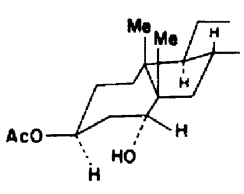
Treatment of the 4aα-hydroxy-A-homo-B-nor compound (Ic; R = α-OH) with thionyl chloride–pyridine unexpectedly failed to follow the pattern established in the

[10] See E. B. Hershberg, *J. Org. Chem.* 13, 542 (1948).

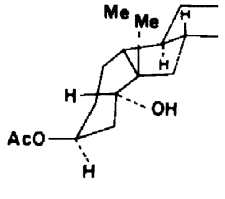
spirostane and androstane series. The structure and transformations of the product obtained, however, are more conveniently discussed below. Elimination of the 4aα-hydroxyl group of compound (Ic; R = α-OH) and rearrangement to a steroid of normal skeleton was ultimately achieved by the preparation of the corresponding 4aα-methanesulphonyloxy derivative, which with hot collidine–pyridine passed into 3β-acetoxy-6-methylene-5β-pregnan-20-one (IIc; R = β-OAc), an isomer of the known 3β-acetoxy-6-methylene-5α-pregnan-20-one.[11] Alkaline saponification of the former compound, and oxidation of the resulting 3β-alcohol (IIc; R = β-OH) with the Jones reagent[12] afforded 6-methylene-5β-pregnane-3,20-dione (IIc; R = :O). Evidence for assigning the β-configuration to the 5-H atom of this dione is based upon ORD studies (*vide infra*).

The product obtained by reaction of the 4aα-hydroxy compound (Ic; R = α-OH) with thionyl chloride–pyridine (*vide supra*) gave elemental analytical and IR data consistent with the bis-sulphite formulation (VI; R = β-OAc). Hydrolysis of this compound with aqueous methanolic potassium carbonate followed by oxidation afforded the corresponding ketone (VI; R = :O), converted by alkali at room temperature into 4aα-hydroxy-6β-methyl-A-homo-B-norpregnane-3,20-dione (VII; R = :O, R_1 = α-OH). Dehydration of this β-keto-alcohol with hot alkali or mineral acid then furnished 5β-methyl-A-homo-B-norpregn-4(4a)-ene-3,20-dione (VIII), characterized by its UV absorption λ_{max} 233 mμ. The isomeric αβ-unsaturated ketone 5β-methyl-A-homo-B-norpregn-3-en-4a,20-dione (IX), having λ_{max} 226·5 mμ, was prepared by alkaline or acid hydrolysis of the 3β-acetoxy-4a-ketone (Ic; R = :O) to 3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (VII; R = β-OH; R_1 = :O) and subsequent treatment of the corresponding 3β-methanesulphonyloxy derivative with hot collidine. Unlike its spirostane and androstane analogues,[2] the 3β-acetoxy-4a-ketone (Ic; R = :O) failed to lose the elements of acetic acid when its benzene solution was passed through a column of alumina.

Dreiding models of the A-homo-B-nor structure reveal that vicinal hydrogen and other interactions are minimal in two possible "chair" conformations represented by X and XI for compounds of type I (R = OH) and their parent 4a-ketones (I; R = :O). The 3β-acetoxy group is equatorial in conformation X, and axial in



X



XI

conformation XI. In addition, the geometries of the C_2–C_3–C_4 centres closely resemble those of normal 3β-acetoxy-5α- and 5β-steroids, respectively. The orientation of C_3-substituents, including the acetoxy group, may be determined in normal steroids from NMR data.[13] Thus, when the substituent is equatorial, the resonance of the

[11] P. F. Beal, M. A. Rebenstorf and J. E. Pike, *J. Amer. Chem. Soc.* **81**, 1231 (1959).
[12] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).
[13] A. Hassner and C. Heathcock, *J. Org. Chem.* **29**, 1350 (1964).

C_3-proton takes the form of a poorly resolved multiplet, the half-intensity band-width (W_H) of which lies in the region 15–30 c/s. A value of 5–10 c/s is obtained, in contrast, when the C_3-substituent is axial. The NMR spectra of the 4a-alcohol (Ic; R = α-OH) and its precursor ketone (Ic; R = :O) were determined during the present investigation, and these reveal broad multiplet signals arising from the C_3-protons, at 4·9 and 5·3τ, respectively, $W_H \approx 20$ c/s in each case. We therefore conclude that the orientation of the 3β-acetoxy group is *equatorial* in both compounds, from which it follows that the conformations of the alcohol and ketone approximate to that represented by Fig. X. It may be mentioned that our earlier explanation[2] of the formation of the A-homo-B-nor-4a-oxo system by rearrangement of a 6β-methyl-5α,6α-epoxide involved the recognition of a conformation corresponding to X for the rearranged product.

Assignment of the α-configuration to the 4a-hydroxyl group resulting from borohydride reduction of a 4a-ketone is based upon the following observations. First, it is necessary to consider the splitting pattern of the 4a-proton resonance as a function of the geometry of the C_4 and C_{4a} centres, employing a Karplus[14] type relationship between J and the dihedral angle ϕ between vicinal protons. Angles determined from Dreiding models of the epimeric 4a-alcohols corresponding to conformation X, and the coupling constants derived from them via the Williamson and Johnson version of the Karplus relation[15] are as follows:

	ϕ_1	ϕ_2	J_1	J_2
4a α-OH	20°	100°	8·5 c/s	0·5 c/s
4a β-OH	90°	150°	0	12·5 c/s

[ϕ_1, ϕ_2, and J_1, J_2 (calc.) refer to 4α and 4β C—H bonds respectively]

The observed resonance signal of the 4a-proton in the spectrum of the 4a-alcohol (Ic; R = α-OH) consists of a broad doublet at 6·3τ (J = 5–6 c/s), the components of the doublet having $W_H \approx 3$ c/s. Although this result favours the α-configuration for the 4a-hydroxyl group, the limitations and accuracy of the Karplus relations are not estimable, so that the conclusion is not unequivocal. More convincing evidence for the configuration assignment is provided, however, by the shift down field of the 3α-proton signal in passing from the 4a-ketone (Ic; R = :O) to the alcohol (Ic; R = α-OH). The new position of this resonance, at 4·9τ, is well below the unperturbed position of a 3α-proton of a normal 3β-acetoxy-5α-steroid (5·2–5·5 c/s) and indicates the proximity of a strongly deshielding group. The effect is consistent only with a 4aα-hydroxyl group. Compounds Ia, Ib and Ic (R = α-OH) are accordingly regarded as having the conformation and structure represented by X.

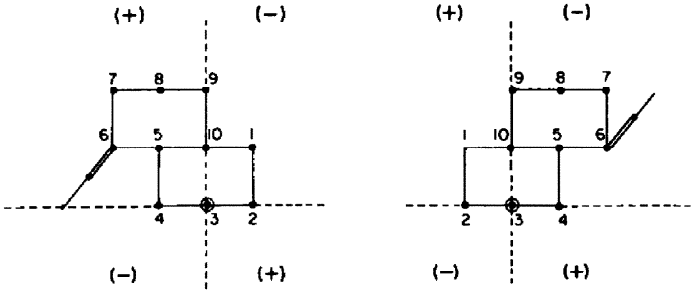
The β-configuration at C-5 *of the 6-methylene-3-ketones* (IIa; R = :O) *and* (IIc; R = :O)

Evidence from ORD studies. The ORD curve of the ketone (IIa; R = :O) consists of a negative Cotton feature superimposed upon the sharply negative plain

[14] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

[15] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry—Illustrations from the Steroid Field* Chap. 3. Holden-Day Inc. (1964).

curve associated with a 25D-sapogenin structure.[16] The negative Cotton effect arises from the n-π^* transition of the 3-oxo function (at 279 mμ, see Table) in the asymmetric environment of the steroid as modified by the methylene group at C-6. The rotatory power (and UV absorption intensity) of keto-functions is known to be markedly sensitive to vicinal unsaturation[17] in the absence of formal conjugation, and is evidenced by enhancement of the n–π^* band intensity. Enhancement of this band is not observed in the UV spectra of the ketones (IIa; R = :O) and (IIc; R = :O), however, so that the charge-transfer effect does not operate in these particular compounds. The magnitude of the observed Cotton effect shown by cholestane-3,6-dione[18] is considerably greater than that calculated by simple addition of the Cotton amplitudes of the individual 3- and 6-ketones, but this enhancement, which is presumably dipolar in origin, may be predicted on the basis of the simple Octant Rule.[19] It follows that valid use of the Rule may be made in the analysis of the Cotton effects of the ketones (IIa; R = :O) and (IIc; R = :O). Conventional octant diagrams A and B (see Fig.) lead to the conclusion that introduction of a C-6 methylene group into saturated 3-oxo steroids would result in increased amplitudes of both +ve (5α) and −ve (5β) 3-keto Cotton effects.[20] The magnitude and sign of the effect given by the ketone (IIa; R = :O) is consistent with a β-configuration at C-5.



A. C_5–α configuration B. C_5–β configuration

The ORD curve of the ketone (IIc; R = :O) shows a positive Cotton feature, the result of the combined contributions of the 3-and 20-oxo groups, the latter group having the predominant effect. Consideration of the data presented in the Table, however, reveals that (i) the effects due to the two ketone functions are quantitatively additive to within an observed deviation of 15% (see values in parentheses), and (ii) introduction of the 6-methylene function markedly *lowers* the amplitude of the combined Cotton effect of the 3- and 20-oxo groups relative to that obtained for 5β-pregnane-3,20-dione. We therefore assign the β-configuration to the 5-hydrogen atom present in the ketone (IIc; R = :O).

[16] C. Djerassi and R. Ehrlich, *J. Amer. Chem. Soc.* **78**, 440 (1956).
[17] R. E. Ballard, S. F. Mason and G. W. Vane, *Trans. Far. Soc.* **59**, 775 (1963); R. Grinter, S. F. Mason and G. W. Vane, *Ibid.* **60**, 285 (1964).
[18] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **78**, 3163 (1956); C. Djerassi and W. Closson, *Ibid.* **78**, 3761 (1956).
[19] R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).
[20] F. C. Nachod and W. D. Phillips, *Determination of Organic Structures by Physical Methods* Vol. 2; Chap. 1; p. 18. Academic Press (1962).

TABLE

Compound	ORD			UV	
	$\lambda_1([\phi])$	$\lambda_2([\phi])$	$10^{-2}a$	λ_{max} mμ	ε(EtOH)
Ketone (IIa; R = :O)	310 mμ (−3190°)	266 mμ (+2030°)	−52°	279	29
Ketone (IIc; R = :O)	308 mμ (+4860°)	273 mμ (−4780°)	+96°	285	75
5α-Cholestan-3-one[21]	307 mμ (+3700°)	267 mμ (−2880°)	+65°	—	—
5β-Cholestan-3-one[21]	307 mμ (−80°)	265 mμ (+2600°)	−27°	—	—
5β-Pregnane-20-one[21]	308 mμ (+8850°)	262 mμ (−8780°)	−178°	—	—
5α-Pregnane-3,20-dione	309 mμ (+10,100°)	267 mμ (−10,900°)	+210°[243°]*	285	62
5β-Pregnane-3,20-dione	309 mμ (+7450°)	266 mμ (−7820°)	153°[151°]*	285	59

* Values in parentheses have been calculated from the quoted amplitudes of the two cholestan-3-ones and 5β-pregnan-20-one.

EXPERIMENTAL

Specific rotations were determined at concentrations of ca. 1% in A.R. $CHCl_3$ at laboratory temp unless otherwise stated. UV spectra were recorded upon either Beckman DK-2 or Perkin–Elmer Model 350 spectrophotometers. Unless otherwise stated, IR spectra were determined with a Hilger H800 spectrophotometer, fitted with CaF_2 and NaCl prisms for the ranges 4000–1300 and 1400–650 cm^{-1} respectively. NMR spectra were determined at 40 Mcs/s. in $CDCl_3$ solution (tetramethylsilane as internal standard) upon a Perkin–Elmer permanent magnet spectrometer, fitted with crystal calibrated decade field shift. ORD spectra were determined in AR methanol by use of a "Polarmatic 62" recording spectropolarimeter.*

*Darzens' dehydration and rearrangement of 5β-methyl-*A*-homo-*B*-nor-25*D*-spirostan-3β,4aα-diol 3-monoacetate* (Ia; R = α-OH). A solution of the diol monoacetate (3·6 g) in anhydrous pyridine (50 ml) at −20° was treated dropwise with freshly purified $SOCl_2$ (6 ml), then allowed to warm to room temp over ½ hr. The brown solution was poured into ice-water and the precipitated solids were dried and dissolved in boiling hexane. The solution was stirred with decolourizing charcoal, filtered, the hexane evaporated, and the residue crystallized from acetone followed by EtOH to give 3β-acetoxy-6-methylene-5β,25*D*-spirostane, needles, m.p. 159–161°, $[\alpha]_D$ −64°, $\nu_{max}^{CCl_4}$ 3066 and 1645 (exocyclic:CH_2) and 1738 cm^{-1} (acetate). (Found: C, 76·9; H, 9·8. $C_{30}H_{46}O_4$ requires: C, 76·55; H, 9·85%.)

The combined mother liquors from the purification of the foregoing compound were evaporated and the residue chromatographed on alumina (65 g). The following main fractions were eluted:

(i) Light petroleum (b.p. 40–60°):benzene (9:1)—6-methyldiosgenin acetate, m.p. 218° to 220° $[\alpha]_D$ −127° (lit[4]: m.p. 218–220, $[\alpha]_D$ −129°) after purification from methanol.

(ii) Light petroleum:benzene (1:1)—3β-acetoxy-6-methyl-5β,25*D*-spirost-6-ene, flakes (from EtOH), m.p. 150·5–151·5°, $[\alpha]_D$ −117°, $\nu_{max}^{CCl_4}$ 1733 (acetate) and 1664 cm^{-1} (Δ^6). (Found: C, 76·25; H, 9·7. $C_{30}H_{46}O_4$ requires: C, 76·55; H, 9·85%.)

(iii) Benzene—A small quantity of the 6-methylene-compound (Ia; R = α-OH).

*6-Methylene-5β,25*D*-spirostan-3β-ol* (IIa; R = β-OH). 3β-Acetoxy-6-methylene-5β,25*D*-spirostane (1 g) in MeOH (50 ml) containing KOH (0·5 g) was heated under reflux for 1 hr. Water was added and the product collected and purified from EtOH to give 6-methylene-5β,25*D*-spirostan-3β-ol in needles, m.p. 217–223°, $[\alpha]_D$ −81°, $\nu_{max}^{CCl_4}$ 3625 (OH), 3069 and 1647 cm^{-1} (exocyclic:CH_2). (Found: C, 78·45; H, 10·5. $C_{28}H_{44}O_3$ requires: C, 78·45; H, 10·35%.)

*6-Methylene-5β,25*D*-spirostan-3-one* (IIa; R = :O). 6-Methylene-5β,25*D*-spirostan-3β-ol (1 g) in anhydrous pyridine (10 ml) was added to the complex prepared from CrO_3 (1 g) and pyridine (10 ml). The mixture was stirred for 4 hr and left for 18 hr at room temp. Benzene (100 ml) was then added and the mixture filtered. The filtrate was washed with water, dried, decolourized (charcoal), and the solvent removed. The residue was purified from MeOH to give 6-methylene-5β,25*D*-spirostan-3-one, blades, m.p. 217–219°, $[\alpha]_D$ −80°, $\nu_{max}^{CCl_4}$ 3071, 1650 (exocyclic:CH_2), 1715 cm^{-1} (3 CO). (Found: C, 78·8; H, 9·7. $C_{28}H_{42}O_3$ requires: C, 78·8; H, 9·9%.)

* Manufactured by Bellingham and Stanley Ltd. in conjunction with Bendix-Ericsson (U.K.) Ltd.

[21] R. A. Raphael, E. C. Taylor and H. Wynberg, *Advances in Organic Chemistry, Methods and Results*, Vol. 1, p. 270, Interscience (1960).

6α-Methyl-25D-spirost-4-en-3-one (IIIa). The foregoing ketone (200 mg) in 98–100% formic acid (6 ml) was heated on the steam bath for 2 hr. The product obtained on the addition of water was purified from MeOH to give 6α-methyl-25D-spirost-4-en-3-one, m.p. 210–212° (lit.[6]: m.p. 211–213°), IR spectrum identical with that of an authentic sample.

6-Methyl diosgenin acetate (IVa). 3β-Acetoxy-6-methylene-5β,25D-spirostane (60 mg) in acetic acid (10 ml) containing toluene-*p*-sulphonic acid (10 mg) was heated for 2 hr at 100°. The product obtained on the addition of water was crystallized from MeOH to give 6-methyl diosgenin acetate, m.p. and mixed m.p. 216–220°. The IR spectrum was identical with that of an authentic specimen.

Conversion of 3β-acetoxy-6-methyl-5β,25D-spirost-6-ene into compound IIa (R = :O). 3β-Acetoxy-6-methyl-5β,25D-spirost-6-ene (45 mg) was hydrolysed with KOH (20 mg) in 90% aqueous MeOH (5 ml) for 1 hr under reflux. Water was added until the product separated in flakes, m.p. 216–218° (30 mg). This crude material in acetone (5 ml) was treated with 3 drops of Jones' chromic acid reagent, the mixture diluted with water, and the precipitated solids purified from MeOH to give 6-methylene-5β,25D-spirostan-3-one, identical in every respect with a specimen prepared by the method described above.

Hydroxylation of 3β-acetoxy-6-methylene-5β,25D-spirostane (IIa: R = β-OAc). The compound IIa (R = β-OAc; 0·5 g) and OsO_4 (0·3 g) in pyridine (10 ml) was left at room temp for 24 hr. A solution of Na_2SO_3 (2 g) in water (40 ml) and pyridine (40 ml) was added, and the brown mixture stirred for 1 hr. The product was isolated with CH_2Cl_2 and purified from aqueous MeOH to give 6ξ-hydroxymethyl-5β,25D-spirostan-3β,6ξ'-diol-3-monoacetate in tenaciously solvated needles, m.p. 165–167°, $[\alpha]_D$ −74°, $\nu_{max}^{CH_2Cl_2}$ 1727 cm^{-1} (acetate); (in Nujol) 3350, 3250 (associated hydroxyl) and 1702 cm^{-1} (associated acetate). [Found: (after drying in air at 100°) C, 69·1; H, 9·6; (after drying at 135°/0·2 mm) C, 70·8; H, 9·6. $C_{29}H_{48}O_6 \cdot H_2O$ requires: C, 68·9; H, 9·6%.]

3β-Acetoxy-5β,25D-spirostan-6-one. The foregoing diol (300 mg) in MeOH (10 ml) was treated overnight at room temp with $NaIO_4$ (400 mg) in water (5 ml). The mixture was stirred and treated with 10% $Na_2S_2O_5$ aq until the liberated I_2 was decolourized. Water was added, and the precipitated solids were purified from hexane to give 3β-acetoxy-5β,25D-spirostan-6-one, prisms, m.p. 199–202°, $[\alpha]_D$ −102° (in dioxan), $\nu_{max}^{CCl_4}$ 1740 (acetate) and 1707 cm^{-1} (6-ketone). (Found: C, 73·3; H, 9·3. $C_{29}H_{44}O_5$ requires: C, 73·7; H, 9·4%.)

3β-Acetoxy-5α,25D-spirostan-6-one. The foregoing compound (60 mg) was treated for ½ hr with KOH (20 mg) in refluxing 90% aqueous MeOH (10 ml). The solution was concentrated, and water was added until the product separated. This material was collected, dried, and treated with acetic anhydride (1 ml) and pyridine (1 ml) for 20 min on the steam bath. The product was purified from MeOH to give 3β-acetoxy-5α,25D-spirostan-6-one, prisms, m.p. 221–224°, $[\alpha]_D$ −88° (lit.[4] gives m.p. 222–224°, $[\alpha]_D$ −93°). IR spectrum identical with that of an authentic sample.

Reduction of 3β-acetoxy-5β-methyl-A-homo-B-norandrostane-4a,17-dione (Ib; R = :O). The dione (8 g) in MeOH (200 ml) was treated with $NaBH_4$ (4 g) and NaOH (4 g) in water (20 ml). The mixture was left overnight at room temp, and the product isolated with $CHCl_3$–ethyl acetate. It was acetylated [acetic anhydride (8 ml) and pyridine (50 ml) for 16 hr at 20°] and purified from acetone–hexane to give 3β,17β-diacetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norandrostane, needles, m.p. 187–190°, $[\alpha]_D$ −30°, $\nu_{max}^{CCl_4}$ 3618 (non-associated O—H), 3460 (associated O—H) and 1735 cm^{-1} (acetate). (Found: C, 70·9; H, 9·1. $C_{24}H_{38}O_5$ requires: C, 70·9; H, 9·4%.)

The *3β,4aα,17β-triol*, obtained by alkaline hydrolysis of the foregoing diacetate, crystallized from aqueous MeOH in plates, m.p. 126–132°, $[\alpha]_D$ −27°. [Found (after drying at 95°/0·5 mm): C, 73·9; H, 10·7. $C_{20}H_{34}O_3$ requires: C, 74·5; H, 10·6%].

6-Methylene-5β-androstane-3β,17β-diol (IIb; R = β-OH). 3β,17β-Diacetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norandrostane (6·15 g) in anhydrous pyridine (61·5 ml) at 0° was treated dropwise with freshly purified $SOCl_2$ (5 ml). The mixture was allowed to warm to room temp over ½ hr, then poured into water, and the product isolated with ether. It was a gum, having IR absorption maxima (in Nujol) at 1735 (acetates), 1655 and 890 cm^{-1} (exocyclic methylene).

This material was hydrolysed with K_2CO_3 (4 g) in 80% aqueous MeOH (300 ml) under reflux for 1 hr. The mixture was concentrated to small bulk, poured into water, and the ppt. collected, dried, and crystallized from acetone–hexane, to give 6-methylene-5β-androstane-3β,17β-diol in needles, m.p. 131–132°, $[\alpha]_D$ −26°, $\nu_{max}^{CCl_4}$ 3610, 3299, 3069, 1643 cm^{-1}. (Found: C, 78·6; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.)

6-Methylene-5β-androstane-3,17-dione. The foregoing diol (0·5 g) in acetone (20 ml) was stirred

and treated dropwise with Jones chromic acid reagent until an excess of oxidant was present as indicated by the colour of the mixture. Dilution with water, and purification of the precipitated solids from aqueous MeOH, gave 6-methylene-5β-androstane-3,17-dione in prisms, m.p. 184–187°, $[\alpha]_D$ +58·5°, $\nu_{max}^{CCl_4}$ 1745 (17-C:O), 1718 (3-C:O) and 1653; (in CS_2) 897 cm^{-1} (exocyclic:CH_2). (Found: C, 79·6; H, 9·2. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%.)

3β,17β-Diacetoxy-6-methylene-5α-androstane. A Wittig reagent was prepared from methyltriphenylphosphonium bromide (17·3 g) in ether (200 ml) and n-butyl-lithium (3·2 g) in hexane (32 ml) under N_2. 3β,17β-Diacetoxy-5α-androstan-6-one (5 g) in anhydrous tetrahydrofuran (150 ml) was added, the mixture was left overnight, then poured into water and the product isolated with ether. It was chromatographed on alumina (100 g), and the fractions eluted with benzene were crystallized from aqueous MeOH to give 3β,17β-diacetoxy-6-methylene-5α-androstane, flakes, m.p. 161–162·5°, $[\alpha]_D$ −40°, $\nu_{max}^{CCl_4}$ 3062, 1645 (exocyclic:CH_2) and 1733 cm^{-1} (acetates); $\nu_{max}^{CS_2}$ 889 cm^{-1} (exocyclic: CH_2). (Found: C, 73·9; H, 9·2. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·3%.)

3β,17β-Diacetoxy-6-methylandrost-5-ene (IVb). 3β,17β-Diacetoxy-6-methylene-5α- or -5β-androstane (50 mg) in acetic acid (10 ml) was treated with 72% perchloric acid (3 drops) for 18 hr at room temp. Water was added, and the crystalline product purified from aqueous MeOH to give 3β,17β-diacetoxy-6-methyl-androst-5-ene, m.p. 124–125° (lit.[8] m.p. 125–127°), IR spectrum identical with that of an authentic sample.

6-Methylene-5α-androstane-3β,17β-diol. 3β,17β-Diacetoxy-6-methylene-5α-androstane (500 mg) was hydrolysed with K_2CO_3 (300 mg) in 80% aqueous MeOH (30 ml) under reflux for 1 hr. Gradual addition of water (100 ml) gave a solid which was purified from aqueous MeOH. The diol separated in solvated flakes, m.p. 164–165°, $[\alpha]_D$ −25°, ν_{max}^{Nujol} 3476, 3392, 3210 (associated OH), 1650 and 890 cm^{-1} (exocyclic:CH_2). [Found: (after drying at 60°) C, 74·05; H, 10·3; (after drying at 100°/0·5 mm) C, 76·3; H, 10·55. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%. $C_{20}H_{32}O_2 \cdot H_2O$ requires: C, 74·5; H, 10·6%.]

The *3β,17β-diacetate* separated from aqueous MeOH in flakes, m.p. 161–162·5°, $[\alpha]_D$ −40°, $\nu_{max}^{CCl_4}$ 3062, 1645 (exocyclic:CH_2), 1733 cm^{-1} (acetate). (Found: C, 73·9; H, 9·2. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·3%.)

6-Methylene-5α-androstane-3,17-dione. 6-Methylene-5α-androstane-3β,17β-diol (200 mg) in acetone (5 ml) was stirred and treated dropwise with Jones' chromic acid reagent until the presence of an excess of oxidant was indicated by the colour. The solid obtained on addition of water was purified from aqueous MeOH. The 3,17-dione was obtained as flakes, m.p. 187–188°, $[\alpha]_D$ +70° $\nu_{max}^{CCl_4}$ 3080, 1747, 1722, 1652, $\nu_{max}^{CS_2}$ 895 cm^{-1}. (Found: C, 79·6; H, 9·2. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%.)

6α-Methylandrost-4-ene-3,17-dione. 6-Methylene-5α- or -5β-androstane-3,17-dione (100 mg) in formic acid (1 ml) was heated on the steambath for ½ hr. Addition of water to turbidity afforded 6α-methyl-androst-4-ene-3,17-dione, which was purified from acetone–hexane to give needles, m.p. 164–167°. The identity of these samples was confirmed by mixed m.p. and by comparison of IR spectra with that of an authentic specimen.

3β-Acetoxy-5α,6α-epoxy-6β-methylpregnan-20-one. Peracetic acid (30 ml of 40%) was added over 15 min to a stirred mixture of 3β-acetoxy-6-methylpregn-5-en-20-one[4] (25 g) and powdered anhydrous sodium acetate (3·1 g) in CH_2Cl_2 (150 ml) at 0°. The mixture was stirred for a further 2 hr, the temp being allowed to rise to 20°. The product was isolated with ether, and the neutral fraction purified from aqueous MeOH to give the 5α,6α-epoxide, needles, m.p. 139°, $[\alpha]_D$ +19°. (Found: C, 74·6; H, 9·3. $C_{24}H_{38}O_4$ requires: C, 74·2; H, 9·3%.)

3β-Acetoxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (Ic; R = :O). The foregoing epoxide (19·5 g) in anhydrous benzene (250 ml) was treated with redistilled BF_3-etherate (20 ml) and the mixture set aside for 3 days at room temp. Thereafter it was poured into sat. $NaHCO_3$ aq, and the mixture shaken to decompose the BF_3. The benzene layer was washed, the solvent was removed under red. press. and the residue purified from acetone–hexane. The dione separated in needles, m.p. 115–118°, $[\alpha]_D$ +66°. (Found: C, 73·9; H, 9·2. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·3%.)

3β-Acetoxy-5β-methyl-4a-oxo-A-homo-B-norpregnane-20-semicarbazone. A mixture of semicarbazide hydrochloride (2·5 g) and anhydrous sodium acetate (2·5 g) in acetic acid (50 ml) was treated with just sufficient water to give a clear solution. The foregoing dione (5 g) was added, the mixture stirred for 6 hr and then set aside overnight. The product obtained on the addition of water was purified from $CHCl_3$–EtOH to give the semicarbazone, plates, m.p. 262–264° (dec). (Found: C, 67·7; H, 8·9; N, 9·4. $C_{25}H_{39}N_3O_4$ requires: C, 67·4; H, 8·8; N, 9·4%.)

3β,4aα-Dihydroxy-5β-methyl-A-homo-B-norpregnane-20-semicarbazone. A suspension of the foregoing compound (5·5 g) and $LiBH_4$ (2·2 g) in anhydrous tetrahydrofuran (140 ml) was heated for 2 hr under reflux. The mixture was cooled to 0° and treated with an excess of dil. acetic acid. Concentration under red. press. gave a solid which was crystallized from tetrahydrofuran–MeOH. The diol formed needles, m.p. 250–251° (dec), $[\alpha]_D$ −14° (in pyridine). (Found: C, 68·0; H, 9·4; N, 10·5. $C_{23}H_{39}N_3O_3$ requires: C, 68·1; H, 8·7; N, 10·4%.)

3β,4aα-Dihydroxy-5β-methyl-A-homo-B-norpregnan-20-one. The foregoing compound (62 g) and pyruvic acid (25 ml) in acetic acid (200 ml) and water (25 ml) were heated for 30 min on the steam-bath. Warm water (250 ml) was then added and the mixture stirred until solid began to separate. Heating on the steam-bath was continued for a further 45 min, during which time more warm water (200 ml) was added portionwise until a permanent turbidity appeared in the supernatant liquor. The product was collected, washed well, and crystallized from aqueous EtOH to give 3β,4aα-dihydroxy-5β-methyl-A-homo-B-norpregnan-20-one, microcrystals, m.p. 183–186°, $[\alpha]_D$ +57°, ν_{max}^{Nujol} 3400 (OH) and 1700 cm^{-1} (20-one). (Found: C, 75·8; H, 10·3. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%.)

3β-Acetoxy-4aα-hydroxy-5β-methyl-A-homo-B-norpregnan-20-one (Ic; R = α-OH), prepared by treating the foregoing diol (40 g) with acetic anhydride (60 ml) and pyridine (100 ml) for 18 hr at 0°, crystallized from aqueous EtOH in needles, m.p. 182°, $[\alpha]_D$ +54°, ν_{max}^{Nujol} 3495 (OH), 1745 (acetate) and 1700 cm^{-1} (20-one). (Found: C, 74·0; H, 10·4. $C_{24}H_{38}O_4$ requires: C, 73·8; H, 9·8%.)

Oxidation in acetone with the Jones' chromic acid reagent gave 3β-acetoxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione, m.p. and mixed m.p. 115–118°.

Acetylation in pyridine (4½ hr at 100°) gave the 3β,4aα-diacetate, plates (from aqueous MeOH), m.p. 125–126°, $[\alpha]_D$ +61°. (Found: C, 72·6; H, 9·6. $C_{28}H_{40}O_5$ requires: C, 72·2; H, 9·3%.)

3β-Acetoxy-4aα-methanesulphonyloxy-5β-methyl-A-homo-B-norpregnan-20-one, prepared by treating the alcohol (Ic; R = α-OH; 10 g) with methanesulphonyl chloride (4·5 ml) in pyridine (25 ml) for 4 hr at room temp, crystallized from CH_2Cl_2–hexane in needles, m.p. 124–125° (dec), $[\alpha]_D$ −44°. (Found: C, 64·1; H, 8·6. $C_{25}H_{40}O_6S$ requires: C, 64·1; H, 8·6%.)

3β-Acetoxy-6-methylene-5β-pregnan-20-one (IIc; R = β-OAc). The foregoing mesylate (20 g) in a mixture of collidine (20 ml) and pyridine (20 ml) was heated for 45 min under reflux. The mixture was poured onto crushed ice and conc. HCl, and the product isolated with ether. Crystallization from aqueous MeOH gave 3β-acetoxy-6-methylene-5β-pregnan-20-one, needles, m.p. 123°, $[\alpha]_D$ +59°, ν_{max}^{Nujol} 3050 and 1650 cm^{-1}. (exocyclic:CH_2). (Found: C, 77·9; H, 9·8. $C_{24}H_{36}O_3$ requires: C, 77·4; H, 9·7%.)

3β-Hydroxy-6-methylene-5β-pregnan-20-one (IIc; R = β-OH), prepared by heating a solution of the foregoing compound (5 g) and KOH (1 g) in 80% aqueous EtOH (50 ml) for 45 min under reflux, crystallized from hexane in soft needles, m.p. 127–128°, $[\alpha]_D$ +61°, ν_{max}^{Nujol} 3350 (OH), 3050 and 1648 cm^{-1} (exocyclic:CH_2). (Found: C, 79·5; H, 10·4. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·4%.) The compound tended to separate as a jelly from hexane and from aqueous MeOH or EtOH. Acetylation gave the parent 3β-acetate.

6-Methylene-5β-pregnane-3,20-dione (IIc; R = :O). The Jones chromic acid reagent (3·4 ml) was added dropwise during 5 min to a stirred solution of 3β-hydroxy-6-methylene-5β-pregnan-20-one (4 g) in acetone (75 ml). The product obtained on the addition of water was crystallized from aqueous MeOH to give the dione, needles, m.p. 113–114° or 120°, $[\alpha]_D$ +51°, $\nu_{max}^{CCl_4}$ 3073, 1647 (exocyclic:CH_2), 1714 and 1707 cm^{-1}. (Found: C, 80·4; H, 9·8. $C_{22}H_{32}O_2$ requires: C, 80·4; H, 9·8%.)

The Bis-sulphite (VI; R = β-OAc). Purified $SOCl_2$ (3 ml) was added dropwise during 2 min to 3β-acetoxy-5aα-hydroxy-5β-methyl-A-homo-B-norpregnan-20-one (5 g) in pyridine (25 ml) at 0°. After 15 min at this temp, the mixture was poured into ice-water and the product isolated with ether. Crystallization from ether–hexane gave the bis-sulphite, prisms, m.p. 179–180°, $[\alpha]_D$ +52°, ν_{max}^{Nujol} 1200 cm^{-1} (—SO). (Found: C, 70·0; H, 8·9; S, 3·9. $C_{48}H_{74}O_9S$ requires: C, 69·7; H, 9·0; S, 3·9%.)

The ketone (VI; R = :O). A solution of the foregoing compound (5 g) and K_2CO_3 (4 g) in MeOH (135 ml) and water (20 ml) was refluxed for 1 hr. The product was isolated with ether and crystallized once from ether–hexane to give needles, m.p. 192–193° (dec), ν_{max}^{Nujol} 3500 (OH) and 1200 cm^{-1} (—SO). This material could not be satisfactorily recrystallized. Acetylation gave the parent 3β-acetate. The Jones reagent (1·6 ml) was added dropwise during 5 min to a stirred solution of the compound, m.p. 192–193° (2·4 g) in acetone (100 ml). Water (200 ml) was then added slowly, when the product separated in crystals. Purified from aqueous EtOH, the ketone formed needles,

m.p. 168° (dec), $[\alpha]_D$ +43°, ν_{max}^{Nujol} 1700 cm^{-1} (3- and 17-CO). (Found: C, 71·2; H, 8·9; S, 4·5. $C_{44}H_{66}O_7S$ requires: C, 71·5; H, 9·0; S, 4·3%.)

4a*α-Hydroxy-5β-methyl*-A-*homo*-B-*norpregnane*-3,20-*dione* (VII; R = :O, R_1 = α-OH). The foregoing compound (2 g) was added to NaOH (0·5 g) in MeOH (19 ml) and water (1 ml). The mixture was stirred for 7 min, during which time the steroid dissolved and a crystalline product separated. The solids obtained on addition of water were purified from aqueous MeOH to give the ketol, needles, m.p. 167–168°, $[\alpha]_D$ +21°, ν_{max}^{Nujol} 3450 cm^{-1} (OH). (Found: C, 76·5; H, 9·8. $C_{22}H_{34}O_3$ requires: C, 76·3; H, 9·9%.)

5β-Methyl-A-*homo*-B-*norpregn*-4(4a)-*ene*-3,20-*dione* (VIII). (a) A solution of the foregoing ketol (1·5 g) and NaOH (0·5 g) in aqueous EtOH (15 ml of 90%) was heated for 5 min under reflux. Water was added and the product isolated with ether. Crystallization from aqueous MeOH gave the αβ-unsaturated ketone, dense irregular crystals, m.p. 107–108°, $[\alpha]_D$ −6°, λ_{max} 233 mμ (ε 9,900). (Found: C, 80·7; H, 10·3. $C_{22}H_{32}O_2$ requires: C, 80·4; H, 9·9%.)

(b) The ketol (VII; R = :O; R_1 = α-OH; 1 g) in EtOH (10 ml) was treated with 2 drops of conc. HCl, and the mixture heated for 15 min under reflux. The product, isolated with ether, was crystallized from aqueous MeOH to give VIII, identical with that prepared by method (a) above.

3β-Hydroxy-5β-methyl-A-*homo*-B-*norpregnane*-4a,20-*dione* (VII; R = β-OH; R_1 = :O). A solution of 3β-acetoxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (4 g) and KOH (0·8 g) in MeOH (50 ml) and water (5 ml) was set aside overnight at room temp. The solid obtained on addition of water was crystallized from aqueous EtOH to give the ketol, needles, m.p. 181–182°, $[\alpha]_D$ +40°, ν_{max}^{Nujol} 3450 cm^{-1} (OH). (Found: C, 76·5; H, 10·1. $C_{22}H_{34}O_3$ requires: C, 76·3; H, 9·9%.) The same compound was also formed, in lower yield, when the parent 3β-acetate (2·5 g) and conc. HCl acid (0·5 ml) in EtOH (20 ml) was heated under reflux for 2 hr. There was no evidence of the formation of αβ-unsaturated ketonic material.

3β-Methanesulphonyloxy-5β-methyl-A-*homo*-B-*norpregnane*-4a,20-*dione*, prepared by treating the foregoing ketol (5·3 g) with methanesulphonyl chloride (3·5 ml) in pyridine (20 ml) for 1 hr at room temp, crystallized from acetone–hexane in needles, m.p. 160–161° (dec), $[\alpha]_D$ +57°. (Found: C, 64·8; H, 8·3. $C_{23}H_{36}O_5S$ requires: C, 65·1; H, 8·55%.)

5β-Methyl-A-*homo*-B-*norpregn*-3-*ene*-4a,20-*dione* (IX). The foregoing mesylate (1·5 g) in collidine (3 ml) was heated for 30 min under reflux. The cooled mixture was poured into dil. HCl acid, and the ppt collected and crystallized from aqueous EtOH. The unsaturated ketone formed needles, m.p. 168–169°, $[\alpha]_D$ −31°, λ_{max} 226·5 mμ (ε 4075). (Found: C, 80·6; H, 9·9. $C_{22}H_{32}O_2$ requires: C, 80·4; H, 9·8%.)

5β-Methyl-A-*homo*-B-*norpregnane*-3,4a-*dione*. The 3β-hydroxy-4a-ketone (VII; R = β-OH; R_1 = O; 3·4 g) suspended in acetone (50 ml) was treated dropwise with Jones reagent (2·6 ml) until an orange colour persisted. Dilution with water gave tiny plates, which were recrystallized from aqueous EtOH. The dione formed needles, m.p. 169–170°, $[\alpha]_D$ −55° λ_{max} 263 mμ (ε 307), $\lambda_{infl.}$ 292 mμ (ε 130). In 0·1 N KOH in EtOH, λ_{max} 298·5 mμ (ε 19,330). (Found: C, 76·4; H, 9·25. $C_{22}H_{32}O_2$ requires: C, 76·7; H, 9·4%.)