Steroids. Part XIV.[1] Transformations of 8α,9α- and 9α,11α-Epoxylanostanes and Related Compounds

By I. G. Guest and B. A. Marples,* The Department of Chemistry, The University of Technology, Loughborough

3β-Acetoxy-8,9-epoxy-5α,8α-lanostane reacts with boron trifluoride–ether complex in benzene to give 3β-acetoxy-5α-lanosta-7,9(11)-diene. Under similar conditions 3β-acetoxy-9,11α-epoxy-5α-lanostane gives a mixture of 3β-acetoxy-5α,9β-lanostan-11-one and 3β-acetoxy-8-methyl-18-nor-5α,8α,14β-lanosta-9(11),13(17)-diene. Treatment of 3β-acetoxy-5α-lanost-9(11)-ene with N-bromoacetamide and perchloric acid gives 3β-acetoxy-7α-bromo-5α-lanost-8-en-11-one.

THE reactions of a number of steroidal epoxides with various Lewis acids, in particular boron trifluoride–ether complex, have been intensively studied.[2] Few

similar studies of 8,9- and 9,11-epoxides have been reported.[3,4] The 8,9-epoxide (1) with boron trifluoride–ether complex in benzene gives the diene (2),[3] and

[1] Part XIII, I. G. Guest and B. A. Marples, *J. Chem. Soc.* (C), 1971, 576.

[2] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, ch. 8.

[3] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596.

[4] J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1989; J. W. ApSimon and J. J. Rosenfeld, *Chem. Comm.*, 1970, 1271.

the 9,11-epoxides (3a and b) similarly give the 11-ketones (4a and b).[3] In contrast, the 9,11-epoxides (5a and b) do not react under these conditions, but react with a solution of gaseous boron trifluoride in benzene to give the aromatic compounds (6a and b) and the $\Delta^{8,14}$-compounds (7a and b).[4] In relation to these and our own studies on steroid 9,10-epoxides,[5] we have examined the reactions of 3β-acetoxy-8,9-epoxy-5α,8α-lanostane (9)[6] and 3β-acetoxy-9,11α-epoxy-5α-lanostane (13) with boron trifluoride–ether complex and with tin(IV) chloride in benzene solution.

(1) → (2)

(3) → (4)

a; 9α 11α   a; 9β
b; 9β 11β   b; 9α

(5) →

(6)

(7)

a; R = O
b; R = β-Ac,H
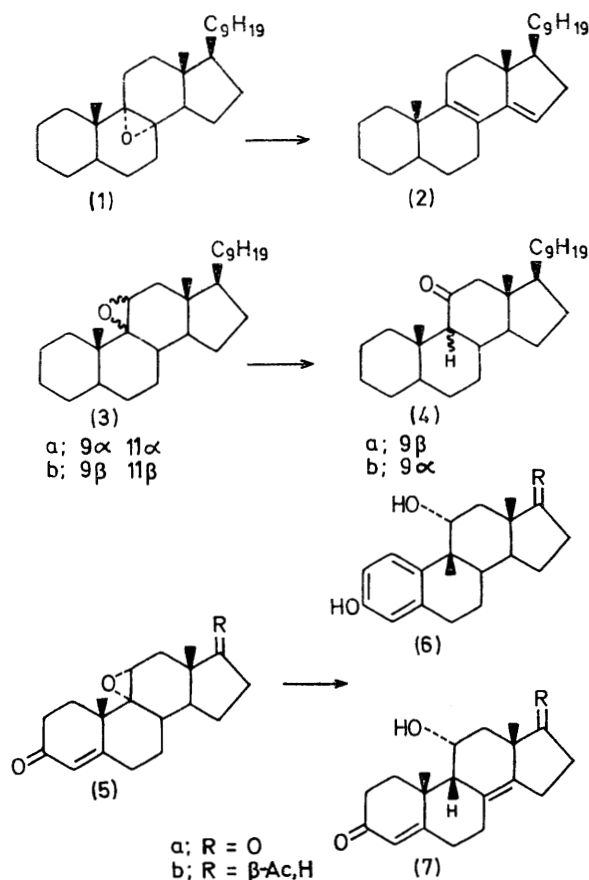
The 8,9-epoxide (9)[6] gave only the diene (10)[7] when treated in benzene solution with either boron trifluoride–ether complex or tin(IV) chloride. The same result has been obtained[6] by treatment of the 8,9-epoxide (9) with mineral acid. The 9,11-epoxide (13) was prepared from the 8,9-epoxide by the route shown. Reduction with lithium in ethylamine (with or without t-butyl alcohol)[6] of the 8,9-epoxide (8),[6] followed by

acetylation and chromatography of the crude product, gave the 9α-hydroxy-compound (11) * and some diene (10). Treatment of compound (11) with thionyl chloride in pyridine,[6] or with sulphuric acid–acetic anhydride–acetic acid, or with toluene-p-sulphonic acid–acetic anhydride gave the 9(11)-olefin (12) and no rearrangement products. Oxidation of the 9(11)-olefin (12) with monoperphthalic acid gave the 9,11-epoxide (13). The α-configuration of the epoxide (13) was confirmed by the [1]H n.m.r. spectrum, in which the 11β-H signal appears as a doublet. Models suggest this is compatible with the 9α,11α-configuration, in which the 11β-H is spin–spin coupled appreciably only to the 12β-H. Treatment of benzene solutions of the 9,11-epoxide (13) with boron trifluoride–ether complex or with tin(IV) chloride gave the 9β-11-ketone (14) (35%) and the $\Delta^{9(11),13(17)}$-compound (16) (45%). The structure of the ketone (14) was clear from its i.r. spectrum ($\nu_{max.}$ 1713 cm.$^{-1}$) and from its conversion by treatment with base and reacetylation into the known 9α-ketone (15).[8] The [1]H n.m.r. spectrum of the $\Delta^{9(11),13(17)}$-compound (16) showed the presence of a vinylic proton (τ 4·7) and a doublet at τ 9·01 and 9·08 (J 21 Hz) collapsed to a singlet on irradiation 149 Hz † downfield. This fact and the presence of an intense peak at $M - 113$ in the mass spectrum confirmed the presence of the 13(17)-double bond.[9,10]

We hoped to be able to prepare the 9β,11β-epimer of epoxide (13) via the bromohydrin (22). To this end, the olefin (12) was treated with N-bromoacetamide and perchloric acid (' HOBr ') in aqueous dioxan.[11] The major product, the bromo-ketone (17), showed u.v. ($\lambda_{max.}$ 267 nm.) and i.r. (1668 cm.$^{-1}$) spectra typical of an αβ-unsaturated ketone. The [1]H n.m.r. spectrum of compound (17) showed a signal at low field (τ 5·00; $W_{\frac{1}{2}}$ ca. 7 Hz) which is assigned to the 7β-methine proton. Hydrogenolysis of the bromo-ketone (17) over palladium gave the ketone (18)[9] ($\lambda_{max.}$ 257 nm.).‡ The m.p. of our product (133—134°) did not agree with that reported[8] (119—120°). Accordingly, the ketone (18) was reduced with lithium in liquid ammonia to the diol (20), from which the acetate (21) was obtained. The m.p.s of these compounds agreed with those in the literature.[12] Treatment of the bromo-ketone (17) with methanolic potassium hydroxide gave the methoxy-compound (19). The 7β-configuration is indicated by the [1]H n.m.r. spectrum of the latter, in which the 7-proton signal is broad (and superimposed on that for the 3-proton).

The failure of the olefin (12) to give the bromohydrin

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* We thank Professor J. Fried for a sample of compound (11).
† 100 MHz spectrum.
‡ The bathochromic shift of ca. 10 nm. due to the 7α-bromine atom is reasonable (cf. A. I. Scott, ' Interpretation of Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964, p. 260).

[5] I. G. Guest and B. A. Marples, Tetrahedron Letters, 1969, 3575.
[6] J. Fried, J. W. Brown, and M. Applebaum, Tetrahedron Letters, 1965, 849.
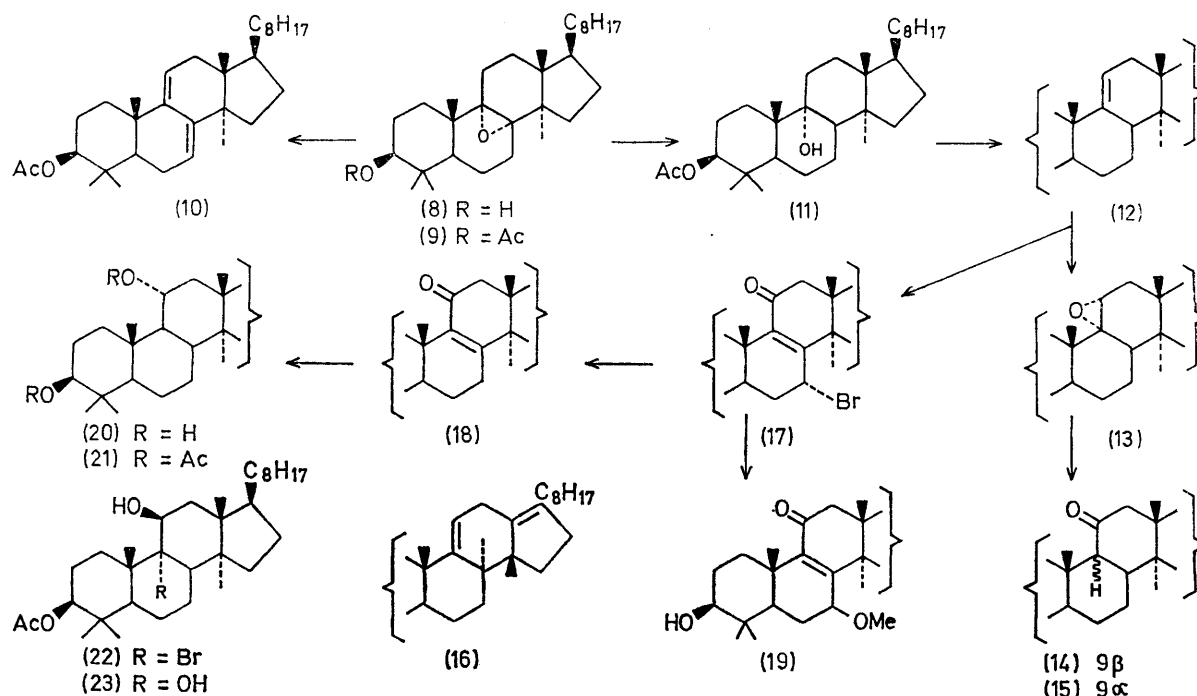[7] L. Ruzicka, R. Denss, and O. Jeger, Helv. Chim. Acta., 1946, 29, 204.

[8] J. F. McGhie, M. K. Pradhan, and J. F. Cavalla, J. Chem. Soc., 1952, 3176.
[9] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, Tetrahedron, 1966, 22, 3195.
[10] (a) G. Snatzke and H.-W. Fehlhaber, Annalen, 1964, 676, 188; (b) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, Tetrahedron Letters, 1966, 2125.
[11] J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, Helv. Chim. Acta, 1963, 46, 1361.
[12] M. V. Mijović, W. Voser, H. Heusser, and O. Jeger, Helv. Chim. Acta, 1952, 35, 964.

(10)   (8) R = H / (9) R = Ac   (11)   (12)

(20) R = H / (21) R = Ac   (18)   (17)   (13)

(22) R = Br / (23) R = OH   (16)   (19)   (14) 9β / (15) 9α

(22) is possibly due to a severe interaction in the transition state between the developing 9α-bromo-substituent and the 14α-methyl group. We have found that the epoxide (13) cannot be hydrolysed to the diol (23) with a variety of acid catalysts, presumably owing to a similar steric interaction between the developing 9α-hydroxy-group and the 14α-methyl group. Alternatively, it is possible that the bromohydrin (22) and the diol (23) are formed, and that these interactions assist their decomposition.

(24)   (25)
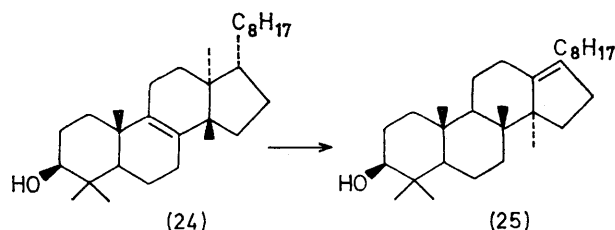
The failure of the 8,9-epoxide (9) to rearrange to a $\Delta^{13(17)}$-compound is probably due, in part, to the *syn*-conformation of the 14α-methyl and 8,9-epoxide groups. Such a conformation requires the full development of a carbonium ion at C-8 before rearrangement can occur. We have noted in the 9,10-epoxides[5] that conjugated diene formation is favoured under similar conditions. In contrast to this, the *anti*-conformation of the 8-proton and the 9,11-epoxide group in the epoxide (13) could allow a more concerted hydride shift from C-8 to C-9, which could compete effectively with elimination. Subsequent consecutive 1,2-methyl shifts from C-14 to C-8, and from C-13 to C-14, followed by proton loss from

C-17 and elimination of the oxygen function from C-11 would lead to the observed product (16). Although the similar acid-catalysed rearrangement of dihydro-euphol (24) to isoeuphenol (25) is well known,[13] the rearrangement of the 13β- and 14α-methyl groups in the lanostanes has not been previously reported. It is surprising that the alternative rearrangement of the 10-methyl group to the 9-position does not occur with either the 8,9-epoxide (9) or the 9,11-epoxide (13). The interaction between the 4β-methyl and the angular methyl groups apparently provides insufficient driving force for this. The failure of the 9α-hydroxy-compound (11) to rearrange to either a 9-methyl or a $\Delta^{13(17)}$-compound in toluene-*p*-sulphonic acid–acetic anhydride or in sulphuric acid–acetic anhydride–acetic acid is similarly surprising, since these reaction conditions and stereo-electronic factors would be expected to allow rearrangement to compete with simple dehydration.[14,15]

EXPERIMENTAL

[13] D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight, *J. Chem. Soc.*, 1955, 876.

[14] J. G. Ll. Jones and B. A. Marples, *Chem. Comm.*, 1969, 689.
[15] J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk, and S. W. Yoong, *Tetrahedron*, 1965, **21**, 1567.

were used for preparative t.l.c. Solutions in organic solvents were dried over anhydrous sodium sulphate and evaporated *in vacuo* with a rotary evaporator.

8,9-Epoxy-5α,8α-lanostan-3β-ol (8).[6]—5α-Lanost-8-en-3β-ol [16] (8 g.) in a solution of monoperphthalic acid in ether (0·26 M; 350 ml.) was set aside at room temperature overnight. The resulting solution was washed free of acid with sodium hydroxide solution (2N), and with water, and dried. Evaporation gave the epoxide (8) (7·2 g.), m.p. 157—159° (from ethyl acetate), $[\alpha]_D$ +5° (c 1·83) (lit.,[6] m.p. 158—162°, $[\alpha]_D$ +7°).

3β-Acetoxy-8,9-epoxy-5α,8α-lanostane (9).[6]—A solution of the epoxide (8) (0·5 g.) in pyridine (10 ml.) and acetic anhydride (0·5 ml.) was set aside at room temperature overnight and then poured on crushed ice. The crude product was filtered off and washed with water to give the epoxide (9) (0·5 g.), m.p. 140—142° (from ethyl acetate), $[\alpha]_D$ +14° (c 0·6) (lit.,[6] m.p. 140—141°, $[\alpha]_D$ +15°).

Reaction of the 8α,9α-Epoxide (9) *with Lewis Acids.*—(a) Boron trifluoride–ether complex (0·5 ml.) was added to a solution of the epoxide (9) (0·5 g.) in dry benzene (10 ml.) at room temperature. After 1 min., ether was added and the solution was poured into sodium hydrogen carbonate solution. The organic layer was dried and evaporated to give 3β-acetoxy-5α-lanosta-7,9(11)-diene (10) (0·4 g.), m.p. 166·5—167°, $[\alpha]_D$ +89° (c 0·8), $\lambda_{max.}$ 244 nm. (ε 13,550) (lit.,[7] 167—168°, $[\alpha]_D$ +88°).

(b) Tin(IV) chloride (0·1 ml.) was added to a solution of the epoxide (9) (0·1 g.) in dry benzene (2 ml.) at room temperature. After 5 min., the solution was worked up as in (a) to give the diene (10) (90 mg.).

3β-Acetoxy-5α-lanostan-9α-ol (11).[6]—Finely cut lithium (0·5 g.) was added slowly in portions to a stirred solution of the epoxide (8) (1·2 g.) in anhydrous ethylamine (50 ml.). After 2 hr. a blue colour had developed. The solution was stirred for a further 1 hr. and the reaction was quenched with acetone. The mixture was poured into water; extraction with ether and the usual work-up gave a mixture of two products which was acetylated as already described. Preparative t.l.c. [benzene–ethyl acetate (10 : 1)] gave the 9α-hydroxy-compound (11) (0·45 g.), m.p. 168—169° (from ethyl acetate), $[\alpha]_D$ +18° (Found: C, 78·6; H, 11·5. Calc. for $C_{32}H_{56}O_3$: C, 78·6; H, 11·55%) (lit.,[6] m.p. 163—164°, $[\alpha]_D$ +7°). Recrystallisation of an authentic sample provided by Professor Fried [6] gave material identical with our sample. A second fraction from the t.l.c. gave the diene (10) (200 mg.). Repetition of this reaction in the presence of t-butyl alcohol (3 or 12 mol.) gave the same products in the same yields but the reaction times were shorter (30 and 10 min., respectively).

3β-Acetoxy-5α-lanost-9(11)-ene (12).[6]—(a) Thionyl chloride (0·8 ml.) was added to a solution of the 9α-hydroxy-compound (11) (3·8 g.) in pyridine (20 ml.) at 0°. After 5 min. the solution was poured on crushed ice and filtered. The crude product gave the olefin (12) (3·5 g.), m.p. 174—176° (from ethyl acetate), $[\alpha]_D$ +89° (c 1·3) (Found: C, 81·7; H, 11·55. Calc. for $C_{32}H_{54}O_2$: C, 81·65; H, 11·55%) (lit.,[6] m.p. 162—165°, $[\alpha]_D$ +85°).

(b) Sulphuric acid (2 drops) was added to a solution of the 9α-hydroxy-compound (0·2 g.) in acetic anhydride (2 ml.) and acetic acid (1 ml.) at room temperature. After 15 min. the solution was poured into brine and the resultant mixture was extracted with ether. The extracts were washed with sodium hydrogen carbonate solution and dried. Evaporation left a crude product which after t.l.c. [benzene–

ethyl acetate (10 : 1)] gave the 9α-hydroxy-compound (11) (25 mg.) and the olefin (12) (150 mg.).

(c) A solution of toluene-p-sulphonic acid (22 mg.) and the 9α-hydroxy-compound (0·1 g.) in acetic anhydride (6·6 ml.) was heated on a boiling water bath for 30 min. and poured into water. The mixture was extracted with ether in the usual way to give the olefin (12).

3β-Acetoxy-9,11α-epoxy-5α-lanostane (13).—The olefin (12) (1 g.) was oxidised with monoperphthalic acid in ether solution for 48 hr. as already described to give the 9,11-epoxide (13) (1·1 g.), m.p. 188—189° (from ethyl acetate), $[\alpha]_D$ +27° (c 0·85), τ 5·65 (m, $W_{\frac{1}{2}}$ ca. 17 Hz, 3-H), 7·04 (d, J ca. 5 Hz, 11β-H), 8·07 (s, OAc), and 9·17 (m, side-chain and other Me), $\nu_{max.}$ 1740 (C=O) and 1245 (C–O) cm.$^{-1}$ (Found: C, 78·95; H, 10·85. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%).

Reaction of the 9,11-Epoxide (13) *with Lewis Acids.*—(a) Boron trifluoride–ether complex (0·8 ml.) was added to a solution of the epoxide (13) (0·8 g.) in dry benzene (16 ml.) at room temperature. After 20 min. the solution was diluted with ether and worked up in the usual way to give a mixture. Preparative t.l.c. [benzene–ethyl acetate (19 : 1)] gave 3β-acetoxy-5α,9β-lanostan-11-one (14) (279 mg.), m.p. 199—200° (from methanol–chloroform), $[\alpha]_D$ +96° (c 0·54), τ 5·5 (m, 3-H), 8·08 (s, OAc), and 9·03, 9·13, 9·23, and 9·25 (side-chain and other Me), $\nu_{max.}$ 1740 (acetate C=O) and 1713 (11-one) cm.$^{-1}$ (Found: C, 79·5; H, 11·25. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%), and 3β-acetoxy-8-methyl-18-nor-5α,8α,14β-lanosta-9(11),13(17)-diene (16) (385 mg.), a gum, $[\alpha]_D$ −18° (c 0·6), τ (CDCl$_3$; 100 MHz) 4·7 [t, J (apparent) ca. 4 Hz, 11-H], 5·51 (m, 3-H, $W_{\frac{1}{2}}$ 18 Hz), 7·9 (s, OAc), 9·01 and 9·08 (d, J ca. 7 Hz, 21-H$_3$), 8·91, 9·03, 9·06, 9·13, and 9·19 (other Me), and 9·08 and 9·17 (d, side-chain methyls); the doublet at τ 9·01 and 9·08 collapsed on irradiation at −149 Hz to give a broadened signal at τ 9·06); M (mass spectrum), 468·3963 ($C_{32}H_{52}O_2$ requires M 468·3967), M − side chain 355·2636 ($C_{24}H_{35}O_2$ requires 355·2637). In common with other $\Delta^{13(17)}$-compounds, compound (16) was too unstable for satisfactory elemental analysis.

(b) Tin(IV) chloride (0·1 ml.) was added to a solution of the epoxide (13) (0·1 g.) in benzene (2 ml.) at room temperature. After 1 hr. the mixture was worked up as before and gave a mixture of the ketone (14) and the $\Delta^{13(17)}$-compound (16).

3β-Acetoxy-5α-lanostan-11-one (15).—The ketone (14) was heated under reflux in ethanol containing sodium ethoxide for 15 min. The usual work-up gave a crude mixture which after reacetylation and preparative t.l.c. gave some starting material (14) and the ketone (15), m.p. 150—151°, $[\alpha]_D$ +60° (c 0·5) (lit.,[8] m.p. 150—152°, $[\alpha]_D$ +62°).

3β-Acetoxy-7α-bromo-5α-lanost-8-en-11-one (17).—N-Bromoacetamide (0·5 g.) was added during 15 min. to a stirred solution at 0° of the olefin (12) (1 g.) in dioxan (10 ml.), perchloric acid (0·74 ml. aqueous 13% w/v), and water (0·5 ml.). After a further 2 hr. at room temperature the solution was poured into sodium thiosulphate solution and the resultant mixture was extracted with ether. The ether layer was washed with sodium hydrogen carbonate solution and water, and dried. Evaporation gave a product containing a large proportion of starting material (12); this was retreated as before but for 14 hr. The crude product was chromatographed on deactivated (grade III) neutral alumina (50 g.) and gave the olefin (12) (150 mg.)

and the *bromo-ketone* (17) (460 mg.), m.p. 176—177° (from methanol–acetone), $[\alpha]_D$ +124° (*c* 0·6), $\lambda_{max.}$ (EtOH) 267 nm. (ε 7660), $\nu_{max.}$ 1735 (acetate C=O) and 1668 (11-one) cm.$^{-1}$, τ 5·00 (m, $W_{\frac{1}{2}}$ *ca.* 7 Hz, 7β-H), 5·45 (m, $W_{\frac{1}{2}}$ *ca.* 19 Hz, 3-H), 8·04 (s, OAc), and 8·70, 8·98, 9·1, 9·15, 9·19, and 9·26 (side-chain and other Me) (Found: C, 67·95; H, 8·9; Br, 14·1. $C_{32}H_{51}BrO_3$ requires C, 68·2; H, 9·1; Br, 14·2%).

3β-Acetoxy-5α-lanost-8-en-11-one (18).—A solution of the bromo-ketone (17) (188 mg.) in ethyl acetate (5 ml.) was stirred with a 5% palladium–charcoal catalyst under *hydrogen at room* temperature for 2 hr. The solution was filtered and evaporated to give the ketone (18) (70 mg.), m.p. 133—134°, $[\alpha]_D$ +138° (*c* 0·6), $\lambda_{max.}$ (EtOH) 257 nm. (ε 9370), $\nu_{max.}$ 1740 (acetate C=O) and 1663 (11-one) cm.$^{-1}$, τ 5·53 (m, $W_{\frac{1}{2}}$ *ca.* 18 Hz, 3-H), 8·02 (s, OAc), and 8·89, 9·08, 9·12, and 9·17 (side-chain and other Me) (Found: C, 78·85; H, 10·4. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%) {lit.,[8] m.p. 119—120°, $[\alpha]_D$ +131·3°, $\lambda_{max.}$ 255 nm. (log ε 3·9)}.

3β,11α-Diacetoxy-5α-lanostane (21) *and* *5α-Lanostane-3β,11α-diol* (20).—Finely cut lithium was added to a solution of the ketone (19) (19·5 mg.) in dry ether (2 ml.) and liquid ammonia (10 ml.) at −4° at a sufficient rate to maintain a blue colouration for 20 min. Methanol was added and the ammonia was allowed to evaporate. Ether and then water were added to the mixture. The organic layer was dried and evaporated to give a crude mixture which was acetylated under the usual conditions. Preparative

t.l.c. gave the diacetate (21), m.p. 128—129° (from methanol) (lit.,[12] m.p. 127—128°). Hydrolysis of the diacetate with aqueous methanolic potassium hydroxide and the usual work-up gave the diol (20), m.p. 195—198° (from dichloromethane–petroleum) (lit.,[12] m.p. 195—196°).

Attempted Hydrolysis of the 9,11-Epoxide (13).—Treatment of the epoxide (13) with (*a*) aqueous periodic acid–dioxan in a sealed tube at 100° for 2 hr., (*b*) aqueous dioxan in a sealed tube at 145° for 2 weeks,[17] or (*c*) aqueous perchloric acid–ethyl methyl ketone[18] failed to give the diol (23). Experiments (*a*) and (*c*) gave the diene (10); the epoxide (13) was unchanged in (*b*).

3β-Hydroxy-7β-methoxy-5α-lanost-8-en-11-one (19).—A solution of the bromo-ketone (11) (100 mg.) in methanolic potassium hydroxide (2·5%) was heated under reflux for 30 min. The solution was diluted with water and extracted with ether in the usual way. Preparative t.l.c. of the crude product gave the methoxy-ketone (19) (15 mg.), $\nu_{max.}$ 3640 (OH) and 1660 (11-one) cm.$^{-1}$, $\lambda_{max.}$ 261 nm., τ 6·89 (s, MeO), 6·5—7·3 (m, 3-H and 7-H), and 8·75, 8·89, 9·01, 9·08, 9·17, 9·21, and 9·30 (side-chain and other Me).

[16] L. W. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 365.

[17] Ref. 16, p. 196.

[18] J. M. Diggle, M. D. Halliday, G. D. Meakins, and M. S. Saltmarsh, *Chem. Comm.,* 1969, 819.