Some Chemistry of 13-Iso-steroids

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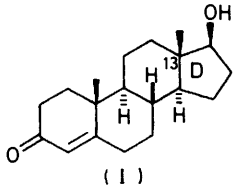
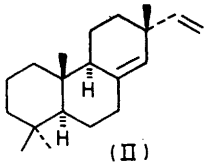
Proton-catalysed rearrangement of 4,4-dimethyl-5α,13α-androst-7-ene proceeds with methyl migration to give 4,4,14α-trimethyl-18-nor-5α-androst-13(17)-ene. The mechanism of the reaction is discussed in comparison with the rearrangement of various triterpenoids. N.m.r. assignments for C–Me resonances are tabulated.

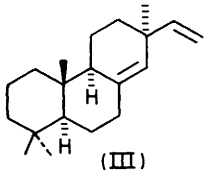
In continuation of our earlier work [1] on the conversion of testosterone (I) into (−)-sandaracopimaradiene (II) we have examined routes from compound (I) to the diterpene (+)-pimaradiene (III) involving photoepimerisation of the steroid nucleus at the 13-position.[2,3,‡] Herein we describe our initial approaches *via* olefin migration which were unsuccessful in achieving the objective, but have intrinsic interest;[5] the successful route by direct degradation of ring D is described elsewhere.[6]



(I)



(II)



(III)

U.v. irradiation of, for example, compound (IV) [1] in dioxan gave the desired product (V) in, at best, 26% yield.§ The yield was improved to 35—37% (*ca.* 54% in terms of consumed starting material) by working in dry benzene under nitrogen. Similarly the ketones (VI) and (VIII) were converted into (VII) and (IX) respectively. The keto-products (V), (VII), and (IX) were initially separated by careful chromatography and their identity established by analogy and by physical data, particularly the molecular rotation differences (ΔM_D) shown in Table 1. Bots has shown [8] that the

TABLE 1

Molecular rotation differences for several 13β- and 13α-steroidal 17-ketones

	ΔM_D
Saturated compounds (IV) and (V)	−630°
Δ^5-Compounds (VI) and (VII)	−530°
Δ^7-Compounds (VIII) and (IX)	−624°
Estrone/lumiestrone [8]	−550°

molecular change, 13β- to 13α-steroid, is accompanied by a molecular rotation change at the sodium D-line of *ca.* −550°. The structures were also confirmed by the nature and sign of the Cotton effect in the o.r.d. curves.[9] In subsequent photochemical preparations of the foregoing ketones, use was made of the relatively fast reduction [10] of the ' normal ' 13β-steroidal ketones with

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‡ Recently an excellent *chemical* method for the preparation of 13-iso-steroids has become available.[4]

§ The mechanism of these reactions has been extensively discussed by Quinkert.[7]

[1] P. Johnston, R. C. Sheppard, C. E. Stehr, and S. Turner, *J. Chem. Soc.*, (*C*), 1966, 1847.

[2] S. Turner, ' The Design of Organic Syntheses ', Elsevier Scientific Publishing Co., Amsterdam, 1976, pp. 24, 52.

[3] A. Butenandt and L. Poschmann, *Ber.*, 1944, **77**, 394.

[4] R. B. Boar, F. K. Jetuah, J. F. McGhie, M. S. Robinson, and D. H. R. Barton, *J.C.S. Chem. Comm.*, 1975, 748. See also J. C. Jacquesy, R. Jacquesy, S. Moreau, and J. F. Patoiseau, *Bull. Soc. chim. France*, 1974, 1959.

[5] R. C. Sheppard and S. Turner, *Chem. Comm.*, 1968, 682.

[6] A. Hesketh, Ph.D. Thesis, Liverpool University, 1970.

[7] G. Quinkert, *Angew. Chem. Internat. Edn.*, 1965, **2**, 211.

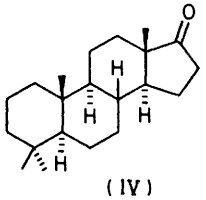
[8] J. P. L. Bots, *Rec. Trav. chim.*, 1958, **77**, 1010.

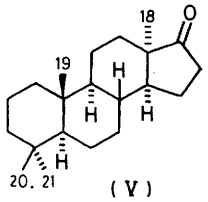
[9] W. Klyne, personal communication.

[10] L. J. Chinn, *J. Org. Chem.*, 1965, **30**, 4165; M. Fetizon and J. C. Gramain, *Bull. Soc. chim. France*, 1967, 1003.

$NaBH_4$, subsequently allowing an easier chromatographic separation of the unreduced 13α-steroidal ketones, for example compound (V).

As an exception, the $\Delta^{8(14)}$-isomer of ketone (VIII) gave, on irradiation, a mixture of products in low yield, presumably because of the allylic nature of the intermediate diradical.[7]


(IV)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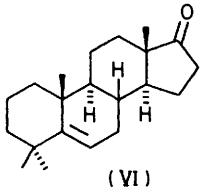
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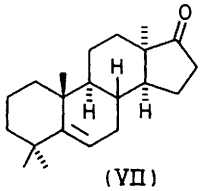
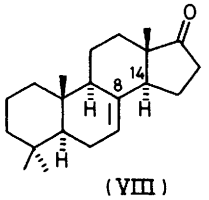
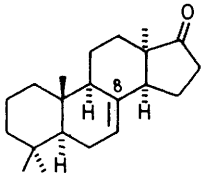
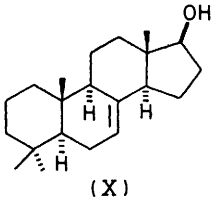
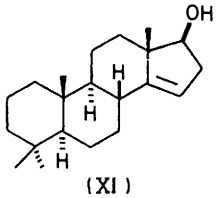

(VII)

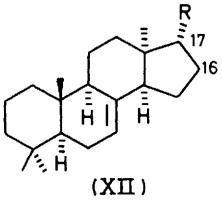

(VIII)

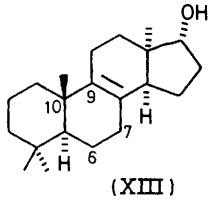

(IX)

Having in hand the key intermediate ketone (IX), it was possible to examine the acid-catalysed olefin migration. First it was shown that the 'normal' Δ^7-compound (X), on treatment with HCl gas in chloroform, gave a 60% yield of the Δ^{14}-compound (XI).[1] To examine the analogous reaction in the 13-iso-steroid series, the ketone (IX) was first treated with sodium borohydride. It was reduced more quickly than the saturated ketone (V) to give substantially one alcohol; this, it is proposed, has the 17α-hydroxy-structure (XII; R = OH), the relative speed of reaction and the stereochemical outcome arising from the absence of the 'hindering' 8β-proton in compound (IX). Treatment of the new alcohol (XII; R = OH) with HCl in $CHCl_3$ gave, in 58% yield, a new chromatographically similar isomeric alcohol, lacking olefinic protons in the n.m.r. spectrum. Assuming no major rearrangements, this new compound can have either a Δ^8- or a $\Delta^{8(14)}$-structure. The former structure (XIII) is favoured on the basis of mass and n.m.r. (*vide infra*) spectrometric arguments. Thus tri- and tetra-cyclic compounds having the $\Delta^{8(14)}$-structure show characteristic fragments in the mass spectrometer arising from cleavage of ring B between the 6- and 7-carbon atoms and between the 9- and 10-carbon atoms.[11] Such fragmentation is *not* shown by the new compound (XIII).


(X)

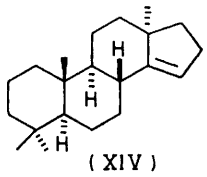

(XI)

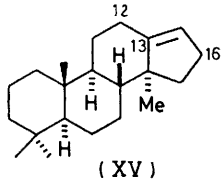

(XII)


(XIII)

In any event the double bond of compound (XII; R = OH) had not migrated to the 14,15-position. Since the ease and direction of these rearrangements is affected by the 17-substituent, the 17-ketone (IX) was next reduced to the hydrocarbon (XII; R = H). The rearrangement of the hydrocarbon (XII; R = H), using dry HCl gas in $CHCl_3$ at −30 °C, was followed by t.l.c. on $AgNO_3$-impregnated silica plates. Very rapidly a new, fast moving compound was formed (Δ^8 or $\Delta^{8(14)}$-isomer?), followed by a slow isomerisation to a mixture in which there was a major new, slow moving component, having an R_F expected for a Δ^{14}-compound.[11a] This substance was isolated by column chromatography on freshly prepared 15% $AgNO_3$-silica; the by-products from the reaction could be reisomerised to yield further quantities of the substance. The analytical data accorded with the new compound being an isomer of the Δ^7-hydrocarbon (XII; R = H), and the presence of one olefinic proton in the n.m.r. spectrum would have been consistent with the desired Δ^{14}-structure (XIV). As will be seen, however, the new substance is identified as the rearranged 14α-methyl-$\Delta^{13(17)}$-steroid (XV).

Thus the new olefin was treated with ozone, and the ozonide reduced to give a mixture of two components in a ratio of *ca.* 3 : 1 in favour of the more polar. By analogy,[1] these products derived from the $\Delta^{13(17)}$-compound (XV) were expected to be the two diols

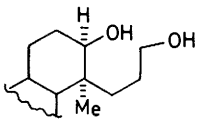

(XIV)

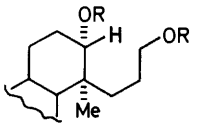

(XV)

(XVI) and (XVII; R = H); the more polar component was purified by crystallisation and characterised as the diacetate (XVII; R = Ac), having an equatorial 13α-OAc group. In particular the magnitude of the larger vicinal coupling (to H-12α) accords with an axial hydro-

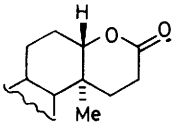
[11] (*a*) S. Turner, Ph.D. Thesis, Liverpool Univ., 1967, p. 130 *et seq.*; (*b*) M. Fetizon and M. Golfier, *Bull. Soc. chim. France*, 1963, 167; H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products, by Mass Spectroscopy', Holden-Day, San Francisco, 1964, vol. 2, p. 155.

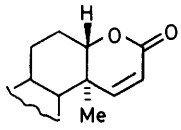
gen at C-13,[12] while the quartet character of the 13-H shows it to be adjacent to *two* hydrogen atoms [the corresponding proton for the diol arising from structure (XIV) would be a doublet]. *A priori*, the foregoing

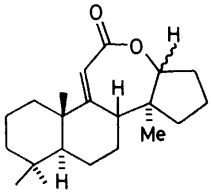

(XVI)

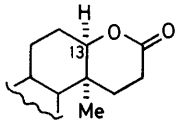

(XVII)

spectral data could also have been shown by a diol arising from the isomer of compound (XV) having a 12,13-double bond. This alternative was eliminated as follows. The diol (XVII; R = H) was oxidised by MnO_2 in high yield to the lactone (XVIII), which in turn was dehydrogenated by dichlorodicyano-*p*-quinone (DDQ) to the unsaturated lactone (XIX). The dehydrolactone (XIX) showed the expected analytical and spectroscopic data; for instance the AB pair of olefinic


(XVIII)


(XIX)

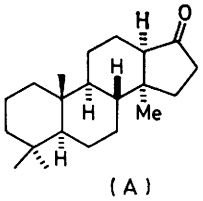

(XX)


(XXI)

protons was apparent in the n.m.r. spectrum. The alternative Δ^{12}-structure mentioned above would have given the didehydrolactone (XX) in such a sequence of transformations, clearly eliminated by the n.m.r. data.

Having in hand the lactone (XVIII), obtained from the pure diol (XVII; R = H), it was of interest to obtain the 13-epimer (XXI). MnO_2 oxidation of the diol mixture remaining after separation of the pure diol (XVII; R = H) (*vide supra*) produced a lactone mixture

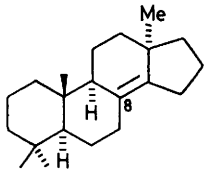
* Nor is it without possible utility. The olefin (XV) was, in preliminary experiments, converted to a crystalline epoxide which in turn was rearranged to a ketone, m.p. 144.5—146.5 °C. This substance, presumably the 17-ketone (A), could serve as a starting point for synthesis of lanostanes (*cf.* R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131 for an illustration of the problem of introducing the 14α-methyl group during a synthesis of lanostanes from cholestanes).


(A)

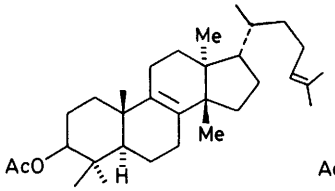
which could be resolved by crystallisation (see Experimental section) into two chromatographically identical but chemically different substances: these were further quantities of the lactone (XVIII), and an isomer identified as the 13-epimer (XXI). The stereochemistry of the latter at C-13 rests on the narrow band width of 13-H in the n.m.r. spectrum, consistent with 13-H being equatorial.[12] The difference in chemical shift between the 13-H resonance in compound (XVIII) and that in compound (XXI) was also consistent with the former having the 13-axial proton.[13] The sign of the Cotton effects in the o.r.d. curves of the two lactones is also consistent with the stereochemistry assigned.[14]

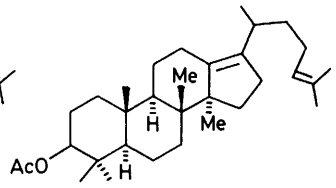
A final confirmation that the double bond in compound (XV) occupies the 13,17-position was provided by rearranging the Δ^7-steroid (XII; R = H), tetradeuteriated at positions 16 and 17 (58% incorporation of deuterium assuming 4D = 100%). A substantial portion (35% of the total) of the deuterium was lost in the rearrangement and in the n.m.r. spectrum of the resulting deuteriated olefin (XV), the olefinic peak (17-H) was reduced in width at half height from 5.00 ± 0.05 Hz (non-deuteriated) to 3.00 ± 0.05 Hz; this accords with the presence of substantial deuteriation at the allylic position (16-H).

We may theorise that the formation of the olefin (XV) from the Δ^7-compound (XII; R = H) passes *via* the intermediacy of the $\Delta^{8(14)}$-compound (XXII). This substance could be protonated at C-8 on the β-face allowing a concerted migration of the 13α-methyl group


(XXII)

to C-14, with elimination of a proton from C-17, to give the stable *trans,anti,trans*-stereochemistry depicted in structure (XV). The rearrangement herein described is not without analogy.* The conversion of euphenyl acetate (XXIII) into isoeuphenyl acetate (XXIV)[15]


(XXIII)


(XXIV)

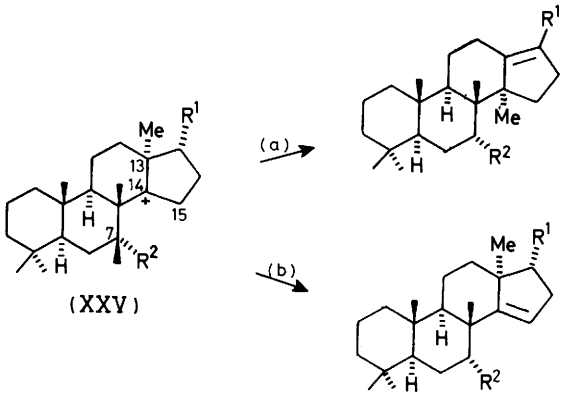
[12] (*a*) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1964, **86**, 2742; (*b*) N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry', Holden-Day, San Francisco, 1964, pp. 81, 135.

[13] Ref. 12*b*, p. 47.

[14] W. Klyne, P. M. Scopes, R. C. Sheppard, and S. Turner, *J. Chem. Soc.* (*C*), 1968, 1954.

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

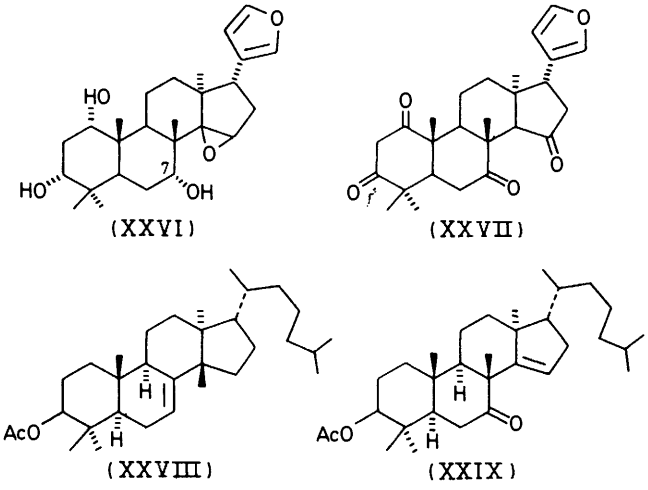
provides a parallel instance which can, however, be a fully concerted process. In our preliminary communication [5] we contrasted the foregoing rearrangements with two examples in which Δ^7-tetracyclic triterpenes were converted into Δ^{14}-olefins *without* migration of the adjacent 13α-methyl group. In subsequently reviewing these and related rearrangements in 1969 we have concluded that the collapse of a carbonium ion (XXV) (Scheme 1) at C-14 (incipient or otherwise), either by migration of the 13α-methyl group [pathway (a)], or by the alternative elimination of a 15-proton [pathway (b)], is determined by the 7α-substituent [R^2 in structure (XXV)]. The 'normal' pathway (a), where R^2 is small (*e.g.* H), is for migration of the 13α-methyl group.[15,*] However, the presence of a bulkier 7α-substituent (*e.g.* R^2 = OH) would lead to a 1,3-diaxial interaction in the transition state as the 13α-methyl group migrates to C-14 so that pathway (b) becomes



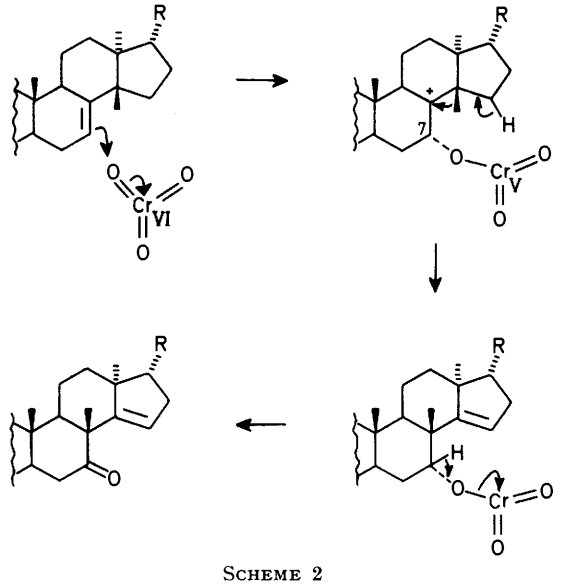
SCHEME 1

thermodynamically competitive.†,[17] This theory has also been put forward by Halsall and Weston,[17] and contrasts with that of Taylor and his co-workers [18] who favour stabilisation of the intermediate carbonium ion at C-14 by electron donation from the 7α-hydroxy-group, thus protecting the ion from attack by the 13α-methyl group.

For our 1,3-diaxial interaction theory, two apparent anomalies [16p,q] are readily explained. Thus the conversion of the 14,15-epoxy-7α-alcohol (XXVI) into the tetraketone (XXVII) [16p] presumably involves an incipient 14-carbonium ion, derived by opening of the epoxide. Apparently this must collapse by loss or migration



of the 15-proton *before* the 7α-alcohol is oxidised, in the acidic medium, to the 7-ketone; hence 13α-methyl migration is not observed. In the case of the olefin (XXVIII) [16q] we propose that a 7α-ester of a chromium(v) acid is formed and that rearrangement and loss of the 15-proton occur in this intermediate (Scheme 2) *before* collapse of the 7α-ester to the 7-ketone (XXIX).



SCHEME 2

Finally, the n.m.r. data obtained for the 13-iso-steroids described above permits an extension of the increment tables of Fetizon *et al.*[19] and Nambara *et al.*[20]

* Cases that follow path (a) in Scheme 1.[16a-d]

† Cases that follow both paths (a) and (b) in Scheme 1.[16e,f] Cases that follow path (b) in Scheme 1.[16g-o]

[16] (*a*) D. Arigoni, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1955, **38**, 222; (*b*) three examples in ref. 16*q*; (*c*) R. Hodges, S. G. McGeachin, and R. A. Raphael, *J. Chem. Soc.*, 1963, 2515; (*d*) C. W. L. Bevan, A. H. Rees, and D. A. H. Taylor, *J. Chem. Soc.*, 1963, 983; (*e*) one example in ref. 16*c*; (*f*) three examples (7α-OAc, 7-oxo, 7β-OH) in ref. 18; (*g*) W. R. Chan, J. A. Gibbs, and D. R. Taylor, *Chem. Comm.*, 1967, 720; (*h*) G. P. Cotterrell, T. G. Halsall, and M. J. Wriglesworth, *ibid.*, p. 1121; (*i*) D. Lavie and E. C. Levy, *Tetrahedron Letters*, 1968, 2097; (*j*) D. A. Okorie and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1968, 1828; (*k*) J. G. St. C. Buchanan and T. G. Halsall, *Chem. Comm.*, 1969, 242; (*l*) one example (7α-OH) in ref. 18; (*m*) G. P. Cotterrell, T. G. Halsall, and M. J. Wriglesworth, *J. Chem. Soc.* (*C*), 1970, 1503; (*n*) W. R. Chan, D. R. Taylor, and T. H. Yee, *J. Chem. Soc.* (*C*), 1971, 2662; (*o*) C. W. Lyons and D. R. Taylor, *J. C. S. Chem. Comm.*, 1976, 647; (*p*) one example in ref. 16*g*; (*q*) W. Lawrie, W. Hamilton, F. S. Spring, and H. S. Watson, *J. Chem. Soc.*, 1956, 3272.

[17] T. G. Halsall and R. J. Weston, *J.C.S. Chem. Comm.*, 1972, 1212.

[18] E. K. Adesogan, D. A. Okorie, and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1970, 205.

[19] M. Fetizon and J. C. Gramain, *Bull. Soc. chim. France*, 1966, 3444.

[20] T. Nambara, H. Hosada, and M. Usui, *Chem. Pharm. Bull.*, 1969, 1687.

for the effects of substituents on *C*-methyl resonances. Assignments for the present compounds are given in Tables 2 and 3 and are partly derived by analogy with published data [19-21] and partly by the need for internal consistency within the group of compounds prepared.

In Tables 2 and 3 the Δ^8-structure (XIII) and *C*-methyl assignments have been given by comparison

TABLE 2

Assignments of *C*-methyl resonances in several 4,4-dimethyl-5α,13α-androstanes (p.p.m. from $SiMe_4$ in $CDCl_3$)

	C-20,C-21	C-18	C-19
4,4-Dimethyl-5α,13α-androstane	0.80,0.84	0.84	0.78
Δ^7-compound (XII; R = H)	0.83,0.87	0.93	0.75
17-Ketone (V)	0.79,0.83	0.93	0.70
Δ^7-17-Ketone (IX)	0.83,0.86	0.99	0.67
Δ^5-17-Ketone (VII)	1.03,1.07	0.94	0.89
Δ^7-17α-alcohol (XII; R = OH)	0.84,0.88	0.97	0.76
Δ^8-17α-alcohol? (XIII)	0.84,0.88	0.92	0.96

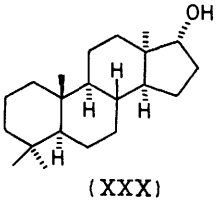
TABLE 3

Mean incremental effects of functional groups on *C*-methyl resonances in 4,4-dimethyl-5α,13α-androstanes (p.p.m. in $CDCl_3$)

	C-20,C-21	C-18	C-19
Δ^5	+0.23	0	+0.19
Δ^7	+0.03	+0.07	−0.03
Δ^8?	+0.03	+0.04	+0.17
17-Oxo	−0.01	+0.08	−0.08
17-α-OH	+0.01	+0.04	+0.01
(4,4-Dimethyl *)		−0.03	+0.07

* By comparison with 5α,13α-androstane.[19]

with the figures calculated for the compound (XXX) (*viz.* C-20, C-21, 0.81, 0.85; C-18, 0.88, C-19, 0.79 p.p.m.). On the assumption that a Δ^8- or $\Delta^{8(14)}$-function would have little effect on the C-4 resonances, but would have a relatively large effect on an allylic *C*-methyl resonance.



(XXX)

With these assumptions, the most reasonable fit is for the Δ^8-structure (XIII), rather than the $\Delta^{8(14)}$-, as given in the Tables.

EXPERIMENTAL

M.p.s are uncorrected. Specific rotations were measured in $CHCl_3$ solution at 21—25 °C. U.v. spectra were determined for solutions in 95% EtOH and n.m.r. spectra for solutions in $CDCl_3$ at 100 Hz (unless stated otherwise). C-Me resonances for 13α-steroids are collected in Table 2.

4,4-*Dimethyl*-5α,13α-*androstan*-17-*one* (V).—4,4-Dimethyl-5α-androstan-17-one [1] (0.150 g) in sodium-dried benzene (4.5 ml) under nitrogen was irradiated with the u.v. light from two high-pressure mercury-vapour lamps (Phillips, 125 W) for 7 h 10 min. The lamps were set *ca.* 4 in from the irradiation vessel, one on either side. The benzene was removed *in vacuo* and the residue dissolved in methanol (15 ml) made basic with methanolic M-potassium hydroxide (24 drops) and treated with sodium borohydride (18 mg) for 45 min at 20 °C. Excess of sodium borohydride was decomposed by the addition of a slight excess of acetic acid and the solvents were removed *in vacuo*. The white residue was extracted with ether and the ether solution filtered and evaporated to dryness to yield the crude product (0.143 g). This product was chromatographed on silica and elution with benzene yielded two fractions. The first fraction was chromatographically pure 4,4-*dimethyl*-5α,13α-*androstan*-17-*one* (0.050 g, 33%) which crystallised from methanol–water with m.p. 142—143 °C, $[\alpha]_D$ −129° (*c* 0.2), o.r.d. (MeOH) $[\phi]_{321}$ −2 700 (tr) and $[\phi]_{288}$ −530 (pk) [Found: C, 83.6; H, 11.35%; *M* (mass spectrum), 302. $C_{21}H_{34}O$ requires C, 83.4; H, 11.3%; *M*, 302].

The second fraction (0.077 g) from the chromatography was largely 4,4-dimethyl-5α-androstan-17β-ol.

4,4-*Dimethyl*-13α-*androst*-5-*en*-17-*one* (VII).—4,4-Dimethylandrost-5-en-17-one [1] (0.157 g) in dry benzene (4.5 ml) under nitrogen was irradiated with the u.v. light from two high-pressure mercury-vapour lamps (Phillips, 125 W) for 20 h. The benzene was removed *in vacuo* and the residue dissolved in methanol (12 ml), made basic with methanolic M-potassium hydroxide (16 drops), and treated with sodium borohydride (24 mg) for 35 min at 20 °C. Excess of borohydride was decomposed with acetic acid and the crude product isolated as for the corresponding saturated compound. Chromatography on silica and elution with benzene gave 4,4-*dimethyl*-13α-*androst*-5-*en*-17-*one* (0.055 g, 35%) which crystallised from methanol–water with m.p. 117—117.5°, $[\alpha]_D$ −199° (*c* 0.2); o.r.d. (MeOH) $[\phi]_{323}$ −3 570 (tr) and $[\phi]_{294}$ −1 740 (pk); τ 4.52 (1 H, t, J = 3.5 H, 6-Hz) [Found: C, 83.9; H, 10.9%; *M* (mass spectrum), 300. $C_{21}H_{32}O$ requires C, 83.9; H, 10.7%; *M*, 300].

4,4-*Dimethyl*-5α-*androst*-7-*en*-17β-*yl Acetate and* -17β-*ol* (X).—4,4-Dimethylandrosta-5,7-dien-17β-yl acetate [1] (7.07 g) in ethanol (700 ml) was hydrogenated at 6—10 atmos. and 50 °C over Raney nickel [22] (16 level spatulas) for 18 h. The catalyst was filtered off through Celite and the solvent removed *in vacuo*. Crystallisation of the residue from methanol–water gave 4,4-dimethyl-5α-androst-7-en-17β-yl acetate (5.43 g, 77%), m.p. 140—141 °C, $[\alpha]_D$ −33° (*c* 0.3); *C*-methyl resonances (60 Hz) 38, 52 (2), and 55.5 Hz [Found: *M* (mass spectrum), 344. $C_{23}H_{36}O_2$ requires *M*, 344].

Saponification in the usual manner yielded the corresponding *alcohol* (5.10 g, 100%) which crystallised from methanol–water with m.p. 147—148 °C, $[\alpha]_D$ −30° (*c* 0.3); *C*-methyl resonances (60 Hz) 35, 52 (2), and 55 Hz. The analytical sample was prepared by sublimation at 140 °C/0.3 mmHg [Found: C, 83.3; H, 11.15%; *M* (mass spectrum), 302. $C_{21}H_{34}O$ requires C, 83.4; H, 11.3%; *M*, 302].

4,4-*Dimethyl*-5α-*androst*-7-*en*-17-*one* (VIII).—4,4-Dimethyl-5α-androst-7-en-17β-ol (5.1 g.) in acetone (800 ml; AnalaR) was oxidised with 8N-chromic–sulphuric acid by the procedure of Jones and his co-workers.[23] Dilution with water and extraction with ether yielded the product which

[21] R. F. Zurcher, *Helv. Chim. Acta*, 1963, **46**, 2054.
[22] A. I. Vogel 'A Textbook of Practical Organic Chemistry, Longmans, London, 3rd edn., 1956, p. 871.
[23] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

crystallised from methanol–water yielding 4,4-*dimethyl*-5α-*androst*-7-*en*-17-*one* (4.14 g, 81%), m.p. 121.5—122.5 °C, $[\alpha]_D$ +48° (*c* 0.2); τ 4.55 (1 H, m, 7-H); *C*-methyl resonances (60 Hz) 43, 53 (2), and 56 Hz [Found: C, 83.9; H, 10.6%; *M* (mass spectrum), 300].

4,4-*Dimethyl*-5α,13α-*androst*-7-*en*-17-*one* (IX).—4,4-Dimethyl-5α-androst-7-en-17-one (4.14 g) in sodium-dried benzene (100 ml) under nitrogen was irradiated as the saturated compound (VI) for 11 h 20 min. The benzene was removed *in vacuo* and the residue dissolved in methanol (350 ml) made basic with M-methanolic potassium hydroxide (43 ml) and treated with sodium borohydride (700 mg) for 25 min at 20 °C. Excess of borohydride was decomposed with acetic acid and the crude product isolated in the same way as the corresponding saturated compound. Chromatography on silica and elution with benzene gave separation into two fractions. The first fraction was pure 4,4-*dimethyl*-5α,13α-*androst*-7-*en*-17-*one* (1.37 g, 33%) which crystallised from methanol–water with m.p. 120.5—121.5 °C, $[\alpha]_D$ −155° (*c* 0.2); o.r.d. (MeOH) $[\phi]_{320}$ −3 270 (tr) and $[\phi]_{293}$ −1 640 (pk); τ 4.32 (1 H, m, 7-H). The analytical sample was crystallised from methanol [Found: C, 83.9; H, 10.7%; *M* (mass spectrum), 300].

The second fraction from the chromatography was largely 4,4-dimethyl-5α-androst-7-en-17β-ol (2.73 g); the combined second fractions (3.08 g) from two experiments were dissolved in acetone (480 ml; AnalaR) and oxidised by the procedure of Jones and his co-workers.[23] The product, isolated in the usual fashion, was eluted through silica in benzene to constant weight (2.14 g). This material, shown by t.l.c. to be 4,4-dimethyl-5α-androst-7-en-17-one (*ca.* 90%) plus the 13α-isomer (*ca.* 5%), could be reirradiated to give further quantities of the 13α-steroid.

4,4-*Dimethyl*-5α-*androst*-8(14)-*en*-17-*one*.— 4,4-Dimethyl-5α-androst-8(14)-en-17β-ol [1] (0.425 g) in acetone (65 ml; AnalaR) was oxidised with 8N-chromic–sulphuric acid solution by the procedure of Jones and his co-workers.[23] Dilution with water and extraction with ether yielded the product which crystallised from methanol–water to give 4,4-*dimethyl*-5α-*androst*-8(14)-*en*-17-*one* (0.318 g, 76% in two crops), m.p. 117—117.5 °C, $[\alpha]_D$ +253° (*c* 0.3), *C*-methyl resonances (60 Hz) 44, 51, 53, and 63 Hz. The analytical sample was prepared by sublimation at 130 °C/0.4 mmHg [Found: C, 84.2; H, 10.75%; *M* (mass spectrum), 300].

Acid-catalysed Isomerisation of 4,4-*Dimethyl*-5α-*androst*-7-*en*-17β-*ol* (X).—Crude 4,4-dimethyl-5α-androst-7-en-17β-ol (1.5 g) and 10% palladium-charcoal (75 mg) in chloroform (75 ml; AnalaR) were treated with dry hydrogen chloride gas at −30 °C for 4 h. Excess of methanolic ammonia was added, followed by water, and the product was extracted with ether. The crude product, isolated in the usual way, crystallised from methanol–water yielding 4,4-dimethyl-5α-androst-14-en-17β-ol (XV) (0.940 g, 63%), m.p. 176—178.5 °C, mixed m.p. with standard sample [1] (m.p. 178—179 °C) 177—178.5°. The i.r. spectrum and t.l.c. behaviour of the product were identical to those of the standard compound.

Treatment of the material in the liquors from the crystallisation of the product with hydrogen chloride gas as above gave further 14-olefinic alcohol (0.331 g, total yield 84%).

4,4-*Dimethyl*-5α,13α-*androst*-7-*en*-17α-*ol* (XII; R = OH).—4,4-Dimethyl-5α,13α-androst-7-en-17-one (0.18 g) in methanol (18 ml) and methanolic M-potassium hydroxide (3 ml) was treated with sodium borohydride (36 mg) at 20 °C for 18 h. The product, isolated in the usual manner, crystallised from methanol–water yielding 4,4-*dimethyl*-5α,13α-*androst*-7-*en*-17α-*ol* (0.124 g, 67%), m.p. 136—136.5 °C, $[\alpha]_D$ −20° (*c* 0.2); τ 6.36 (1 H, t, 17-H), 4.60 (1 H, m, 7-H). The analytical sample crystallised from light petroleum (b.p. 60—80 °C) [Found: C, 83.5; H, 11.6%; *M* (mass spectrum), 302. $C_{21}H_{34}O$ requires C, 83.4; H, 11.3%; *M*, 302].

Acid-catalysed Isomerisation of 4,4-*Dimethyl*-5α,13α-*androst*-7-*en*-17α-*ol*.— 4,4-Dimethyl-5α,13α-androst-7-en-17α-ol (79 mg) and 10% palladium–charcoal (8 mg) in chloroform (4 ml; AnalaR) were treated with dry hydrogen chloride gas for 15 min at 20 °C. The flask was stoppered for 24 h when an excess of concentrated aqueous ammonia was added. The product, extracted with ether, crystallised from methanol–water yielding 4,4-*dimethyl*-5α,13α-*androst*-8-*en*-17α-*ol* (45 mg, 58%), m.p. 109—111 °C, $[\alpha]_D$ +14° (*c* 0.2); $\nu_{max.}$ (mull) 3 250 cm^{-1}; τ 6.20 (m, 17-H). The analytical sample, crystallised from methanol–water, had m.p. 117—119 °C [Found: C, 83.1; H, 11.4%; *M* (mass spectrum), 302].

4,4-*Dimethyl*-5α,13α-*androst*-7-*ene* (XII; R = H).—To a solution of sodium (0.130 g) in diethylene glycol (6.5 ml; redistilled) were added 4,4-dimethyl-5α,13α-androst-7-en-17-one (0.320 g) and anhydrous hydrazine (1.5 ml). The reaction was heated under reflux for 4 h and the condenser then removed while the pot temperature rose to 220 °C. Heating under reflux was continued for 23 h when the hot solution was poured into water (13 ml) and extracted with ether. The product, isolated in the usual manner, crystallised from ether–methanol with trituration yielding 4,4-*dimethyl*-5α,13α-*androst*-7-*ene* (0.246 g, 81%), m.p. 45—46 °C, $[\alpha]_D$ −57° (*c* 0.3); τ 4.55 (1 H, m, 7-H) [Found: C, 88.3; H, 12.1%; *M* (mass spectrum), 286. $C_{21}H_{34}$ requires C, 88.0; H, 12.0%; *M*, 286].

The 16,16,17,17-tetradeuterio-7-olefin was prepared as follows: 4,4-dimethyl-5α,13α-androst-7-en-17-one (0.356 g) and anhydrous hydrazine (2 ml) in diethylene glycol (11 ml) were heated under reflux for 4 h. The hot solution was poured into excess of water, cooled to 0 °C, and the hydrazone (0.310 g, 84%), m.p. 104—111 °C, was filtered off.

Diethylene glycol (3 ml) was exchanged with CH_3OD (3 × 2 ml), and dry benzene (2 ml) added and distilled from the glycol to remove most remaining methanol. Sodium (60 mg) was dissolved in the warm glycol and the above hydrazone (0.160 g) added to it. The solution was heated under reflux for 22 h, poured into water (7 ml), and extracted with ether. Evaporation of the ether gave a brown oil (0.192 g) which was filtered through silica in light petroleum (b.p. 60—80 °C) solution to constant weight (32 mg). Chromatography of the 32 mg on 15% silver nitrate silica (see below) and elution with light petroleum (b.p. 60—80 °C) gave the deuteriated 4,4-dimethyl-5α,13α-androst-7-ene (18 mg, 13%) (oil) identified by its i.r. and mass spectra (*M*, 287—290, 58% incorporation of deuterium, assuming 4 × D = 100%) and t.l.c. behaviour.

15% *Silver Nitrate–Silica for Column Chromatography*.—A solution of silver nitrate (7.5 g) in distilled water (7.5 ml) was diluted with ethanol (125 ml). Silica gel (50 g; 200—300 mesh) was added gradually with stirring and the mixture set aside for 0.25 h. The aqueous alcohol was removed by suction filtration and the residue dried *in vacuo*. It was finally activated at 110 °C for 1.5 h; yield *ca.* 50 g.

4,4,14α-*Trimethyl*-18-*nor*-5α-*androst*-13(17)-*ene* (XV).—4,4-Dimethyl-5α,13α-androst-7-ene (0.225 g) and 10% palladium–charcoal (12 mg) in chloroform (7 ml; AnalaR) were

treated with dry hydrogen chloride gas at −30 °C for 7.75 h. Excess of methanolic ammonia was added, followed by water, and the product was extracted with ether. The crude product was chromatographed on freshly prepared 15% silver nitrate–silica (50 g). Fore-fractions (0.075 g) were eluted with light petroleum (b.p. 60—80 °C) (200 ml). Elution with benzene to constant weight gave chromatographically pure 4,4,14α-*trimethyl*-18-*nor*-5α-*androst*-13(17)-*ene* (0.117 g, 51%) which crystallised from ether–methanol with m.p. 67.5—68 °C, $[\alpha]_D$ −68° (*c* 0.3); τ 4.96 (1 H, m, 17-H); *C*-methyl resonances (100 MHz) 80, 83, 86, and 89 Hz [Found: C, 88.0; H, 11.8%; *M* (mass spectrum), 286].

The fore-fractions from the chromatography could be retreated as above to yield further quantities of the 13(17)-olefin; in a more typical experiment a mixture of 4,4-dimethyl-5α,13α-androst-7-ene (0.382 g) and the fore-fractions (0.665 g) from a previous experiment yielded 13(17)-olefin (0.415 g, 40%) on isomerisation for 5.25 h.

Isomerisation of the deuteriated 7-olefin: the 16,16,-17,17-tetradeuterio-4,4-dimethyl-5α,13α-androst-7-ene (18 mg, prepared above) and 10% palladium–charcoal (2 mg) in chloroform (1 ml) were treated with dry hydrogen chloride gas at −30 °C for 5 h. The crude product (20 mg) was isolated in the same way as the non-deuteriated material above and the deuteriated 4,4,14α-trimethyl-18-nor-5α-androst-13(17)-ene (10 mg, 56%) separated by chromatography on 15% silver nitrate–silica. The deuteriated 13(17)-olefin was identified by its i.r. spectrum and t.l.c. behaviour and its mass spectrum (*M*, 286—289; 38% incorporation of deuterium, assuming 4 × D = 100%) and n.m.r. spectrum, τ 4.94 (1 H, br, s, 17-H); *C*-methyl resonances (100 MHz) 79, 82, 85, and 88 Hz.

4,4,14α-*Trimethyl*-13,17-*seco*-18-*nor*-5α-*androstane*-13α,-17-*diol* (XVII; R = H).—4,4,14α-Trimethyl-18-nor-5α-androst-13(17)-ene (0.427 g) in ethyl acetate (43 ml) and n-hexane (11 ml) was treated with ozonised oxygen at −15 °C for 2 h, followed by oxygen for 1.5 h. The solvents were removed *in vacuo* and the residue reduced with lithium aluminium hydride (430 mg) in boiling ether (54 ml) for 2.5 h. Excess of hydride was decomposed with ethyl acetate and chloroform (54 ml), saturated ammonium chloride solution (54 ml), and 2N-hydrochloric acid (20 ml). After shaking, the organic layer was separated and the aqueous layer extracted with chloroform (2 × 40 ml). Isolation in the usual manner gave a solid (0.497 g) which was treated with methanol (6 ml) for 0.5 at 20 °C. The methanol solution was removed by pipette and the residual solid (0.312 g) crystallised from methanol–water to yield 4,4,14α-trimethyl-13,17-seco-18-nor-5α-androstane-13α,17-diol (0.196 g, 41%), m.p. 194.5—196 °C, $[\alpha]_D$ −18° (*c* 0.3) [Found: *M* (mass spectrum), 322. $C_{21}H_{38}O_2$ requires *M*, 322].

The *diacetate* (100%) crystallised from methanol–water with m.p. 78.0—78.5 °C, $[\alpha]_D$ −3° (*c* 0.2); τ 5.34 (1 H, quart, *J* = 11 and 4 Hz, 13-H), 6.06 (2 H, t, 17-H), and 8.00 (6 H, s, 2 × CH_3CO). The quartet at *ca.* τ 5.4 was unchanged at 75 and 100 °C ($CDCl_3$) [Found: C, 73.7; H, 10.3. $C_{25}H_{42}O_4$ requires C, 73.85; H, 10.4%].

4,4,14α-*Trimethyl*-17a-*oxa*-D-*homo*-18-*nor*-5α,13β-*androstan*-17-*one* (XVIII) *and the* 5α,13α-*Isomer* (XXI).—4,4,14α-Trimethyl-13,17-seco-18-nor-5α-androstane-13α,17-diol (100 mg) in pyridine (3 ml) and dry acetonitrile (30 ml) was stirred with active manganese dioxide [24] (2 g) for 4 days at 20 °C. Water (30 ml) was added and sulphur dioxide bubbled into the mixture until all manganese dioxide had dissolved. The product (103 mg), extracted with chloroform, was dissolved in ether–chloroform and washed with M-sodium hydroxide (×3) and water and then dried ($MgSO_4$). Evaporation of the solvent gave 4,4,14α-*trimethyl*-17a-*oxa*-D-*homo*-18-*nor*-5α,13β-*androstan*-17-*one* (84 mg, 84%), which crystallised from chloroform–light petroleum (b.p. 60—80 °C), m.p. 222—224 °C; $[\alpha]_D$ −87° (*c* 0.2); o.r.d. (MeOH) $[\phi]_{221}$ −5 650 (tr); τ 7.4 (2 H, m, 16-H), 6.15 (1 H, q, *J* = 11 and 4 Hz, 13-H) [Found: C, 79.0; H, 10.55%; *M* (mass spectrum), 318. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%; *M*, 318].

(b) The mixture (0.523 g) of 13α,17- and 13β,17-diols remaining after separation of the pure 13α,17-diol, in pyridine (17 ml) and dry acetonitrile (170 ml) was stirred with active manganese dioxide [24] (11.5 g) for 4 days at 20 °C. Water (160 ml) was added and sulphur dioxide bubbled into the mixture until all manganese dioxide had dissolved. The product was extracted with chloroform and acidic by-products (97 mg) washed out with M-sodium hydroxide as in the foregoing experiment. Evaporation of the chloroform yielded the lactones (0.375 g, 74%) which crystallised from chloroform–light petroleum (b.p. 60—80 °C) to yield 4,4,14α-trimethyl-17a-oxa-D-homo-18-nor-5α,13β-androstan-17-one (0.130 g, 26%), m.p. 214—218 °C, mixed m.p. with a sample prepared above 216—220 °C.

Crystallisation of the material in the mother liquors, from chloroform–light petroleum (b.p. 60—80 °C) gave a solid (27 mg), m.p. 126—150 °C. The material in the second mother liquors was recrystallised from methanol–water three times to constant m.p. to yield 4,4,14α-*trimethyl*-17a-*oxa*-D-*homo*-18-*nor*-5α,13α-*androstan*-17-*one* (30 mg, 6%), m.p. 149—151 °C, $[\alpha]_D$ −9° (*c* 0.2), o.r.d. (MeOH) $[\phi]_{227}$ +2 000 (pk); τ 7.52 (2 H, q, 16-H), 5.96 (1 H, poorly-resolved triplet, total band width = 6 Hz, 13-H) (Found: C, 79.2; H, 10.9%).

4,4,14α-*Trimethyl*-17a-*oxa*-D-*homo*-18-*nor*-5α,13β-*androst*-15-*en*-17-*one* (XIX).—4,4,14α-Trimethyl-17a-oxa-D-homo-18-nor-5α,13β-androstan-17-one (100 mg) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (150 mg) in dioxan (10 ml; purified as Vogel [25]) and acetic acid (1 ml) were heated under reflux for 3 days. The solvents were removed *in vacuo* and the residue eluted through neutral alumina in chloroform solution to constant weight (66 mg).

Crystallisation from methanol–water gave 4,4-14α-*trimethyl*-17a-*oxa*-D-*homo*-18-*nor*-5α,13β-*androst*-15-*en*-17-*one* (52 mg, 52%), m.p. 144—145.5 °C, $[\alpha]_D$ −9° (*c* 0.3); $\lambda_{max.}$ 214 nm (ε 9 000), τ 6.02 (1 H, q, *J* = 11 and 4 Hz, 13-H), 4.14 (1 H, d, *J* = 10 Hz, 16-H), 3.01 (1 H, d, *J* = 10 Hz, 15-H). The analytical sample crystallised from light petroleum (b.p. 60—80 °C), m.p. 149.5—150° [Found: C, 79.6; H, 10.0%; *M* (mass spectrum), 316. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%; *M*, 316.].

4,4-*Dimethyl*-5α,13α-*androstane*.—To a solution of sodium (87 mg) in diethylene glycol (4.5 ml) were added 4,4-dimethyl-5α,13α-androstan-17-one (195 mg) and anhydrous hydrazine (1 ml). The solution was heated under reflux for 4.5 h and the condenser then removed while the pot temperature rose to 210 °C. Heating under reflux was continued for 3 days. The reaction was poured into water (9 ml) and extracted with ether. Crystallisation of the

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[25] Ref. 22, p. 177.

product from ether–methanol gave **4,4-*dimethyl*-5α,13α-*androstane*** (0.165 g, 90% in two crops), m.p. 83—83.5 °C, $[\alpha]_D$ −71° (*c* 0.2) [Found: C, 87.7; H, 12.4%; *M* (mass spectrum), 288. $C_{21}H_{36}$ requires C, 87.4; H, 12.6%; *M*, 288].

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