Conformational Studies. Part 5.[1] Functionalisation of Methyl Groups in 4,4-Dimethyl Steroids

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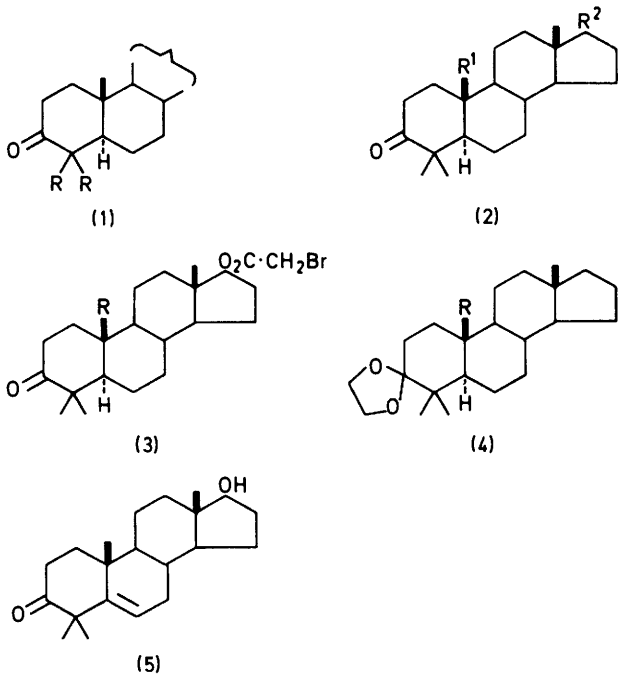
Hydroboration of 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (6; R^1 = Me, R^2 = H_2) gave (a) the 5α-androstan-6α-ol (9; R^1 = Me, R^2 = H), (b) the 5β-androstan-6β-ol (10; R^1 = Me, R^2 = H), and (c) the 5α-androstan-7α-ol (7). Oxidation of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (9; R^1 = Me, R^2 = H) furnished the 5α-6-ketone (12; R = Me), which on reduction with lithium aluminium hydride gave the 6β-ol (11; R^1 = Me, R^2 = H). Oxidation of 3,3-ethylenedioxy-4,4-dimethyl-5β-androstan-6β-ol (10; R^1 = Me, R^2 = H) afforded the corresponding 5β-6-ketone (13). Deacetalisation of (12; R = Me) and of (13) gave 4,4-dimethyl-5α-androstane-3,6-dione (15; R = Me) and 4,4-dimethyl-5β-androstane-3,6-dione (16), respectively, which were interconverted by acid.

Oxidation of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-7α-ol (7) gave the 7-ketone (17), which was also synthesised from 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (6; R^1 = Me, R^2 = H_2) as starting material.

3,3-Ethylenedioxy-4,4-dimethyl-19-norandrost-5-ene (6; R^1 = H, R^2 = H_2) was hydroborated to afford the 19-nor-5α-androstan-6α-ol (9; R^1 = R^2 = H) in high yield; this alcohol was oxidised to the 5α-6-ketone (12; R = H), reduction of which gave the corresponding 6β-ol (11; R^1 = R^2 = H).

The nitrites of 6α- and 6β-hydroxy-3,3-ethylenedioxy-4,4-dimethyl-5α-androstane, of 4,4-dimethyl-3-oxo-5α-androstan-6α-ol, of 6α- and 6β-hydroxy-3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstane, and of 6α- and 6β-hydroxy-4,4-dimethyl-3-oxo-19-nor-5α-androstane were irradiated (u.v.) and the products characterised. The results are interpreted in terms of the conformations of the substrates.

THE conformation of ring A in 4,4-dimethyl-3-oxo-5α-steroids has been the subject of considerable investigation since the observation [2] that the introduction of two 4-methyl substituents into a 3-oxo-5α-steroid of type (1; R = H) changes the characteristically positive Cotton curve to a negative curve, albeit of decreased amplitude. This inversion extends even to the visible region of the spectrum where the positive rotation at the sodium D-line of the 3-oxo-5α-steroids becomes negative in the 4,4-dimethyl analogues of type (1; R = Me). In a substantial contribution to this problem, Allinger and DaRooge [3] studied various physical parameters, including diple moments, i.r. spectra, and o.r.d. curves of 4,4-dimethyl-3-oxo-5α-androstan-17β-ol (2; R^1 = Me, R^2 = OH), the 19-nor-analogue (2; R^1 = H, R^2 = OH), and cognate derivatives. They deduced that ring A in (2; R^1 = Me, R^2 = OH) had a flattened chair conformation. In the 19-nor-analogue (2; R^1 = H, R^2 = OH) they concluded that, in the absence of the 10-methyl, 4β-methyl interaction, ring A was essentially in a 'normal' chair conformation. Robinson and Whalley,[4] in a modification of an earlier view,[5] and Ourisson *et al.*[6] generally concurred. The work of Allinger and DaRooge [3] was probably performed on impure materials (*cf.* ref. 7), but fortunately the general validity of their conclusions remains. Recently [8] an *X*-ray crystallographic examination of compounds (3; R = Me) and (3; R = H) has confirmed the existence of ring A in (3; R = Me) in a flattened chair conformation, but, as anticipated, ring A in the 19-nor-analogue (3; R = H), although still somewhat flattened, is less distorted than in the androstane derivative (3; R = Me). *X*-Ray crystallography, however, is limited in that the results refer to the conformation in the solid state, and this conformation may not be preferred in solution. In an attempt to circumvent this dilemma we now report another approach to the problem, employing photolysis as a molecular probe.



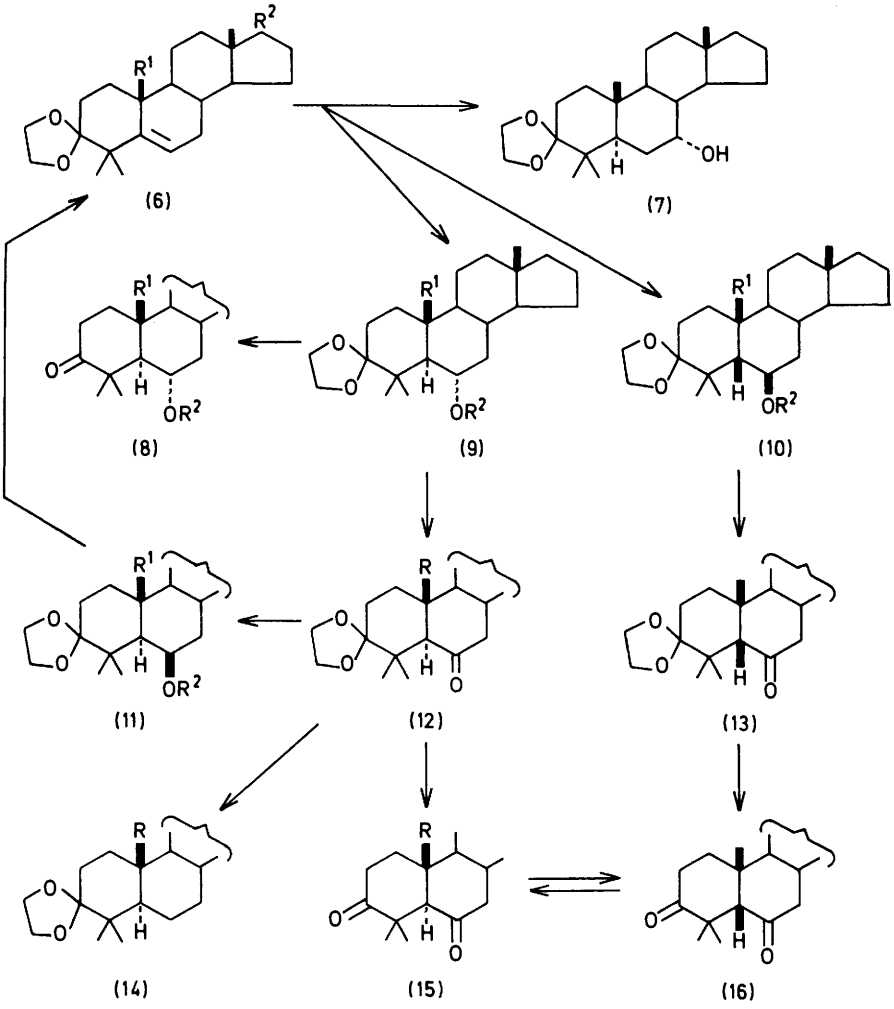
Molecular models indicate that an alkoxyl radical at

[1] Part 4, A. F. A. Wallis and W. B. Whalley, preceding paper.
[2] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 1957, **22**, 602; C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.
[3] N. L. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1962, **84**, 4561.
[4] M. J. T. Robinson and W. B. Whalley, *Tetrahedron*, 1963, **19**, 2123.
[5] J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 1961, 464.
[6] J. M. Lehn, J. Levisalles, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1096.
[7] J. M. Midgley, W. B. Whalley, P. A. Dodson, G. F. Katekar, and B. A. Lodge, *J.C.S. Perkin I*, 1977, 823.
[8] G. Ferguson, E. W. Macauley, J. M. Midgley, J. M. Robertson, and W. B. Whalley, *Chem. Comm.*, 1970, 954.

C-6 in the 4,4-dimethyl-5α-steroid system could, depending upon its orientation as α or β and the degree of deviation of ring A from a 'normal' chair, abstract a hydrogen atom from the 4α-, 4β-, or 10-methyl group. It was hoped that reaction time and product composition of such an abstraction reaction could be interpreted in terms of ring A conformation. Photolysis of appropriate nitrate esters (the Barton reaction [9]) was selected as a suitable probe, and we now report the preparation and photolysis of a series of 6α- and 6β-nitrites derived from 4,4-dimethyl-5α-androstan-3-one (2; R^1 = Me, R^2 = H), thus seemed to us that such critical geometrical requirements could reflect modest changes in conformation and hence provide an insight into the geometry of ring A in the substrate.

To simplify presentation this work is reported in three sections, which are concerned with (a) synthesis of the substrates, (b) their photolyses, and (c) interpretation of the photolysis results.

Syntheses.—17β-Hydroxy-4,4-dimethylandrost-5-en-3-one (5) was converted into the ethylene acetal (6; R^1 = Me, R^2 = H,OH); oxidation (Sarett reagent) then gave



its ethylene acetal (4; R = Me), and the corresponding 19-nor-analogues [*e.g.* (4; R = H)]. It was appreciated that the introduction of this substituent (in place of hydrogen) at C-6, might modify the original conformation of the substrate, but this was unavoidable.

The distance [10] between an alkoxyl radical centre and the carbon atom carrying an abstractable proton is critical, and in the range 2.5—2.7 Å. At a distance greater than 2.8 Å the rate of intramolecular abstraction becomes much less than the rates of intermolecular hydrogen abstraction and fragmentation reactions. It

the 17-ketone (6; R^1 = Me, R^2 = O), which on reduction gave 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (6; R^1 = Me, R^2 = H_2). Hydroboration of this 5-ene proceeded with difficulty under a variety of conditions to yield 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (9; R^1 = Me, R^2 = H) and 3,3-ethylenedioxy-4,4-dimethyl-5β-androstan-6β-ol (10; R^1 = Me, R^2 = H), together with the 7α-alcohol (7), which was frequently the major

[9] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1960, **82**, 2640; 1961, **83**, 4076.
[10] K. Heusler and J. Kalvoda, *Angew. Chem.*, 1964, **76**, 518.

product. The structures of these alcohols were assigned as follows.

The hydroboration technique results in *cis*-addition of the elements of water, in a non-Markovnikov manner. Hence the products arising directly from the 5-ene (6; R^1 = Me, R^2 = H_2) would be the 5α-androstan-6α-ol (9; R^1 = Me, R^2 = H), from α-face attack on the ring A chair conformation, and the 5β-androstan-6β-ol (10; R^1 = Me, R^2 = H), produced by β-face attack on a non-chair ring A conformation. Oxidation of the 6α-alcohol (9; R^1 = Me, R^2 = H) furnished the 6-ketone (12; R = Me) which was reduced, in high yield, by lithium aluminium hydride to 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6β-ol (11; R^1 = Me, R^2 = H). The ready dehydration of the 6β-ol (11; R^1 = Me, R^2 = H) to the parent 3,3-ethylenedioxy-4,4-dimethyl-5-ene (6; R^1 = Me, R^2 = H_2) with pyridine–phosphoryl chloride confirmed the 5α,6β-configuration of the alcohol. Additionally the n.m.r. spectra of the epimeric alcohols (11; R^1 = Me, R^2 = H) and (9; R^1 = Me, R^2 = H) (Table 1)

TABLE 1
N.m.r. data

Compound	τ(H-6)	$W_{\frac{1}{2}}$/Hz of H-6	τ(10-Me)
6α-OH (9; R^1 = Me, R^2 = H)	6.10	25	9.06
6β-OH (11; R^1 = Me, R^2 = H)	5.64	7	8.73
6α-ONO (9; R^1 = Me, R^2 = NO)	4.14	26	*
6β-ONO (11; R^1 = Me, R^2 = NO)	3.90	7	8.88
6β-OH (10; R^1 = R^2 = H)	5.84	7	*

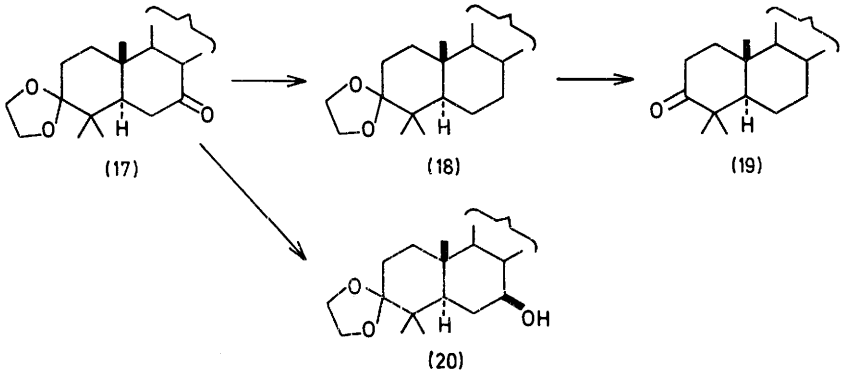
* No assignment made.

substantiate the configurational assignments. The methine proton signal in, for example, the 6α-ol (9; R^1 = Me, R^2 = H) and the nitrite (9; R^1 = Me, R^2 = NO) occurs at higher field than the corresponding signal in the axial 6β-compounds, in accord with precedent.[11] The half-band widths of the C-6 methine proton signals are also in agreement [11] with these structures. Collateral evidence is provided by the signals for the 10-methyl groups, which appear at lower field in the 6β- than in the 6α-alcohol.[12] Oxidation of the 5β-6β-alcohol (10; R^1 = Me, R^2 = H) gave the 5β-6-ketone (13).

Attempts to epimerise (at C-5) the epimeric 6-ketones (12; R = Me) and (13) with base were unsuccessful. The ketone (12; R = Me) was resistant to reduction to (14; R = Me) by the Wolff–Kishner method, even under the most vigorous conditions. Mild hydrolysis with acid of the epimeric 6-ketones gave the epimeric 3,6-diones (15; R = Me) and (16), respectively. 4,4-Dimethyl-5α-androstane-3,6-dione (15; R = Me) is a known compound,[13] and the physical properties agreed with those reported. More vigorous treatment of (12; R = Me) or (13) with acid gave a mixture of (15; R = Me) and (16) in the ratio 3 : 1, respectively. Comparison of the o.r.d. data for (12; R = Me) and (13) with the data reported [13,14] for analogous compounds provided additional confirmation of the assignment at C-5 in (12; R = Me) and (13).

Oxidation of the 7α-ol (7) with pyridine–chromic oxide furnished the 7-ketone (17), reduction of which with sodium borohydride regenerated the 7α-ol (7) (58%), together with the isomeric 7β-ol (20) (10%). The configurations of these two alcohols were assigned from their n.m.r. spectra. Since ring B will have a chair conformation, the 7α-hydroxy-group is axial and the 7β-hydroxy-group equatorial. As required,[11] the axial methine proton signal in the 7β-ol occurs at a higher field (τ 6.62) than that for the equatorial proton (τ 6.10) in the 7α-alcohol. Direct comparison of the half-band widths of these two signals was not possible since the signal from the 7α-alcohol was partially obscured by that due to the ethylene acetal. However, the half-band width for the 7β-alcohol (17 Hz) was within the expected range.[15]

The 5α-configuration of the 7α- and 7β-alcohols was established by reduction of the 7-ketone (17) to 3,3-ethylenedioxy-4,4-dimethyl-5α-androstane (18); deacetalisation gave 4,4-dimethyl-5α-androstan-3-one (19), identical with an authentic specimen prepared by catalytic reduction of 4,4-dimethylandrost-5-en-3-one.



The position of the carbonyl group at C-7 in (17) was confirmed by an unequivocal synthesis. Thus allylic bromination [16] of 3,3-ethylenedioxy-4,4-dimethylandrost-

[11] N. S. Bhacca and D. H. Williams, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Holden–Day, San Francisco, 1964, p. 79.

[12] *E.g.* J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 250.

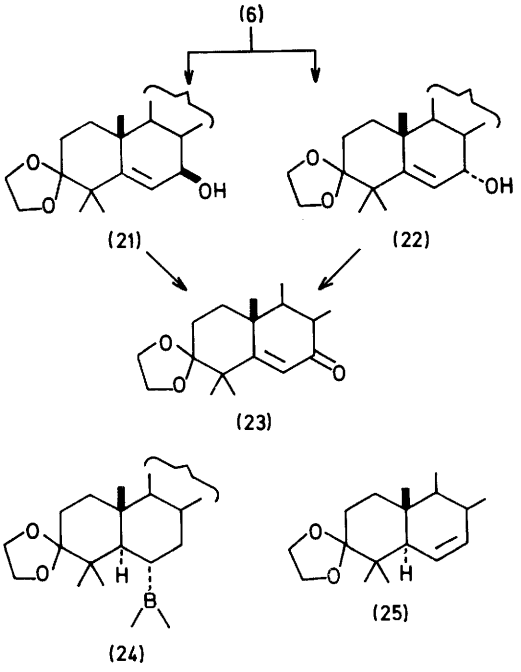
[13] T. G. Halsall, E. R. H. Jones, E. L. Tan, and G. R. Chaudry, *J. Chem. Soc.* (*C*), 1966, 1374.

[14] M. Fetizon and P. Foy, *Bull. Soc. chim. France*, 1967, 2653.

[15] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1350.

[16] R. H. Lenhard and S. Bernstein, *J. Amer. Chem. Soc.*, 1956, **78**, 989.

5-ene (6; R^1 = Me, R^2 = H_2) followed by hydrolysis of the halogen gave the 7α-alcohol (22) (45%) and the 7β-alcohol (21) (15%). The assignment of configuration of these alcohols by n.m.r. was not possible because of overlapping signals—but was made on the basis of molecular rotation differences. It has been demonstrated [17] that in 7-hydroxy-$\Delta^{5,6}$-steroids the molecular rotation difference for the 7α-isomer is negative whereas for the 7β-isomer it is positive. On this basis, the major allylic



alcohol was assigned the α-configuration (22) (see Table 2). Oxidation of both allylic alcohols with pyridine–chromic oxides gave the same αβ-unsaturated ketone (23), which

TABLE 2

Molecular rotation differences

Compound	$[M]_D$ (°)	$\Delta[M]_D$ (°)
Alkene (6; R^1 = Me, R^2 = H_2)	−365	
7α-OH (22)	−536	−171
7β-OH (21)	−256	+109

was reduced by lithium in liquid ammonia to the 5α-ketone (17), identical with the product derived from the 7α- and 7β-ols (7) and (20).

The formation of this 7α-alcohol during hydroboration of (6; R^1 = Me, R^2 = H_2) is to be attributed to steric factors. Thus the low yield and long reaction time necessary for hydroboration, particularly from the α-face, will give initially the 5α-androstan-6α-ylborane (24). But hydroboration is reversible and secondary alkylboranes are slowly isomerised *inter alia* to primary ones,[18] the isomerisation being catalysed by an excess of diborane. It is thus probable that under our conditions the initially formed borane (24) underwent elimination to form the 5α-6-ene (25). Hydroboration of this, again from the α-face, would yield the 7α-ol (7). That this isomerisation should take place so readily was unexpected, but is not without precedent.[19] The driving force may be the combination of the heteroannular interaction between the boron at C-6α and the 4α-methyl group, together with the distorting influence upon ring A of the 4β-methyl,10-methyl interaction (see later).

Removal of the ethylene acetal from (9; R^1 = Me, R^2 = H) gave 6α-hydroxy-4,4-dimethyl-5α-androstan-3-one (8; R^1 = Me, R^2 = H).

To elucidate certain structural and mechanistic problems in the photochemical work several deuteriated substrates were synthesised. Methylation of androst-4-en-3-one with trideuteriomethyl iodide furnished 4,4-bis(trideuteriomethyl)androst-5-en-3-one (26). Hydroboration of the 3,3-ethylene acetal (27) gave the 6α-alcohol (28) (28%), which was transformed by way of the 6-ketone (29) into the 6β-alcohol (30; R = H).

Methylation of androst-4-en-3-one by the method of Atwater [20] gave 4-methylandrost-4-en-3-one, which was in turn methylated with trideuteriomethyl iodide to yield a product which is regarded as 4β-methyl-4α-trideuteriomethylandrost-5-en-3-one (33), in accord with the demonstration [14] that 4-methyl-$\Delta^{4,5}$-3-oxo-steroids are alkylated from the less hindered α-face. The sequence of acetalisation [to (32)], hydroboration [to (31)], and deacetalisation furnished 6α-hydroxy-4β-methyl-4α-trideuteriomethyl-5α-androstan-3-one (34; R = H). N.m.r. spectroscopy demonstrated that this 4α-trideuteriomethylsteroid had *ca.* 90% isotopic purity.

A series of compounds analogous to the unlabelled androstanes was prepared in the 19-norandrostane series, from 3,3-ethylenedioxy-4,4-dimethyl-19-norandrost-5-en-17β-ol (6; R^1 = H, R^2 = H,OH) which was converted by way of the ketone (6; R^1 = H, R^2 =O) into the androst-5-ene (6; R^1 = H, R^2 = H_2). Hydroboration of (6; R^1 = H, R^2 = H_2) proceeded in much higher yield and more quickly than with the androstane series to yield (70%) 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6α-ol (9; R^1 = R^2 = H). This stereochemical assignment is based on oxidation of (9; R^1 = R^2 = H) to the 6-ketone (12; R = H), which with sodium borohydride afforded the isomeric 6β-ol (11; R^1 = R^2 = H), and in accord with the relative chemical shifts [11] for the C-6 methine protons and the half-band widths of the signals [11] (Table 3).

The ketone (12; R = H) could not be epimerised with base, but treatment with acid yielded the 3,6-dione (15; R = H) without C-5 epimerisation. Hence it was concluded, in accord with the o.r.d. evidence, that the configuration was 5α. Collateral evidence for this was provided by the ease of dehydration of the 6β-alcohol (11; R^1 = R^2 = H) to the parent-5-ene (6; R^1 = H, R^2 =

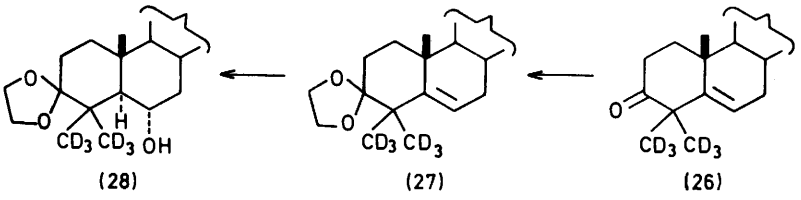
[17] L. F. Fieser and M. Fieser, 'Steroids,' Chapman and Hall, London, 1959, p. 177, and references cited therein.

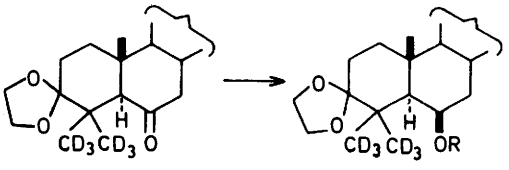
[18] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1966, **88**, 1433.

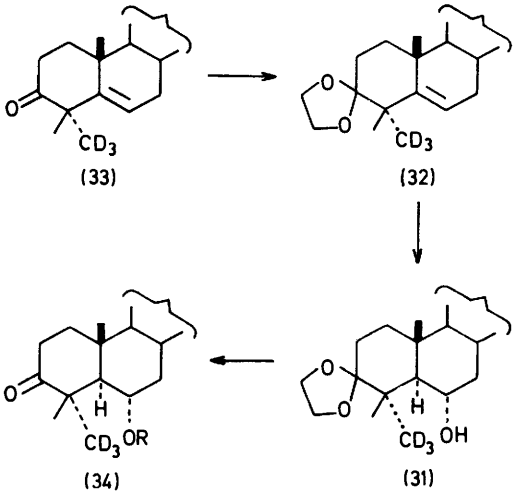
[19] A. M. Krubiner, N. Gottfried, and E. P. Olivetto, *J. Org. Chem.*, 1968, **33**, 1715; P. Pesnelle and G. Ourisson, *ibid.*, 1965, **30**, 1744.

[20] N. W. Atwater, *J. Amer. Chem. Soc.*, 1960, **82**, 2847.

H_2). More definitive evidence for the 5α-assignment was available from the Wolff–Kishner reduction of (12; R = H) [contrast the behaviour of (12; R = Me)] to 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstane (14; R = H), which was converted into 4,4-dimethyl-19-nor-5α-androstane, identical with an authentic specimen. This was synthesised by reductive methylation [21,22] of 4-methyl-19-nortestosterone to yield (2; R^1 = H, R^2 = OH), which was converted into 4,4-dimethyl-19-nor-5α-androstane by way of the intermediate 3,17-dione.







Photochemical Transformations.—The photolysis of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-yl nitrite (9; R^1 = Me, R^2 = NO) was complete in 20 h and furnished the oxime (35; R = Me) in 56% yield together with the 6α-alcohol (9; R^1 = Me, R^2 = H) and 6-ketone (12; R = Me) (3%), which arises from disproportionation of the alkoxyl radical. The oxime was assigned the structure (35; R = Me) on the basis of spectral data, mechanistic considerations, and the reasonable assumption, which was later confirmed, that rings A and B in (9; R^1 = Me, R^2 = NO) exist in chair conformations in which the 6α-alkoxyl radical can abstract a hydrogen atom from the 4α-methyl group only. Mild acidic treatment of the oxime gave the isoxazoline (36; R = Me); more vigorous treatment of (35; R = Me) and of (36; R = Me) gave the nitrile (37; R = Me).

Photolysis of the corresponding 3-ketone (8; R^1 = Me, R^2 = NO) proceeded very slowly (72 h) to form a blue oil which was assumed to contain nitroso-dimers and hence was refluxed with propan-2-ol to isomerise the dimers to the corresponding oximes. The mixed product contained the ketone (15; R = Me) (3.5%), the 6α-alcohol (8; R^1 = Me, R^2 = H) (27%), 6α-hydroxy-4a-methyl-A-homo-5α-androst-4-en-3-one (38) (17%), 4β-methyl-5α-androstano[4,3-*d*]isoxazoline-3ξ,6α-diol (36; R = Me) (1.5%) and a substance tentatively formulated as 6α-hydroxy-4β-methyl-3-oxo-5α-androstane-4α-carboxamide (39).

TABLE 3

N.m.r. data

Compound	τ(H-6)	$W_{\frac{1}{2}}$/Hz
6α-OH (9; R^1 = R^2 = H)	6.37	17
6β-OH (11; R^1 = R^2 = H)	5.27	7
6α-ONO (9; R^1 = H, R^2 = NO)	4.50	24
6β-ONO (11; R^1 = H, R^2 = NO)	4.00	7
6α-OH (8; R^1 = R^2 = H)	6.24	20
6β-OH (53; R = H)	5.73	6
6α-ONO (8; R^1 = H, R^2 = NO)	4.41	27
6β-ONO (53; R = NO)	4.20	8

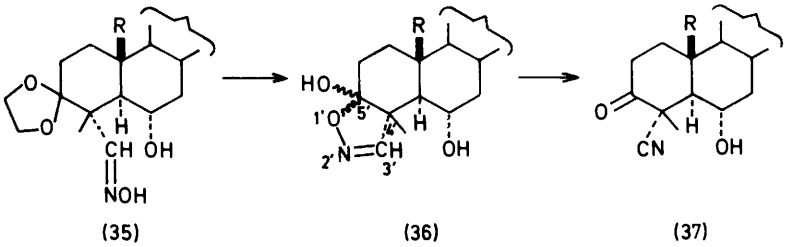
The structure of the A-homo-steroid (38) was assigned on the basis of the following evidence. The i.r. spectrum (CCl_4) showed bands at 3 410 (OH) and 1 665, 1 645, and 1 620 cm^{-1} (αβ-unsaturated ketone). In Nujol this carbonyl region exhibited two bands only, at 1 645 and 1 620 cm^{-1}. This is compatible [23] with the presence in a seven-membered ring of an αβ-unsaturated ketone system which exists in solution as a mixture of conformers. The u.v. spectrum, $\lambda_{max.}$ 237 nm (ε 10,200), supported the

[21] J. M. Midgley, W. B. Whalley, G. F. Katekar, and B. A. Lodge, *Chem. Comm.*, 1965, 169.

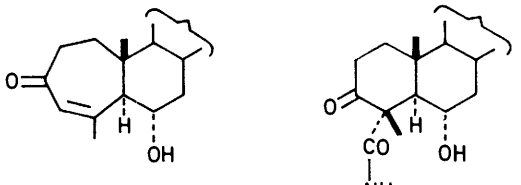
[22] G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 1965, **87**, 275.

[23] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 145.

presence of an αβ-unsaturated ketone. The n.m.r. spectrum had signals at τ 9.25 (3 H, s, H_3-18), 9.11 (3 H, s, H_3-19), 7.84br (3 H, s, $W_{\frac{1}{2}}$ 4 Hz, allylic 4a-Me), 6.03 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, H-6β), and 4.10 (1 H, m, $W_{\frac{1}{2}}$ 4 Hz, H-4). Decoupling experiments showed that the H-6β was coupled to a proton whose signal was in the multiplet at τ 7.65, and that the vinylic proton (τ 4.10) was coupled to the 4a-methyl protons (τ 7.84). Similar photolytic ring expansions have been observed [24] with, for example, 11β-nitrites, which give D-homo-steroids. The mechanism is discussed later.



(35) (36) (37)



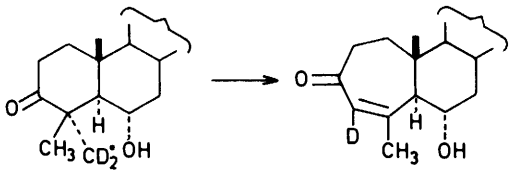
(38) (39)

The structure of the isoxazoline (36; R = Me) is based on spectroscopic evidence and its conversion into the oxo-nitrile (37; R = Me). This, coupled with the formation of the isoxazoline (36; R = Me) from the oxime (35; R = Me) under mild, acidic conditions confirmed this structure, except for the stereochemistry at C-3. Ths structure of the amide (39) was deduced from spectroscopic evidence.

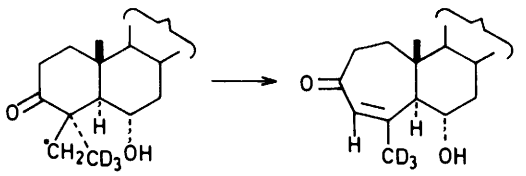
Photolysis of the corresponding 3-oxo-nitrites in the 19-norandrostane series, in which the crude reaction mixture was not refluxed with propan-2-ol, gave the corresponding isoxazoline in high yield; the amide was absent. Thus, the amide (39) may have been formed at the expense of the isoxazoline (36; R = Me); if true, this would define the configuration at C-4 of the amide residue as α. The difficulty of obtaining adequate supplies of (8; R^1 = Me, R^2 = H) precluded a repetition without propan-2-ol in the isolation stage.

In an attempt to identify the methyl group involved in hydrogen abstraction to furnish the A-homo-steroid (38), we examined the photolysis of 4β-methyl-4α-trideuteriomethyl-3-oxo-5α-androstan-6α-yl nitrite (34; R = NO). If the proposed mechanism were valid the product formed by way of the 4α-dideuteriomethylene radical (40) would be (41), whereas if product formation took place through the 4β-methylene radical (42), the ketone (43) would result (see ref. 25 for mechanism).

The photolysis of the oxo-nitrite (34; R = NO) required 98 h for completion and furnished the 6α-alcohol (34; R = H) (42%), with only 5.2% of the ring expansion product (38). The molecular ion region of the mass spectrum showed that considerable scrambling of the label had occurred; the n.m.r. spectrum indicated the presence of *ca.* 70% of hydrogen at C-4 and in the 4a-methyl group. These albeit equivocal results seem to be compatible only with deuterium–hydrogen exchange occurring during work-up, and/or product formation by way of an intermediate of type (44).



(40) (41)

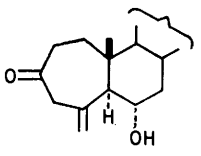


(42) (43)

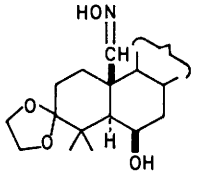
That the yield of (38) was only 5.2% from the photolysis of (34; R = NO) as opposed to 17% from the unlabelled oxo-nitrite is in accord with ring expansion occurring predominantly (if not exclusively) through the 4α-methylene radical; the extended reaction time and decreased yield may be attributed to the isotope effect. Because of its synthetic inaccessibility, photolysis of 4,4-dimethyl-3-oxo-5α-androstan-6β-yl nitrite was not examined.

[24] H. Reimann, A. S. Capomaggi, T. Strauss, E. P. Oliveto, and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1961, **83**, 4481.
[25] M. Akhtar, *Adv. Photochem.*, 1963, **2**, 263.

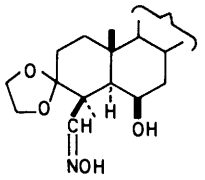
The photolysis of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6β-yl nitrite (11; R^1 = Me, R^2 = NO) gave the 6-ketone (12; R = Me) (7%) and the 6β-alcohol (11;



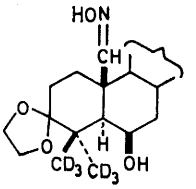
(44)



(45)



(46)



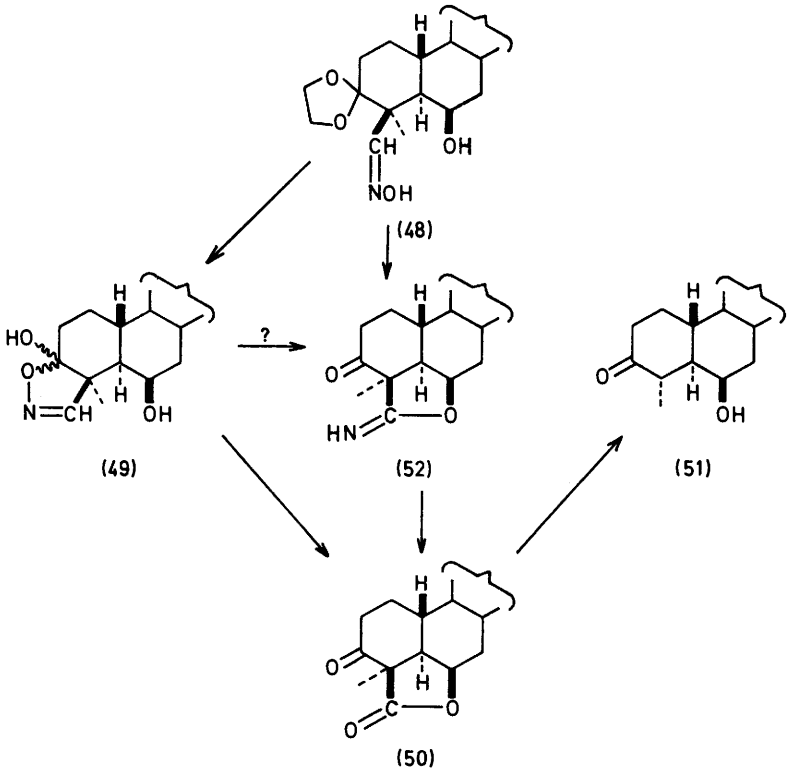
(47)

R^1 = Me, R^2 = H) (17%), together with the oximes (45) and (46) in yields of 25 and 6.5%, respectively. These structures are compatible with the spectral data and subsequent chemical transformations. Thus (45) exhibited i.r. absorption (Nujol) at 3 450 and 3 270 cm^{-1} (OH). The n.m.r. spectrum contained signals at τ 9.31 (3 H, s, H_3-18), 9.04 and 8.84 (6 H, s, 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), 5.72 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, H-6α), 2.45 (1 H, s, H-19), and −0.6 (1 H, s, :N·OH, exchangeable with deuterium oxide). Likewise (46) showed $\nu_{max.}$ 3 210 and 3 130 (OH) and 1 650 cm^{-1} (oxime). The n.m.r. spectrum exhibited signals at τ 9.26 (3 H, s, H_3-18), 8.94 and 8.80 (6 H, s, H_3-19 and 4α-Me), 6.00 (4 H, s, O·CH_2·CH_2·O), 5.57 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, H-6α), 2.15 (1 H, s, 4β-CH), and −0.83 (1 H, s, :N·OH, exchangeable with deuterium oxide).

The spectroscopic evidence did not unequivocally differentiate (45) from (46), so to this end we examined the photolysis of 3,3-ethylenedioxy-4,4-bis(trideuteriomethyl)-5α-androstan-6β-yl nitrite (30; R = NO), which formed only the oxime (47), identified by the n.m.r. and mass spectra, and the identity of the m.p., mixed m.p., $[\alpha]_D$ value, i.r. data, and R_F value with the corresponding constants for (45).

Failure to obtain any of the 4β-hydroxyiminomethyl derivative is most probably attributable to the isotope effect, and provides collateral evidence for the validity of our conclusions concerning the photolysis of (34; R = NO).

Similar results were obtained in the 19-norandrostane series, where 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6α-yl nitrite (9; R^1 = H, R^2 = NO) furnished the oxime (35; R = H) in 59% yield. The structural assignment was based upon the spectroscopic data and



(48)

(49)

(52)

(51)

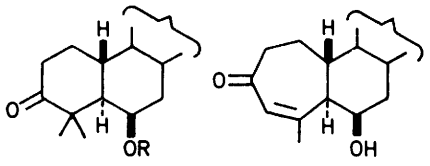
(50)

general mechanistic considerations. In addition, treatment of (35; R = H) with acid gave the isoxazoline (36; R = H) and thence the nitrile (37; R = H). Similar results with the 3-oxo-6α-nitrite (8; R^1 = H, R^2 = NO) yielded the isoxazoline (36; R = H) (55%). Photolysis of the 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6β-yl nitrite (11; R^1 = H, R^2 = NO) afforded the

4β-hydroxyiminomethyl product (48) in 63% yield. Hydrolysis of (48) gave, in high yield, the γ-lactone (50) which with hydroxide ion yielded 6β-hydroxy-4α-methyl-19-nor-5α-androstan-3-one (51). The behaviour of the epimeric 4α-hydroxyiminomethyl (35; R = H) and 4β-hydroxyiminomethyl (48) derivatives are thus in contrast, since the former (with acid) yields the nitrile (37; R = H). It is unlikely, however, that the γ-lactone (50) is formed by way of the corresponding nitrile since hydrolysis of tertiary nitriles is normally difficult. Further, if this were true the equatorial nitriles (37; R = H) and (37; R = Me) would be expected to undergo hydrolysis with similar facility, but they do not. A possibility is neighbouring group participation by the 6β-hydroxy-substituent to give an imino-ether (52) which is then hydrolysed to the γ-lactone (50). This would be compatible with the greater steric compression experienced by the axial substituents.

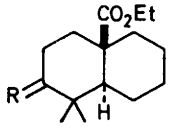
Very mild, acidic hydrolysis of the oxime (48) furnished the isoxazoline (49).

Photolysis of the corresponding 3-oxo-6β-nitrite (53; R = NO) gave the isoxazoline (49) in 42.5% yield,



(53)

(54)



(55)

comparable to that of the oxime (48) from the 3,3-ethylenedioxy-derivative (11; R^1 = H, R^2 = NO), together with the ring expansion product (54) (10%), the 3,6-diketone (15; R = H) (3.5%), and the 6β-alcohol (53; R = H) (14%). The structure of the A-homo-derivative (54) is based upon analytical and spectroscopic data. The i.r. spectrum showed $\nu_{max.}$ 3 390 (OH) and 1 640 and 1 615 cm^{-1} (αβ-unsaturated ketone), and the n.m.r. spectrum contained signals at τ 9.24 (3 H, s, H_3-18), 8.00br (3 H, s, $W_{\frac{1}{2}}$ 4 Hz, 4a-Me), 5.70 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, H-6α), and 4.04 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, H-4).

Interpretation.—Caution must be exercised in drawing conformational conclusions concerning substrates from the ratios of products from substrates where conformational mobility is possible. In such systems, if two conformers can give rise to different products, then, provided the rate of conformational interconversion is greater than the rate of reaction of the individual conformers, the product ratio will depend only on the free-energy difference between the two transition states.[26] Thus product development need not necessarily reflect the geometry of the more stable conformer.

However, despite these reservations, together with our assumption that ring B in our various steroidal substrates is held rigidly in a ' normal ' chair conformation, we believe that reasonable conclusions may be drawn from our observations.

Thus the photolysis of the nitrites (9; R^1 = Me, R^2 = NO), (9; R^1 = H, R^2 = NO), and (11; R^1 = H, R^2 = NO) resulted in the functionalisation of one methyl group only, in high yield in each case: this strongly indicates that in the transition state (and hence most probably in the ground state also) the distances for the relevant hydrogen abstractions are within the optimum value,[10] and that ring A in the corresponding alkoxyl radicals, and hence in the parent ethylene acetals, has an essentially ' normal ', or only slightly distorted from ' normal ', chair-like conformation.

Of particular significance are the results from the photolysis of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6β-yl nitrite (11; R^1 = Me, R^2 = NO), since in this case both the 4β- and 10-methyl groups are candidates for hydrogen abstraction. Our experiments showed that 10-methyl functionalisation predominates over 4β-methyl functionalisation in the ratio 4.5 : 1, which clearly indicates that the 4β-methyl,6β-alkoxyl distance is less favourable (greater) than the 10-methyl,6β-alkoxyl distance. Thus it may be concluded from these results, together with general principles, that ring A in (11; R^1 = Me, R^2 = NO) has a chair conformation in which the 10-methyl,4β-methyl interaction together with the 4-substituent,6-substituent interactions flatten (or distort) ring A to minimise these interactions, in a manner which appears analogous [3,4,8] to that of the corresponding 3-ketones which are devoid of 6-hydroxy-substituents. The conclusions derived from theoretical considerations,[3,4] *X*-ray crystallography,[8] and our present work are thus satisfyingly similar.

Collateral evidence for the essential similarity of the conformation of ring A in this series of four 3-ethylene acetals resides in the close similarity between the times (*ca.* 20 h) for each photolysis to proceed to completion, although the profound influence upon chemical reactivity of subtle changes in conformation is dramatically illustrated by the resistance of the ketone (12; R = Me) to Wolff–Kishner reduction, whereas (12; R = H) is reduced normally.

Photolyses of 4,4-dimethyl-3-oxo-19-nor-5α-androstan-6β-yl nitrite (53; R = NO) and of the 6α-yl nitrite (8; R^1 = H, R^2 = NO) occurred in a similar time (*ca.* 20 h) and appeared to proceed by way of favourable transition states, since the yields were high. The 6β-nitrite (53; R = NO) gave the A-homo-steroid (54) in 10% yield, but no homo-steroid was obtained from the 6α-nitrite (8; R^1 = H, R^2 = NO). This indicates that ring A in (53; R = NO) and in (8; R^1 = H, R^2 = NO) is essentially rigid and chair-like, since the mechanism [25] for ring expansion to yield an A-homo-steroid requires the methylene radical to be axial or at least pseudoaxial. That the products from the 6α-yl nitrite (8; R^1 = H,

[26] Ref. 23, p. 27.

R^2 = NO) are devoid of ring expansion product indicates that the transition state and parent ketone have ring A in an essentially ' normal ' chair conformation.

The seventh member of the series under examination, 4,4-dimethyl-3-oxo-5α-androstan-6α-yl nitrite (8; R^1 = Me, R^2 = NO), required 72 h for complete photolysis, and gave a complex mixture of products in which the parent alcohol (8; R^1 = Me, R^2 = H) and the ketone (15; R = Me), from disproportion reactions, predominated. In addition, one of the principal photolysis products was the A-homo-steroid (38), the production of which requires [24,25] that the participating methylene radical be axial or quasiaxial. These results strongly suggest that whereas the sp^3-hybridised nature of C-3 in the acetal (9; R^1 = Me, R^2 = OH) ensures that ring A retains an essentially chair-like conformation, the sp^2-hybridised C-3 in (8; R^1 = Me, R^2 = H) allows relief of the heteroannular 4-methyl,6-substituent interaction, and of the homoannular 10-methyl,4β-methyl interaction by permitting ring A to adopt a skew-boat conformation. In such a conformation the distance between the 6α-alkoxyl radical and either of the C-4 methyl groups would be at least 3.0 Å, *i.e.* considerably in excess of the critical optimum of 2.5—2.8 Å. Hence hydrogen abstraction would (*a*) be energetically unfavourable, in agreement with the long reaction time; (*b*) produce a methylene radical of pseudoaxial orientation as required for ring expansion; and (*c*) be in accord with the dominance of the ketone (15; R = Me) and the alcohol (8; R^1 = Me, R^2 = H) in the photolysis mixture.

Additional collateral evidence for the conformation of the ground state of the ketone (8; R^1 = Me, R^2 = H) is provided by a comparison of the n.m.r. spectra of (8; R^1 = Me, R^2 = H) and 4,4-dimethyl-5α-androstan-3-one. In the latter ketone, the 10-methyl signal occurs at τ 8.94, whereas in the 6α-hydroxy-derivative (8; R^1 = Me, R^2 = H) the corresponding signal is at τ 9.22. This upfield shift cannot be attributed to field effects from the 6α-hydroxy-group,[27] but is compatible with the existence of ring A in a skew-boat conformation in which the 10-methyl group is situated within the shielding cone of the C-3 carbonyl group.[28] Thus the difference in energy between the 4- and 6-substituent interaction in for example (2; R^1 = Me, R^2 = OH) and (8; R^1 = Me, R^2 = H) is sufficient to change dramatically the conformation of ring A from a flattened chair in (2; R^1 = Me, R^2 = OH) to a skew-boat in (8; R^1 = Me, R^2 = H).

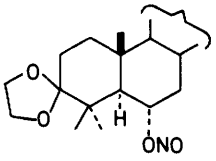
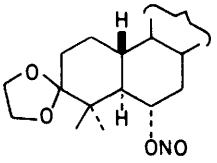
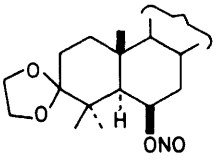
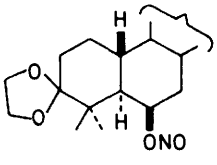
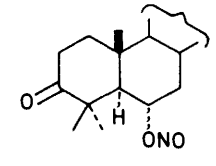
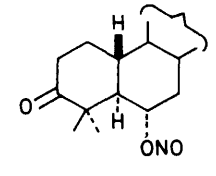
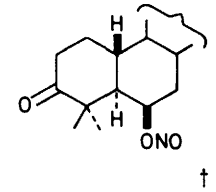
A close analogy of this situation is provided by some *trans*-decalins.[29] N.m.r. studies show that the ester group in (55; R = H_2) suffers restricted rotation, occasioned by the axial 4β-methyl group. Hence ring A must be in a chair conformation. In the corresponding decalone (55; R = O), however, there is no restriction to the rotation of the ester group, from which it may be concluded that ring A in (55; R = O) has a non-chair conformation.

[27] Ref. 11, p. 14.

[28] B. B. Dewhust, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pete, *Bull. Soc. chim. France*, 1964, 3259.

Our conclusions are summarised in Table 4.

TABLE 4

Nitrite	Reaction time (h)	Me group functionalised	Remarks †
	21	4α-	Favourable TS
	18	4α-	Favourable TS
	19	10- 4β-	Favourable TS
	20	4β-	Favourable TS
	72	4α-? 4β-?	Unfavourable TS; ring expansion occurred
	20	4α-	Favourable TS; no ring expansion occurred
	18	4β-	Favourable TS; ring expansion occurred

† TS = transition state.

EXPERIMENTAL

Optical rotations were determined for solutions in chloroform. Trideuteriomethyl iodide was of greater than 99% isotopic purity. Light petroleum refers to the fraction of b.p. 60—80°.

Photolyses were carried out at room temperature, under nitrogen, with Hanovia medium-pressure mercury arc (Pyrex filter). The course of reaction was followed by the i.r. spectrum (loss of nitrite absorption at 1 640 cm^{-1}) and by t.l.c.

[29] W. L. Meyer, D. L. Davis, L. Foster, A. S. Levinson, V. L. Sawin, D. C. Shew, and R. L. Weddleton, *J. Amer. Chem. Soc.*, 1965, **87**, 1573.

Hydroboration of 3,3-*Ethylenedioxy*-4,4-*dimethylandrost*-5-*ene*.—A solution of 3,3-ethylenedioxy-4,4-dimethylandrost-5-en-17-one (2 g) in diethylene glycol (20 ml) containing hydrazine hydrate (0.7 ml) and potassium hydroxide (0.78 g) was refluxed for 1.5 h; the condenser was then removed and the temperature of the mixture allowed to rise to 200 °C. After 3 h at 200 °C the product was isolated. Purification from methanol gave 3,3-*ethylenedioxy*-4,4-*dimethylandrost*-5-*ene* (1.5 g) in needles, m.p. 161°, $[\alpha]_D^{23}$ −106° (*c* 0.9), τ 9.28 (3 H, s, H_3-18), 8.84 (3 H, s, H_3-19), 8.94 and 8.74 (6 H, s, 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), and 4.42 (1 H, m, H-6) (Found: C, 80.4; H, 10.2. $C_{23}H_{36}O_2$ requires C, 80.2; H, 10.5%).

Diborane [generated from sodium borohydride (0.85 g) in bis-(2-methoxyethyl) ether (30 ml) containing boron trifluoride–ether (5 ml)] was passed (in a stream of nitrogen) into a solution of 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (1 g) in tetrahydrofuran (60 ml), during 1.5 h. After 48 h water was added to destroy the excess of diborane, followed by 15% sodium hydroxide solution (20 ml) and 30% hydrogen peroxide (20 ml). The mixture was stirred vigorously for 3 h, diluted with water, and extracted with ether to yield an oil which was purified by chromatography on alumina from light petroleum. Elution with ethyl acetate–light petroleum (1 : 99) gave starting material (12 mg); ethyl acetate–light petroleum (3 : 97) eluted 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6α-*ol* (9; R^1 = Me, R^2 = H) (0.18 g), which formed needles, m.p. 175—176° (from hexane), $[\alpha]_D^{23}$ −23.5° (*c* 1.1) (Found: C, 76.0; H, 10.3. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%).

Continued elution with this solvent system gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-7α-*ol* (7) (0.12 g) in needles, m.p. 168° (from hexane), $[\alpha]_D^{23}$ −62.5° (*c* 1.0) (Found: C, 76.1; H, 10.3. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%). Further elution with ethyl acetate–light petroleum (1 : 24) gave an oil (0.5 g) which was acetylated (pyridine–acetic anhydride) and chromatographed on alumina [ethyl acetate–light petroleum (1 : 199)] to yield 6β-*acetoxy*-3,3-*ethylenedioxy*-4,4-*dimethyl*-5β-*androstane* (10; R^1 = Me, R^2 = Ac) (0.14 g) which formed needles, m.p. 194—196° (from methanol), $[\alpha]_D^{23}$ +8.3° (*c* 0.4) (Found: C, 74.2; H, 9.8. $C_{25}H_{40}O_4$ requires C, 74.2; H, 10.0%). Further elution with ethyl acetate–light petroleum (1 : 24) produced more 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-7α-ol (0.15 g).

When this hydroboration was repeated at 0 °C during 6 days with 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (2.5 g), the only identified product was 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (0.65 g).

Oxidation of this 6α-ol (0.13 g) dissolved in pyridine (2 ml) with chromic oxide (0.26 g) in pyridine (3 ml) during 2 h, gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6-*one* (12; R = Me) (0.12 g) in prisms, m.p. 218—220° (from methanol), $[\alpha]_D^{23}$ −35.5° (*c* 1.05) (Found: 76.7; H, 10.4. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%), o.r.d. (*c* 0.066 in dioxan), [*M*] +215° (312 nm) and −1 190° (270 nm).

Hydrolysis of this acetal (0.14 g) with 2% hydrochloric acid–methanol during 0.5 h, at the b.p., gave 4,4-*dimethyl*-5α-*androstane*-3,6-*dione* (15; R = Me) as prisms, m.p. 168—169° (from methanol), $[\alpha]_D^{25}$ −66° (*c* 0.85), $\nu_{max.}$ 1 718 and 1 708 cm^{-1} (C=O) (Found: C, 79.5; H, 10.2. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%).

When a solution of this dione (0.12 g) in dioxan (20 ml) containing concentrated sulphuric acid (0.1 ml) was refluxed during 18 h, and the product separated by t.l.c. [ether–hexane (3 : 17)], there was obtained the parent 5α-dione (60 mg) and the 5β-dione (see later) (20 mg).

3,3-*Ethylenedioxy*-4,4-*dimethyl*-5β-*androstan*-6-*one* (13).—Hydrolysis of 6β-acetoxy-3,3-ethylenedioxy-4,4-dimethyl-5β-androstane (0.1 g) with boiling 15% sodium hydroxide (5 ml) and methanol (30 ml) during 18 h (under nitrogen) gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5β-*androstan*-6β-*ol* (10; R^1 = Me, R^2 = H) (0.08 g) in needles, m.p. 141° (from hexane), $[\alpha]_D^{23}$ +22° (*c* 1.0), $\nu_{max.}$ 3 620 cm^{-1} (OH) (Found: C, 76.0; H, 10.9. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%).

Oxidation of this alcohol (0.25 g) with chromic oxide–pyridine during 2 h gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5β-*androstan*-6-*one* (13) (0.24 g) in needles, m.p. 185°, $[\alpha]_D^{25}$ −75° (c 0.8), $\nu_{max.}$ 1 695 cm^{-1} (C=O) (Found: C, 76.8; H, 10.1. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%), o.r.d. (*c* 0.07 in dioxan) [*M*] −6 350° (320 nm), −2 160° (311 nm), +5 460° (283 nm), and +2 730° (244 nm).

Hydrolysis of this acetal (0.2 g) in boiling methanol (30 ml) containing 2% hydrochloric acid (0.4 ml) during 0.5 h gave 4,4-dimethyl-5β-androstane-3,6-dione (16) (0.12 g), which formed needles, m.p. 139° (from hexane), $[\alpha]_D^{25}$ −138° (*c* 1.2), $\nu_{max.}$ 1 720 and 1 705 cm^{-1} (C=O) (Found: C, 79.5; H, 10.1. Calc. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2%) (lit.,[13] m.p. 139—140°, $[\alpha]_D$ −144°). The mother liquors from the purification contained (t.l.c.) the corresponding 5α-dione (15; R = Me).

Epimerisation of this 5β-dione (0.15 g) as for the 5α-diastereoisomer gave unchanged 5β-dione (20 mg) and the 5α-dione (73 mg), after purification.

3,3-*Ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6β-*ol* (11; R^1 = Me, R^2 = H).—Reduction of a solution of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6-one (0.2 g) in ether (30 ml), containing lithium aluminium hydride (0.11 g) during 16 h afforded 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6β-*ol* (0.16 g), which separated from hexane in needles, m.p. 199—200°, $[\alpha]_D^{23}$ −52.5°, $\nu_{max.}$ 3 630 cm^{-1} (OH), τ 9.27 (3 H, s, H_3-18), 8.73 (3 H, s, H_3-19), 9.04 and 8.62 (6 H, s, 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), and 5.64 (1 H, m, H-6α) (Found: C, 76.0; H, 10.6. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%).

Dehydration of this alcohol (60 mg) dissolved in pyridine (4 ml) with phosphoryl chloride (0.5 ml) furnished 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (6; R^1 = Me, R^2 = H_2) (40 mg), identical with an authentic specimen.

6α-*Hydroxy*-4,4-*dimethyl*-5α-*androstan*-3-*one* (8; R^1 = Me, R^2 = H).—Hydrolysis of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (3 g) in boiling methanol (100 ml) containing 2% hydrochloric acid (2 ml) gave 6α-*hydroxy*-4,4-*dimethyl*-5α-*androstan*-3-*one* (2.4 g) in needles, m.p. 194—195° (from hexane), $[\alpha]_D^{23}$ +152° (*c* 1.2), $\nu_{max.}$ 3 590 (OH) and 1 710 cm^{-1} (C=O) (Found: C, 79.3; H, 10.7. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%).

3,3-*Ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-7-*one* (17).—(i) Oxidation of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-7α-ol (0.3 g) dissolved in pyridine (10 ml) with chromic oxide (0.6 g) in pyridine (10 ml) gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-7-*one* (0.27 g) in plates, m.p. 208—210° (from methanol), $[\alpha]_D^{23}$ −86° (*c* 0.9), $\nu_{max.}$ 1 710 cm^{-1} (C=O) (Found: C, 76.4; H, 10.2. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%).

Reduction of this ketone (0.25 g) during 3 h with sodium borohydride (1.2 g) in methanol (30 ml), followed by chromatography of the product gave (a) 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-7β-*ol* (20) (25 mg.) which formed needles, m.p. 184—186° (from hexane), $[\alpha]_D^{22}$ −31° (*c* 1.4),

$\nu_{max.}$ 3 660 and 3 620 cm^{-1} (OH) (Found: C, 76.3; H, 10.5. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%); and (b) the corresponding 7α-ol (0.15 g).

(ii) Potassium carbonate (0.13 g) and *N*-bromosuccinimide (0.22 g) were added to a solution of 3,3-ethylenedioxy-4,4-dimethylandrost-5-ene (0.4 g) in carbon tetrachloride (30 ml). The mixture was refluxed during 5 min, while being irradiated with a Photospot lamp. The cooled solution was filtered and stirred with neutral alumina (4 g) during 16 h. Chromatography on alumina furnished (a) 3,3-*ethylenedioxy*-4,4-*dimethylandrost*-5-*en*-7β-*ol* (21) (60 mg) in needles, m.p. 209—210° (from hexane), $[\alpha]_D^{25}$ −71° (*c* 1.0), $\nu_{max.}$ 3 010 (OH) cm^{-1}, τ 9.24 (3 H, s, H_3-18), 8.91, 8.78, and 8.72 (9 H, s, H_3-19 and 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), 5.96 (1 H, m, H-7), and 4.47 (1 H, d, *J* 3 Hz, H-6) (Found: C, 76.9; H, 10.0. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%); and (b) 3,3-*ethylenedioxy*-4,4-*dimethylandrost*-5-*en*-7α-*ol* (22) (0.19 g) in prisms, m.p. 154—155° (from hexane), $[\alpha]_D^{25}$ −149° (*c* 0.8), $\nu_{max.}$ 3 010 cm^{-1} (OH), τ 9.28 (3 H, s, H_3-18), 8.91, 8.86, and 8.74 (9 H, s, H_3-19 and 4-Me_2), 6.10 (1 H, m, H-7 proton), and 4.24 (1 H, d, *J* 5 Hz, H-6) (Found: C, 76.5; H, 10.1. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%).

Oxidation of the 7α- and the 7β-ol with chromic oxide–pyridine gave, in high yield, the same 3,3-*ethylenedioxy*-4,4-*dimethylandrost*-5-*en*-7-*one* (23) in needles, m.p. 165—168° (from methanol), $[\alpha]_D^{25}$ −103° (*c* 0.95), $\nu_{max.}$ 1 670 and 1 610 cm^{-1} (αβ-unsaturated ketone), τ 4.07 (1 H, s, H-6) (Found: C, 77.1; H, 9.6. $C_{23}H_{34}O_3$ requires C, 77.1; H, 9.6%).

A solution of this ketone (70 mg) in dioxan (5 ml) was added during 10 min to a stirred solution of lithium (30 mg) in ammonia (40 ml). After 0.5 h ammonium chloride (1 g) was added. Isolation in the normal manner followed by p.l.c. on alumina [developed with ether–hexane (1 : 4)] gave 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-7-one (17) (35 mg), identical with an authentic specimen.

Reduction of this ketone (100 mg) during 2 h in a refluxing mixture of hydrazine hydrate (0.3 ml), potassium hydroxide (60 mg), and diethylene glycol (10 ml) and then for a further 5 h at 200 °C gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstane* (18) (70 mg) in plates, m.p. 191° (from acetone), $[\alpha]_D^{25}$ −36° (*c* 2.0), τ 9.31 (3 H, s, H_3-18), 9.16, 9.08, and 9.05 (9 H, s, H_3-19 and 4-Me_2), and 6.04 (4 H, s, O·CH_2·CH_2·O) (Found: C, 79.6; H, 11.1. $C_{23}H_{38}O_2$ requires C, 79.7; H, 11.1%).

Hydrolysis of this acetal (50 mg) with boiling methanol (20 ml) containing 2% hydrochloric acid (0.2 ml) during 0.5 h gave 4,4-dimethyl-5α-androstan-3-one (19) (35 mg), m.p. 120°, identical with an authentic specimen prepared by catalytic reduction of 4,4-dimethylandrost-5-en-3-one.

Photolysis of 3,3-*Ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6α-*yl Nitrite*.—A solution of 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (100 mg) in pyridine (3 ml) was treated with nitrosyl chloride until a red colouration persisted. Purified from acetone, 3,3-*ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6α-*yl nitrite* (9; R^1 = Me, R^2 = NO) (95 mg) formed plates, m.p. 139—140°, $[\alpha]_D^{24}$ +37° (*c* 3.0), $\nu_{max.}$ 1 640 cm^{-1} (nitrite), τ 4.14 (1 H, m, H-6β) (Found: 70.5; H, 9.4; N, 3.6. $C_{23}H_{37}NO_4$ requires C, 70.6; H, 9.5; N, 3.6%).

Photolysis of a solution of this nitrite (2.2 g) in benzene (200 ml) was complete in 21 h, to yield 3,3-*ethylenedioxy*-4α-*hydroxyiminomethyl*-4β-*methyl*-5α-*androstan*-6α-*ol* (35; R = Me) (1.2 g) in needles, m.p. 234—238° (from acetone), $[\alpha]_D^{24}$ −68° (*c* 1.4), $\nu_{max.}$ (Nujol) 3 510 and 3 470 (OH) and 1 645 cm^{-1} (oxime), τ [$(CD_3)_2SO$] 9.32 (3 H, s, H_3-18), 9.08 and 8.76 (6 H, s, H_3-19 and 4β-Me), 6.20 (5 H, m, O·CH_2·CH_2·O and H-6β), 2.82 (1 H, s, 4α-CH), and 0.25 (1 H, s, NOH, exchangeable with D_2O) (Found: C, 70.7; H, 9.6; N, 3.2%; M^+, 391. $C_{23}H_{37}NO_4$ requires C, 70.6; H, 9.5; N, 3.6%; *M*, 391).

Purification of the residues remaining from the separation of this hydroxyiminomethyl compound by chromatography on neutral alumina furnished (*a*) with benzene–light petroleum (3 : 7) 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6-one (60 mg), and (*b*) with chloroform–benzene (1 : 9) 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6α-ol (0.16 g).

Photolysis of 4,4-*Dimethyl*-3-*oxo*-5α-*androstan*-6α-*yl Nitrite*.—Prepared (90% yield) as for the corresponding ethylene acetal, this *nitrite* (8; R^1 = Me, R^2 = NO) formed needles, m.p. 112—113° (from methanol), $[\alpha]_D^{24}$ +238° (*c* 0.9), $\nu_{max.}$ 1 645 (nitrite) and 1 710 cm^{-1} (C=O), τ 9.25 (3 H, s, H_3-18), 9.06, 8.88, and 8.83 (9 H, s, H_3-19 and 4-Me_2), and 4.38 (1 H, m, H-6β) (Found: C, 72.2; H, 9.5; N, 4.5. $C_{21}H_{33}NO_3$ requires C, 72.6; H, 9.6; N, 4.1%).

Photolysis of this nitrite (2.2 g) in benzene (200 ml) required 72 h for completion. Chromatography of the product on alumina gave on elution (*a*) with methylene chloride–light petroleum (1 : 4) 4,4-dimethyl-5α-androstane-3,6-dione (70 mg); (*b*) with methylene chloride–light petroleum (1 : 1) 6α-hydroxy-4,4-dimethyl-5α-androstan-3-one (0.55 g); (*c*) with methanol–methylene chloride (1 : 199) 6α-*hydroxy*-4α-*methyl*-A-*homo*-5α-*androst*-4-*en*-3-*one* (38) (0.34 g) which formed needles, m.p. 180—182° (from ether–hexane), $[\alpha]_D^{24}$ +220° (*c* 2.1), $\nu_{max.}$ 3 410 (OH), 1 645, 1 665, and 1 620 cm^{-1} (αβ-unsaturated ketone), $\lambda_{max.}$ (hexane) 237 nm (ε 10 190) (Found: C, 79.6; H, 10.2. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%); (*d*) with methanol–methylene chloride (1 : 24) 4β-*methyl*-5α-*androstano*[4,3-d]*isoxazoline*-3ξ,6α-*diol* (36) (35 mg) which formed needles, m.p. 221—224° (from acetone–hexane), $[\alpha]_D^{24}$ −92° (*c* 0.4) (Found: M^+, 347.2460. $C_{21}H_{33}NO_3$ requires *M*, 347.2460); and (*e*) with methanol–methylene chloride (3 : 47) 6α-*hydroxy*-4β-*methyl*-3-*oxo*-5α-*androstane*-4α-*carboxamide* (39) (0.11 g) in plates, m.p. 198—200° (from acetone–hexane), $[\alpha]_D^{24}$ +164° (*c* 0.9), $\nu_{max.}$ (Nujol) 3 570, 3 480, 3 280, 3 170 (amide and OH), 1 685, 1 605 (amide), and 1 705 cm^{-1} (ketone) (Found: M^+, 347.2490. $C_{21}H_{33}NO_3$ requires *M*, 347.2460).

Acidic Hydrolysis of 3,3-*Ethylenedioxy*-4α-*hydroxyiminomethyl*-4β-*methyl*-5α-*androstan*-6α-*ol*.—(*a*) A solution of this oxime (100 mg) in dioxan (10 ml) and 2% hydrochloric acid (3 ml) was refluxed for 0.5 h to give 6α-*hydroxy*-4β-*methyl*-3-*oxo*-5α-*androstane*-4α-*carbonitrile* (37; R = Me) (67 mg) in prisms, m.p. 192—195° (from methylene chloride–hexane), $[\alpha]_D^{23}$ +10° (*c* 0.6) (Found: C, 76.9; H, 9.5; N, 4.1. $C_{21}H_{31}NO_2$ requires C, 76.6; H, 9.5; N, 4.3%).

(*b*) A solution of this oxime (60 mg) in 80% acetic acid was kept for 10 days. Purification of the product by t.l.c. [methanol–benzene (1 : 9)] followed by crystallisation from acetone–hexane gave 4β-methyl-5α-androstano[4,3-*d*]isoxazoline-3ξ,6α-diol (36) (25 mg), identical with the previous specimen.

When this isoxazole (15 mg) was hydrolysed as in (*a*), 6α-hydroxy-4β-methyl-3-oxo-5α-androstane-4α-carbonitrile (8 mg), identical with the previous specimen, was obtained.

Photolysis of 3,3-*Ethylenedioxy*-4,4-*dimethyl*-5α-*androstan*-6β-*yl Nitrite* (11; R^1 = Me, R^2 = NO).—Prepared (almost quantitatively) as for the 6α-nitrite, this *nitrite* formed needles, m.p. 178—180° (from acetone), $[\alpha]_D^{24}$ −126° (*c* 1.0), $\nu_{max.}$ 1 640 cm^{-1} (nitrite), τ 9.30 (3 H, s, H_3-18), 8.88 (3 H, s, H_3-19), 9.06 and 8.96 (6 H, s, 4-Me_2), 6.06 (4 H, s, O·CH_2·CH_2·O), and 3.90 (1 H, m, H-6α) (Found: C, 70.6; H, 9.6;

N, 3.5. $C_{23}H_{37}NO_4$ requires C, 70.6; H, 9.5; N, 3.6%).

Photolysis of a solution of this nitrite (2.2 g) in benzene (250 ml) was complete in 19 h. The product was purified by chromatography on neutral alumina from light petroleum to yield on elution with (*a*) chloroform–light petroleum (1 : 4) 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6-one (0.14 g); (*b*) chloroform–light petroleum (2 : 3) 3,3-ethylenedioxy-4,4-dimethyl-5α-androstan-6β-ol (0.36 g); (*c*) chloroform–light petroleum (3 : 2) 3,3-*ethylenedioxy*-19-*hydroxyimino*-4,4-*dimethyl*-5α-*androstan*-6β-*ol* (45) (0.55 g) in needles, m.p. 254—256° (from hexane), $[\alpha]_D^{24}$ −42° (*c* 1.2) (Found: C, 70.4; H, 9.5; N, 3.5%; M^+, 391. $C_{23}H_{37}NO_4$ requires C, 70.6; H, 9.5; N, 3.6%; *M*, 391); (*d*) chloroform–light petroleum (4 : 1) 3,3-*ethylenedioxy*-4β-*hydroxyiminomethyl*-4α-*methyl*-5α-*androstan*-6β-*ol* (46) (0.14 g) in prisms, m.p. 227—229° (from acetone–hexane), $[\alpha]_D^{24}$ −7.2° (*c* 1.4) (Found: C, 70.2; H, 9.5; N, 3.7%; M^+, 391. $C_{23}H_{37}NO_4$ requires C, 70.6; H, 9.5; N, 3.6%; *M*, 391).

3,3-*Ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)*androstan*-6α- *and* -6β-*ol*.—A solution of androst-4-en-3-one (8.0 g) in benzene (100 ml) was trideuteriomethylated by addition of a solution of potassium t-butoxide [from potassium (3.2 g)] in t-butyl alcohol (100 ml) followed by (at 0 °C) trideuteriomethyl iodide (10 g) in benzene (10 ml), during 10 min. After 4 h the product was isolated and acetalised (as for the 4,4-dimethyl analogue) to yield 3,3-*ethylenedioxy*-4,4-*bis*-(*trideuteriomethyl*)*androst*-5-*ene* (27) (8.2 g), which separated from methanol in needles, m.p. 159—160°, undepressed upon admixture with unlabelled material, $[\alpha]_D^{23}$ −109° (*c* 0.6), $\nu_{max.}$ 2 220 and 2 230 cm^{-1} (C–D str.), τ 9.28 (3 H, s, H_3-18), 8.84 (3 H, s, H_3-19), 6.04 (4 H, s, O·CH_2·CH_2·O), and 4.42 (1 H, m, H-6) (Found: C, 78.7; H, 10.6%; M^+, 350. $C_{23}H_{30}D_6O_2$ requires C, 78.8; H, 10.5%; *M*, 350).

Hydroboration of this compound as for the non-labelled analogue gave 3,3-*ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6α-*ol* (28) (28%) in needles, m.p. 174—175° (undepressed on admixture with the unlabelled analogue) (from hexane), $[\alpha]_D^{23}$ −22° (*c* 0.8), $\nu_{max.}$ 3 610 (OH) and 2 210 cm^{-1} (C–D str.) (Found: C, 75.0; H, 10.6%; M^+, 368. $C_{23}H_{32}D_6O_3$ requires C, 75.0; H, 10.6%; *M*, 368). Oxidation of this 6α-ol, as for unlabelled material, gave 3,3-*ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6-*one* (29) (87%) in prisms, m.p. 217—218° (undepressed on admixture with unlabelled material) (from methanol), $[\alpha]_D^{23}$ −34° (*c* 0.5), $\nu_{max.}$ 1 710 (C=O) and 2 220 cm^{-1} (C–D str.) (Found: C, 75.1; H, 10.0%; M^+, 366. $C_{23}H_{30}D_6O_3$ requires C, 75.4; H, 10.0%; *M*, 366).

Reduction of this 6-one with lithium aluminium hydride gave 3,3-*ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6β-*ol* (30; R = H) (80%) in needles, m.p. 200—202° (from methanol), $[\alpha]_D^{23}$ −48° (*c* 0.9), $\nu_{max.}$ 3 630 (OH) and 2 220 cm^{-1} (C–D str.) (Found: C, 75.3; H, 10.4%; M^+, 368. $C_{23}H_{32}D_6O_3$ requires C, 75.0; H, 10.6%; *M*, 368).

Photolysis of 3,3-*Ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6β-*yl Nitrite* (30; R = NO).—The foregoing 6β-ol was converted (85%) as for unlabelled material into 3,3-*ethylenedioxy*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6β-*yl nitrite*, which formed needles, m.p. 179—180° (from acetone), $[\alpha]_D^{23}$ −125° (*c* 1.5), $\nu_{max.}$ 1 640 (nitrite) and 2 220 cm^{-1} (C–D str.) (Found: C, 69.5; H, 9.9; N, 3.3. $C_{23}H_{31}D_6NO_4$ requires C, 69.5; H, 9.9; N, 3.5%).

When a solution of this 6β-nitrite (1.1 g) in benzene (200 ml) was irradiated as for the unlabelled material, reaction was complete in 20 h to yield (*a*) 3,3-ethylenedioxy-4,4-bis-(trideuteriomethyl)-5α-androstan-6-one (64 mg); (*b*) the parent 6β-ol (0.17 g); and (*c*) 3,3-*ethylenedioxy*-19-*hydroxyiminomethyl*-4,4-*bis*(*trideuteriomethyl*)-5α-*androstan*-6β-*ol* (47) (0.46 g), which formed needles, m.p. 257—258° (undepressed on admixture with the unlabelled analogue) (from hexane), $[\alpha]_D^{22}$ −43° (*c* 0.95), $\nu_{max.}$ (Nujol) 3 450 and 3 270 (OH), and 1 620 cm^{-1} (oxime), τ 9.30 (3 H, s, H_3-18), 6.03 (4 H, s, O·CH_2·CH_2·O), 5.70 (1 H, m, H-6α), and 2.44 (1 H, s, H-19) (Found: C, 69.7; H, 9.6; N, 3.3%; M^+, 397. $C_{23}H_{31}D_6NO_4$ requires C, 69.5; H, 9.9; N, 3.5%; *M*, 397).

Photolysis of 4β-*Methyl*-3-*oxo*-4α-*trideuteriomethyl*-5α-*androstan*-6α-*yl Nitrite* (34; R = NO).—Methylation of a solution of androst-4-en-3-one (10 g) in t-butyl alcohol (170 ml) containing potassium t-butoxide [from potassium (2.2 g)] by addition of methyl iodide (5.74 g, 1.1 mol. equiv.) during 2.5 h at the b.p., followed by 0.5 h at the b.p., gave 4-*methylandrost*-4-*en*-3-*one* (4.2 g) in needles, m.p. 107—108° from hexane), $[\alpha]_D^{23}$ +119° (*c* 1.3), $\nu_{max.}$ 1 680 and 1 610 cm^{-1} (αβ-unsaturated ketone), τ 9.26 (3 H, s, H_3-18), 8.83 (3 H, s, H_3-19), and 8.23 (3 H, s, 4-Me) (Found: C, 83.5; H, 10.5. $C_{20}H_{30}O$ requires C, 83.9; H, 10.6%).

This ketone (12 g) was added to a solution of potassium t-butoxide [from potassium (4 g)] in t-butyl alcohol (300 ml) and the solution refluxed for 1 h. The solution was cooled to 0 °C and a solution of trideuteriomethyl iodide (10.0 g) in benzene (100 ml) added. After 4 h the product was isolated to yield 4β-*methyl*-4α-*trideuteriomethylandrost*-5-*en*-3-*one* (33) (5.1 g) in plates, m.p. 175—177° (from acetone), $[\alpha]_D^{23}$ −18° (*c* 0.7), $\nu_{max.}$ 2 220 (C–D str.) and 1 712 cm^{-1} (ketone) (Found: C, 83.2; H, 11.0%; M^+, 303. $C_{21}H_{29}D_3O$ requires C, 83.1; H, 10.7%; *M*, 303).

Formed (80% yield) as for the unlabelled analogue, 3,3-*ethylenedioxy*-4β-*methyl*-4α-*trideuteriomethylandrost*-5-*en*-3-*one* (32) separated in needles, m.p. 159—160° (undepressed on admixture with unlabelled material) (from methanol), $[\alpha]_D^{23}$ −108° (*c* 1.3), $\nu_{max.}$ 2 220 cm^{-1} (C–D str.), τ 9.27 (3 H, s, H_3-18), 8.85 (3 H, s, H_3-19), 8.75 (3 H, s, 4β-Me), 6.04 (4 H, s, O·CH_2·CH_2·O), and 4.46 (1 H, m, H-6) (Found: C, 79.5; H, 10.6%; M^+, 347. $C_{23}H_{33}D_3O_2$ requires C, 79.5; H, 10.5%; *M*, 347).

Hydroboration of this 5-ene as for the analogues gave (28% yield) 3,3-*ethylenedioxy*-4β-*methyl*-4α-*trideuteriomethyl*-5α-*androstan*-6α-*ol* (31) in needles, m.p. 173—175° (undepressed on admixture with unlabelled material) (from hexane), $[\alpha]_D^{23}$ −21.2° (*c* 1.1), $\nu_{max.}$ 3 610 (OH) and 2 220 cm^{-1} (C–D str.) (Found: C, 75.7; H, 10.7%; M^+, 365. $C_{23}H_{35}D_3O_3$ requires C, 75.6; H, 10.6%; *M*, 365).

Acidic hydrolysis of this acetal, as for the unlabelled analogue, gave (in 91% yield) 6α-*hydroxy*-4β-*methyl*-4α-*trideuteriomethyl*-5α-*androstan*-3-*one* (34; R = H) in needles, m.p. 194—195° (from hexane), $[\alpha]_D^{23}$ +143° (*c* 0.8), $\nu_{max.}$ (Nujol) 3 450 (OH), 2 220 (C–D str), and 1 700 cm^{-1} (C=O) (Found: C, 78.2; H, 10.6. $C_{21}H_{31}D_3O_2$ requires C, 78.5; H, 10.6%).

Prepared (in 82% yield) the 6α-*nitrite* (34; R = NO) formed needles, m.p. 111—113° (from methanol), $\nu_{max.}$ 2 220 (C–D str.), 1 710 (C=O), and 1 650 and 1 610 cm^{-1} (nitrite) (Found: C, 71.8; H, 9.4; N, 3.8. $C_{21}H_{30}D_3NO_3$ requires C, 72.0; H, 9.6; N, 4.0%).

Photolysis of this nitrite (2.0 g) dissolved in benzene (200 ml) was complete in 98 h. Purification of the mixed product by chromatography on alumina gave (*a*) with ethyl acetate–light petroleum (1 : 19) the parent 6α-ol (0.7 g); (*b*) with ethyl acetate–light petroleum (2 : 3) 6α-hydroxy-4a-methyl-A-homo-5α-androst-4-en-3-one (0.10 g).

3,3-*Ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6α-*ol*

(9; $R^1 = R^2 = H$) *and* -6β-*ol* (11; $R^1 = R^2 = H$).—Acetalisation of 17β-hydroxy-4,4-dimethyl-19-norandrost-5-en-3-one (15.0 g) under the conditions employed in the androstane series gave (in 90% yield) 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*norandrost*-5-*en*-17β-*ol* in needles, m.p. 138—141° (from methylene chloride–hexane), $[\alpha]_D^{23}$ −9.6° (*c* 1.0), $\nu_{max.}$ 3 590 cm^{-1} (OH), τ 4.36 (1 H, m, H-6) (Found: C, 76.1; H, 10.0. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%).

Oxidation of this 17β-ol (8.0 g) dissolved in pyridine (100 ml) with chromic oxide (16 g) dissolved in pyridine (120 ml) afforded 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*norandrost*-5-*en*-17-*one* (6.80 g), which separated from hexane in needles, m.p. 152—154°, $[\alpha]_D^{23}$ +55° (*c* 0.8), $\nu_{max.}$ 1 740 cm^{-1} (C=O) (Found: C, 77.0; H, 9.3. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.4%).

Reduction of this ketone (4 g) by the Wolff–Kishner process, as for the androstane analogue, gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*norandrost*-5-*ene* (6; $R^1 = H$, $R^2 = H_2$) (3.2 g) in needles, m.p. 118—119° (from methanol), $[\alpha]_D^{23}$ −18° (*c* 1.0), $\nu_{max.}$ 3 020 cm^{-1}, τ 4.38 (1 H, m, H-6) (Found: C, 79.9; H, 10.4 $C_{22}H_{34}O_2$ requires C, 80.0; H, 10.4%).

Hydroboration of this 5-ene (10.0 g) in tetrahydrofuran (600 ml) at 0 °C during 48 h, by the process used for the androstane analogue, gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6α-*ol* (9; $R^1 = R^2 = H$) (8.3 g), which formed prisms, m.p. 125° (from hexane), $[\alpha]_D^{23}$ +0.2° (*c* 0.9), $\nu_{max.}$ 3 590 cm^{-1} (OH), τ 9.28 (3 H, s, H_3-18), 8.90 and 8.80 (6 H, s, 4-Me_2), 6.03 (4 H, s, O·CH_2·CH_2·O), and 6.37 (1 H, m, H-6β) (Found: C, 75.8; H, 10.5. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%). Acidic hydrolysis of this acetal (0.5 g), as for the androstane analogue, gave 6α-*hydroxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-3-*one* (8; $R^1 = R^2 = H$) (0.4 g) in needles, m.p. 149° (from hexane), $[\alpha]_D^{21}$ +22° (*c* 1.0), $\nu_{max.}$ 3 590 (OH) and 1 710 cm^{-1} (C=O) (Found: C, 78.6; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%).

Oxidation of 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6α-ol (8.0 g) dissolved in pyridine (100 ml) with chromic oxide (16.0 g) in pyridine (120 ml) gave 3,3-*ethylene*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6-*one* (12; R = H) (7.2 g) in plates, m.p. 121—123° (from methanol), $[\alpha]_D^{23}$ −21° (*c* 1.6), $\nu_{max.}$ 1 708 cm^{-1} (C=O) (Found: C, 76.1; H, 9.7. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%).

Sodium borohydride (2.0 g) was added during 1.5 h to a stirred solution of this 6-one (0.5 g) in methanol (40 ml), 4 h later the product was isolated and purified from hexane to yield 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6β-*ol* (11; $R^1 = R^2 = H$) (0.4 g) in needles, m.p. 121° (from hexane), $[\alpha]_D^{23}$ −25° (*c* 0.8), $\nu_{max.}$ 3 600 cm^{-1} (OH), τ 9.25 (3 H, s, H_3-18), 9.02 and 8.80 (6 H, s, 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), and 5.27 (1 H, m, H-6α) (Found: C, 76.1; H, 10.9. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%). The 6α-ol (58 mg) was isolated from the residues.

Acidic hydrolysis of the 6β-alcohol, as for the 6α-diastereoisomer, gave 6β-*hydroxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-3-*one* (0.4 g) in needles, m.p. 187° (from hexane), $[\alpha]_D^{24}$ −57° (*c* 0.9), $\nu_{max.}$ 3 600 (OH) and 1 710 cm^{-1} (ketone) (Found: C, 78.9; H, 10.5. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%).

Dehydration of 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6β-ol (120 mg) dissolved in pyridine (8 ml) with phosphoryl chloride (1.0 ml) at 0 °C during 16 h gave 3,3-ethylenedioxy-4,4-dimethyl-19-norandrost-5-ene (60 mg) identical with an authentic specimen.

4,4-*Dimethyl*-19-*nor*-5α-*androstane*-3,6-*dione* (15; R = H).—Hydrolysis of 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6-one (0.3 g) during 0.5 h with boiling methanol (20 ml) containing 2% hydrochloric acid (2.5 ml) gave the 3,6-*dione* (0.25 g) in prisms, m.p. 112° (from hexane), $[\alpha]_D^{21}$ −57° (*c* 0.9), $\nu_{max.}$ 1 708 and 1 722 cm^{-1} (C=O) (Found: C, 79.7; H, 9.9. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%).

4,4-*Dimethyl*-19-*nor*-5α-*androstane*.—A solution of 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6-one (0.5 g) in hydrazine hydrate (1.1 ml) and diethylene glycol (25 ml) was refluxed for 1 h, and for a further 4 h at 210 °C. Purification of the product from ether–methanol gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstane* (0.4 g), $[\alpha]_D^{21}$ −14.4° (*c* 0.9), τ 9.27 (3 H, s, H_4-18), 9.12 and 9.05 (6 H, s, 4-Me_2), and 6.04 (4 H, s, O·CH_2·CH_2·O) (Found: C, 79.5; H, 10.9. $C_{22}H_{36}O_2$ requires C, 79.5; H, 10.9%).

Acidic hydrolysis of this acetal (150 mg) gave 4,4-dimethyl-19-nor-5α-androstan-3-one (100 mg), identical with an authentic specimen [21] (Found: C, 83.0; H, 11.3. Calc. for $C_{20}H_{32}O$: C, 83.3; H, 11.2%).

Reduction of this ketone (80 mg) by the Wolff–Kishner process gave 4,4-*dimethyl*-19-*nor*-5α-*androstane* (55 mg) in needles, m.p. 48° (from ether–methanol), $[\alpha]_D^{25}$ +15° (*c* 0.5) (Found: C, 87.2; H, 12.3. $C_{20}H_{34}$ requires C, 87.5; H, 12.5%), identical with the product prepared from 4,4-dimethyl-19-nor-5α-androstane-3,17-dione by the same process.

Photolysis of 3,3-*Ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6α-*yl Nitrite* (9; $R^1 = H$, $R^2 = NO$).—Prepared from the corresponding 6α-ol (100 mg) in the manner already described, the 6α-*nitrite* (84 mg) formed needles, m.p. 105° (from ether–methanol), $[\alpha]_D^{23}$ +74° (*c* 0.3), $\nu_{max.}$ 1 640 cm^{-1} (nitrite), τ 9.25 (3 H, s, H_3-18), 9.18 and 8.94 (6 H, s, 4-Me_2), 6.04 (4 H, s, O·CH_2·CH_2·O), and 4.50 (1 H, m, H-6β) (Found: C, 69.6; H, 9.1; N, 3.8. $C_{22}H_{35}NO_4$ requires C, 70.0; H, 9.4; N, 3.7%).

Photolysis of this 6α-nitrite (1.8 g) dissolved in benzene (200 ml) was complete in 18 h, to yield 3,3-*ethylenedioxy*-4α-*hydroxyiminomethyl*-4β-*methyl*-19-*nor*-5α-*androstan*-6α-*ol* (35; R = H) (1.0 g), which separated from ether–hexane in needles, m.p. 215—217°, $[\alpha]_D^{21}$ −52° (*c* 0.7), $\nu_{max.}$ 3 580, 3 460, and 3 300 (OH), and 1 635 cm^{-1} (oxime), τ 9.29 (3 H, s, H_3-18), 8.27 (3 H, s, 4β-Me), 6.70 (4 H, s, O·CH_2·CH_2·O), 6.40 (1 H, m, H-6β), 2.40 (1 H, s, 4α-CH), and 0.15 (1 H, s, NOH, exchangeable with D_2O) (Found: C, 70.1; H, 9.3; N, 4.1%; M^+, 377. $C_{22}H_{35}NO_4$ requires C, 70.0; H, 9.4; N, 3.7%; *M*, 377).

The residues remaining from the separation of this oxime were purified by chromatography on alumina, from light petroleum, to yield on elution with (*a*) methylene chloride–light petroleum (1 : 9) 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6-one (80 mg); (*b*) methylene chloride–light petroleum (1 : 1) the corresponding 6α-ol (0.3 g); and (*c*) methanol–methylene chloride (1 : 99) the hydroxyiminomethyl derivative (35; R = H) (92 mg). Hydrolysis (*a*) of 3,3-ethylenedioxy-4α-hydroxyiminomethyl-4β-methyl-19-nor-5α-androstan-6α-ol (120 mg) with boiling 2% hydrochloric acid (1.5 ml) in dioxan (6 ml) during 0.5 h gave 6α-*hydroxy*-4β-*methyl*-3-*oxo*-19-*nor*-5α-*androstane*-4α-*carbonitrile* (37; R = H) (84 mg) in needles, m.p. 200° (from ether–hexane), $[\alpha]_D^{21}$ −46° (*c* 0.8), $\nu_{max.}$ (Nujol) 3 450 (OH), 2 240 (C≡N), and 1 720 cm^{-1} (C=O), τ 9.27 (3 H, s, H_3-18), 8.38 (3 H, s, 4β-Me), and 6.32 (1 H, m, H-6β) (Found: C, 76.3; H, 9.3; N, 4.2. $C_{20}H_{29}NO_2$ requires C, 76.2; H, 9.3; N, 4.4%). Hydrolysis (*b*) of the oxime (100 mg) in 80% acetic acid during 10 days gave this carbonitrile (37; R = H)

(40 mg) together with the isoxazoline (36; R = H) (27 mg). Further hydrolysis of the isoxazoline (36; R = H) afforded (81% yield) the carbonitrile (37; R = H).

Photolysis of 4,4-*Dimethyl*-3-*oxo*-19-*nor*-5α-*androstan*-6α-*yl Nitrite* (8; R^1 = H, R^2 = NO).—Prepared from the 6α-ol (in 78% yield) this 6α-*nitrite* formed needles, m.p. 120° (from ether–methanol), $[\alpha]_D^{23}$ +86° (*c* 0.6), $\nu_{max.}$ 1 710 (C=O) and 1 640 and 1 600 cm^{-1} (nitrite) (Found: C, 71.9; H, 9.2· N. 4.0. $C_{20}H_{31}NO_3$ requires C, 72.0; H, 9.4; N, 4.2%).

Photolysis of a solution in benzene (200 ml) of this nitrite (2.0 g) was complete in 20 h, to yield 4β-*methyl*-19-*nor*-5α-*androstano*[4,3-d]*isoxazoline*-3ξ,6α-*diol* (36; R = H) (0.8 g) in needles, m.p. 180—183° (from acetone–hexane), $[\alpha]_D^{21}$ −115° (*c* 0.6), $\nu_{max.}$ (Nujol) 3 400 and 3 250 (OH) and 1 610 cm^{-1} (isoxazoline) (Found: C, 72.3; H, 9.8; N, 4.0%; M^+, 333. $C_{20}H_{31}NO_3$ requires C, 72.0; H, 9.4; N, 4.2%; *M*, 333).

Purification of the residue from the separation of this isoxazoline by chromatography on alumina from light petroleum gave on elution with (*a*) methanol–methylene chloride (1 : 99) 4,4-dimethyl-19-nor-5α-androstane-3,6-dione (90 mg); (*b*) methanol–methylene chloride (3 : 97) 6α-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (220 mg); and (*c*) the same solvent system, the isoxazoline (36; R = H) (0.4 g).

Photolysis of 3,3-*Ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6β-*yl Nitrite* (11; R^1 = H, R^2 = NO).—Prepared from the 6β-ol the *nitrite* (85% yield) formed needles, m.p. 113° (from ether–methanol), $[\alpha]_D^{23}$ −105° (*c* 0.4), $\nu_{max.}$ 1 645 and 1 600 cm^{-1} (nitrite) (Found: C, 70.0; H, 9.1; N, 3.7. $C_{22}H_{35}NO_4$ requires C, 70.0; H, 9.4; N, 3.7%).

Photolysis of this nitrite (2.0 g) dissolved in benzene (200 ml) was complete in 20 h, to yield on chromatography from methylene chloride on silica gel (*a*) with methanol–methylene chloride (1 : 249) 3,3-ethylenedioxy-4,4-dimethyl-19-nor-5α-androstan-6-one (74 mg); (*b*) with methanol–methylene chloride (1 : 99) the 6β-ol (11; R^1 = R^2 = H) (170 mg); (*c*) with methanol–methylene chloride (1 : 49) 3,3-*ethylenedioxy*-4β-*hydroxyiminomethyl*-4α-*methyl*-19-*nor*-5α-*androstan*-6β-*ol* (48) (1.26 g), which formed a solid, m.p. 125—131°, which did not crystallise; $\nu_{max.}$ (Nujol) 3 210 and 3 110 cm^{-1} (OH), M^+ 377. Prepared in 77% yield by the pyridine–acetic anhydride method the *diacetate* formed prisms, m.p. 137° (from methanol), $[\alpha]_D^{25}$ −62° (*c* 0.95), $\nu_{max.}$ 1 770 and 1 735 (acetate), and 1 620 cm^{-1} (C≡N), τ 9.26 (3 H, s, H_3-18), 8.78 (3 H, s, 4α-Me), 8.04 and 7.85 (6 H, s, 2 AcO), 6.02 (4 H, s, O·CH_2·CH_2·O), 4.73 (1 H, m, H-6α), and 7.92 (1 H, s, CH=N) (Found: C, 67.9; H, 8.4; N, 3.2. $C_{26}H_{39}NO_6$ requires C, 67.7; H, 8.5; N, 3.0%).

Hydrolysis of this oxime (48) (150 mg) with boiling dioxan (10 ml) containing 2% hydrochloric acid (2 ml) during 1 h gave 4α-*methyl*-3-*oxo*-19-*nor*-5α-*androstane*-4β,6β-*carbolactone* (50) (78 mg) in needles, m.p. 178° (from hexane), $[\alpha]_D^{24}$ −34° (*c* 0.5) (Found: C, 76.0; H, 9.0%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316).

Hydrolysis of the oxime (48) in 80% acetic acid during 10 days gave (74% yield) 4α-*methyl*-19-*nor*-5α-*androstano*-[4,3-d]*isoxazoline*-3ξ,6β-*diol* (49) (0.8 g) in needles, m.p. 239° (from chloroform) (Found: C, 71.7; H, 9.0; N, 4.1. $C_{20}H_{31}NO_3$ requires C, 72.0; H, 9.4; N, 4.2%). More vigorous treatment of (49) with hydrochloric acid gave (70%) the lactone (50).

When a solution of this lactone (60 mg) in methanol (20 ml) containing potassium hydroxide (0.2 g) was refluxed (nitrogen) during 2 h, 6β-*hydroxy*-4α-*methyl*-19-*nor*-5α-*androstan*-3-*one* (51) was produced (40 mg) and formed needles, m.p. 135—137° (from hexane), $[\alpha]_D^{22}$ −16° (*c* 0.5), $\nu_{max.}$ 3 590 (OH) and 1 710 cm^{-1} (C=O), τ 9.23 (3 H, s, H_3-18), 8.95 (3 H, d, *J* 7 Hz, 4α-Me), and 5.92 (1 H, m, H-6α) (Found: C, 78.7; H, 10.3%; M^+, 290. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%; *M*, 290).

Photolysis of 4,4-*Dimethyl*-3-*oxo*-19-*nor*-5α-*androstan*-6β-*yl Nitrite* (53; R = NO).—The *nitrite* of the 6β-ol (85% yield) formed needles, m.p. 142° (from ether–methanol), $[\alpha]_D^{24}$ −124° (*c* 0.9), $\nu_{max.}$ 1 645 and 1 610 (nitrite) and 1 713 cm^{-1} (C=O) (Found: C, 72.3; H, 9.1; N, 4.3. $C_{20}H_{31}NO_3$ requires C, 72.0; H, 9.4; N, 4.2%).

Photolysis of this nitrite (2.0 g) dissolved in benzene (200 ml) was complete in 20 h to give the isoxazoline (49).

Purification, by chromatography on silica gel, from methylene chloride of the residues from the separation of the isoxazoline (49) gave (*a*) [eluted with methylene chloride–methanol (997 : 3)] the 3,6-dione (15; R = H) (70 mg); (*b*) [eluted with methylene chloride–methanol (99 : 1)] a mixture of alcohols (see later); (*c*) [eluted with methylene chloride–methanol (1 : 9)] the isoxazoline (49) (70 mg).

The mixture of alcohols from fraction (*b*) was rechromatographed on alumina; elution with ethyl acetate–light petroleum furnished 6β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (0.3 g); continued elution with ethyl acetate–light petroleum (1 : 9) gave 6β-*hydroxy*-4a-*methyl*-A-*homo*-19-*nor*-5α-*androst*-4-*en*-3-*one* (54), which formed prisms (0.2 g), m.p. 131° (from hexane), $[\alpha]_D^{24}$ −99° (*c* 0.7) (Found: C, 79.4; H, 10.1%; M^+, 302. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%; *M*, 302).

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