The Functionalisation of Methyl Groups in 4,4-Dimethyl-steroids

By J. M. MIDGLEY, J. E. PARKIN, and W. B. WHALLEY*

(*The School of Pharmacy, The University, London, W.C.*1)

Summary Functionalisation of methyl groups in 4,4-dimethyl-5α-19-nor- and 4,4-dimethyl-5α-androstanes has been investigated.

ALTHOUGH functionalisation of the 14α-methyl residue in lanostane derivatives has been extensively investigated,[1] there is only one report[2] of the similar modification of the 4,4-dimethyl groups. We now report an investigation in this area which is of potential biogenetic interest and relevant to the problem of the conformation of the A-ring in 4,4-dimethyl-steroids.

Thus, hydroboration of (1; R = Me) [prepared from testosterone] gave (i) the 6α-hydroxy-5α-androstan-3-one derivative (2; R^1 = Me, R^2 = H), (ii) the corresponding 6β-hydroxy-5β-androstane (3), and (iii) the 7α-hydroxy-5α-androstane (4), the structure of which was established by an unexceptional series of reactions.

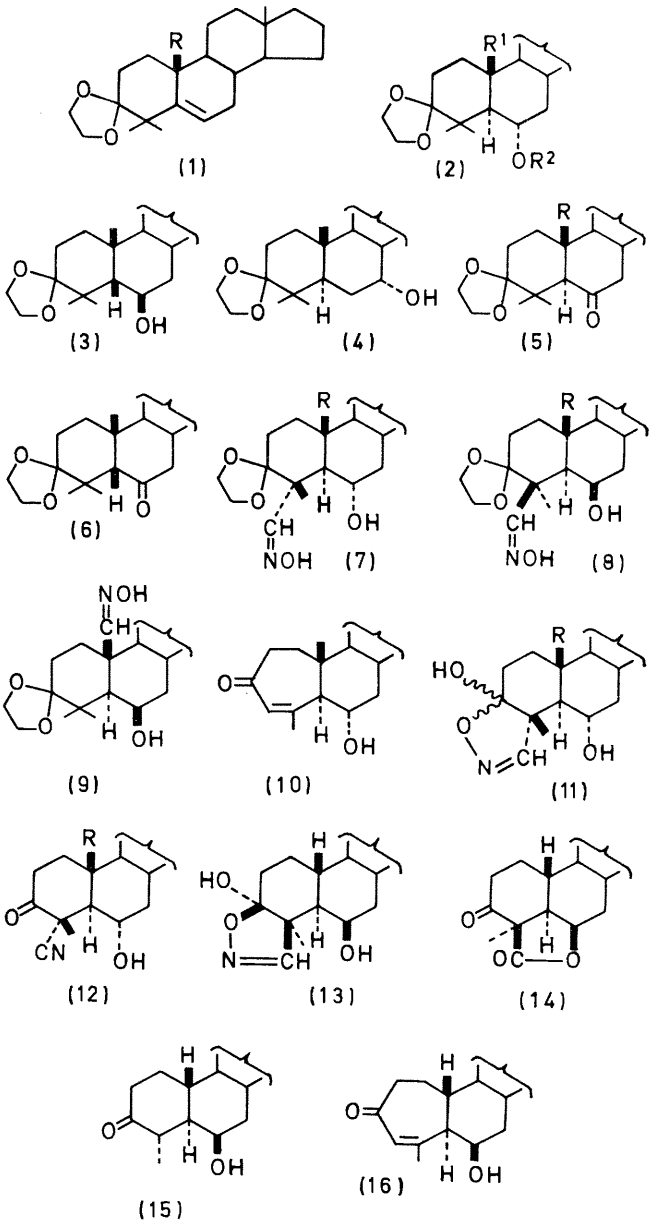
Sarett oxidation of (2; R^1 = Me, R^2 = H) gave the ketone (5; R = Me) which was reduced by lithium aluminium hydride (but not by sodium borohydride) to the 3,3-ethylene acetal of 4,4-dimethyl-6β-hydroxy-5α-androstan-3-one which with phosphorus oxychloride–pyridine smoothly re-formed (1; R = Me). Similarly, oxidation of (3) gave the 5β-6-oxo-androstane (6). Both (5; R = Me) and (6) resisted epimerisation by base, but formed an equilibrium mixture of the corresponding 3,6-diketones with acid.

Hydroboration of (1; R = H) gave (2; R^1 = R^2 = H) (80%) which was oxidised to (5; R = H). This, with sodium borohydride furnished the 6α-ol (2; R^1 = R^2 = H) (10%) and the 6β-ol (80%), which with phosphorus oxychloride–pyridine re-formed (1; R = H). Stepwise Wolff–Kishner reduction of (5; R = H) gave 4,4-dimethyl-19-nor-5α-androstane identical with a specimen prepared from 3-oxo-4,4-dimethyl-19-nor-5α-androstan-17β-ol.[3]

Photolysis of the 6α-nitrite (2; R^1 = Me, R^2 = NO) gave *inter alia* the oxime (7; R = Me) (56%). Similarly, the corresponding 6β-nitrite gave the 4β-oxime (8; R = Me) (5%) and the 19-oxime (9) (21%). Identification of (8; R = Me) and (9) followed from the n.m.r. and mass spectra of the corresponding products from the analogous 4,4-bis-trideuteriomethyl-steroids. Treatment of (7; R = Me) with acid furnished, successively, the isoxazoline (11; R = Me) and the cyanide (12; R = Me). Photolysis of 4,4-dimethyl-6α-nitrito-5α-androstan-3-one furnished a complex mixture containing, *inter alia*, a compound to which the structure (10) (17%) is assigned, from spectral evidence.

In the 19-nor-series, photolysis of the 6α-nitrite (2; R^1 = H, R^2 = NO) gave the oxime (7; R = H) (54%) which, with acid, gave successively the isoxazoline (11; R = H) [also obtained by photolysis of the 3-ketone corresponding to (2; R^1 = H, R^2 = NO)], and the cyanide (12; R = H). Photolysis of the 6β-nitrite gave the 4-oximino-derivative (8; R = H) (60%) which was converted by acid into the isoxazoline (13) and thence into the γ-lactone (14). This, with base, furnished (15). Photolysis of 4,4-dimethyl-19-nor-6β-nitrito-5α-androstan-3-one gave (13) (42%) together with the ring-A expansion product (16) (10%).

Our photolyses, particularly those with the 6β-nitrito-derivatives, provide evidence for the conformation (at least in the transition state) of ring A. Thus, the high yield (60%) of (8; R = H) suggests that ring A approximates closely to the 'normal' chair in the 19-nor-series. In contrast, the preferential production of the 19-oxime (9)



rather than (8; R = Me) is compatible (in accord with other evidence[4]) with the deformation of ring A to a flattened chair, in the androstane series.

All new compounds had the requisite spectral and analytical characteristics.

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