The Synthesis of 17β-Hydroxy-4,4-dimethyl-19-nor-5α- and 17β-Hydroxy-4,4-dimethyl-19-nor-5β-androstan-3-one

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17β-HYDROXY-4,4-DIMETHYL-19-NOR-5α-ANDROSTAN-3-ONE (I) is important in connection with certain conformational problems.[1,2] A substance assumed to have structure (I) has previously been available[3] only by the catalytic hydrogenation of 17β-hydroxy-4,4-dimethyl-19-norandrost-5(6)en-3-one (III; R = H), although neither its stereochemical homogeneity (at C–5) nor the configuration (at C–5) has been defined with any certainty. We have now resolved these dubieties.

Thus, in our hands, catalytic hydrogenation of the 17β-acetate (III; R = Ac) gave a mixture of 3α-hydroxy- and 3β-hydroxy-17β-acetoxy-4,4-dimethyl-19-nor-5α-androstane (IV), together with the corresponding 5β-derivatives (IV). This mixed product was oxidised to a mixture of 17β-acetoxy-4,4-dimethyl-19-nor-5α- and -5β-androstan-3-ones and again submitted to catalytic hydrogenation. In contrast to the previous mixed products this was amenable to separation by column chromatography to yield 17β-acetoxy-4,4-dimethyl-19-nor-5α-androstan-3ξ-ol and the corresponding 5β-derivative. Oxidation of 17β-acetoxy-4,4-dimethyl-19-nor-5α-androstan-3ξ-ol with Jones' reagent followed by de-acetylation of the resultant ketone gave 17β-hydroxy-4,4-di-methyl-19-nor-5α-androstan-3-one (I), m.p. 162–163°, $[\phi]_{500} - 110^\circ$, $[\phi]_{400} - 200^\circ$, $[\phi]_{313} - 1050^\circ$, $[\phi]_{270} + 670^\circ$, $[\phi]_{265}$ *ca.* $+ 500$—600°,* $[\phi]_{217} - 310^\circ$; *a* − 17. Bowers and Ringold[3] record m.p.

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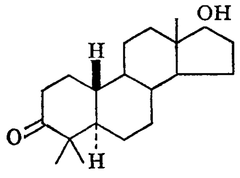
* Since this point lies on a very steep portion of the curve, it cannot be defined with a high degree of accuracy.

[1] N. L. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1962, **84**, 4561.

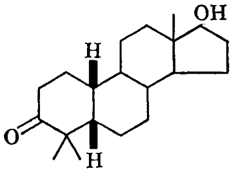
[2] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

[3] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 424.

150—152°. Djerassi *et al.*[2] record: $[\phi]_{700} - 76^\circ$, $[\phi]_{589} - 79^\circ$, $[\phi]_{310} - 974^\circ$, $[\phi]_{272\cdot5} + 1070^\circ$, $[\phi]_{265} + 790^\circ$; *a* − 20. 17β-Acetoxy-4,4-dimethyl-19-nor-5β-androstan-3ξ-ol was similarly converted into 17β-hydroxy-4,4-dimethyl-19-nor-5β-androstan-3-one (II), m.p. 124—125°, $[\phi]_{400} - 60^\circ$, $[\phi]_{309} - 1065^\circ$, $[\phi]_{268} + 1480^\circ$, $[\phi]_{265} + 1480^\circ$, $[\phi]_{242} + 1180^\circ$, $[\phi]_{208} + 1780^\circ$; *a* = 25.



(I)



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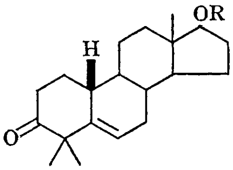
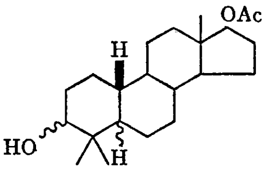
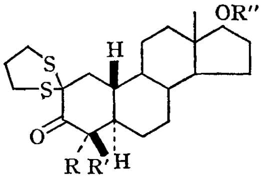


(III)



(IV)



(V)

Inspection of the o.r.d. data, including the molecular amplitude, for (I) and (II) and those recorded[3] for the compound previously regarded[1–3] as (I) clearly indicates that the latter material was most probably a mixture of (I) and (II). Physical constants[1,2] derived from this material must therefore be accepted with reserve.

The 5α-derivative (I) has been unequivocally synthesised. Thus, 17β-hydroxy-19-nor-5α-androstan-3-one[4] was converted by way of the 2-hydroxymethylene derivative into the 2-spiro-2′-(1′,3′-dithian) (V; R = R′ = R″ = H). Methylation of this with potassium t-butoxide and methyl iodide gave a mixture of (V; R = R′ = Me, R″ = H), (V; R′ = R″ = H, R = Me) and (V; R = R′ = R″ = Me), from which the 17β-methyl ether was removed by chromatography. The mixed residue was then separated by chromatography of the 17β-acetates to yield (V; R = R′ = Me, R″ = Ac), m.p. 187°, $[\alpha]_D + 120^\circ$, and (V; R′ = H, R = Me, R″ = Ac), m.p. 207—209°, $[\alpha]_D + 198^\circ$. Desulphurisation of (V; R = R′ = Me, R″ = Ac) with Raney nickel followed by oxidation of the product with Jones' reagent and then deacetylation gave 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (I), identical (including o.r.d.) with the corresponding product from the hydrogenation of (III; R = Ac). Similar results were obtained by methylation of the 17β-tetrahydropyranyl ether (V; R = R′ = H, R″ = tetrahydropyranyl).

We have also devised a one-step synthesis of (I) from 17β-hydroxy-4-methyl-19-norandrost-4-en-3-one.[5] This was reduced by the action of lithium in liquid ammonia and the resultant enolate anion treated with methyl iodide to give (I) in high yield. A similar process has recently been described[6] independently for the preparation of 17β-hydroxy-4,4-dimethyl-5α-androstan-3-one.

$[\alpha]_D$'s are recorded in chloroform and o.r.d. curves in methanol. All new compounds analysed satisfactorily and had the requisite infrared and n.m.r. spectra.

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[4] A. Bowers, H. J. Ringold, and E. Denot, *J. Amer. Chem. Soc.*, 1958, **80**, 6115.

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

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