

## The Configuration of 1 $\alpha$ -Methyl-5 $\alpha$ -androst-3-ones

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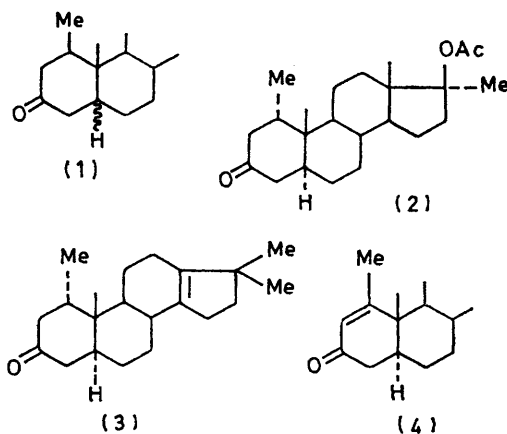
The  $\alpha$ -configuration of the 1-methyl group in 1 $\alpha$ ,17 $\alpha$ -dimethyl-17 $\beta$ -acetoxy-5 $\alpha$ -androst-3-one has been unambiguously confirmed (a) by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone, and (b) by use of the paramagnetic shift reagent trisdipivalomethanatoeuropium(III). Ring A has been shown to possess a chair conformation.

DOUBT has recently been expressed about the configuration of 1-methyl-5 $\alpha$ -androst-3-one derivatives prepared from 5 $\alpha$ -androst-1-en-3-ones by treatment with methylmagnesium bromide in the presence of copper(I) chloride,<sup>1,2</sup> and it has been reported that both the 5 $\alpha$ - and the 5 $\beta$ -series give 1 $\beta$ -methyl compounds.<sup>3,4</sup>

In order to verify the configuration in a series of 1-methylandrostanes,<sup>2,5-7</sup> 17 $\beta$ -acetoxy-1 $\alpha$ ,17 $\alpha$ -dimethyl-5 $\alpha$ -androst-3-one (2)<sup>7</sup> was subjected to dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). In 5 $\alpha$ -androst-3-ones with a chair conformation of ring A, DDQ abstracts the 1 $\alpha$ -hydrogen atom to form  $\Delta^1$ -3-oxo-derivatives; in the case of 1 $\alpha$ -methyl-3-ones compound no hydrogen abstraction has been observed.<sup>8</sup> In our case dehydrogenation with DDQ in benzene or dioxan did not give any  $\Delta^1$ -3-oxo-compound (4) even under more drastic conditions.

The chair conformation of ring A and the  $\alpha$ -stereochemistry of the 1-methyl group have been proved unambiguously by n.m.r. spectroscopy. The position of the doublet due to the 1-methyl group (see Table) suggested, by comparison with the data of Wechter

*et al.*,<sup>3</sup> that the methyl group was in the  $\alpha$ -position. This was in agreement with the chemical evidence but



did not constitute unambiguous proof, which was provided by using the paramagnetic shift reagent<sup>9</sup>

<sup>1</sup> D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 196.

<sup>2</sup> B. Pelc, *Coll. Czech. Chem. Comm.*, 1964, **29**, 3089.

<sup>3</sup> W. J. Wechter, G. Slomp, F. A. McKeller, R. Wiechert, and U. Kerb, *Tetrahedron*, 1965, **21**, 1625.

<sup>4</sup> D. Bertin and J. Perronnet, *Bull. Soc. chim. France*, 1964, 2782.

<sup>5</sup> B. Pelc, *Coll. Czech. Chem. Comm.*, 1965, **30**, 3468.

<sup>6</sup> B. Pelc and J. Hodkova, *Coll. Czech. Chem. Comm.*, 1965, **30**, 3575.

<sup>7</sup> B. Pelc and J. Hodkova, *Coll. Czech. Chem. Comm.*, 1966, **31**, 1064.

<sup>8</sup> A. B. Turner and H. J. Ringold, *J. Chem. Soc. (C)*, 1967, 1720.

<sup>9</sup> J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

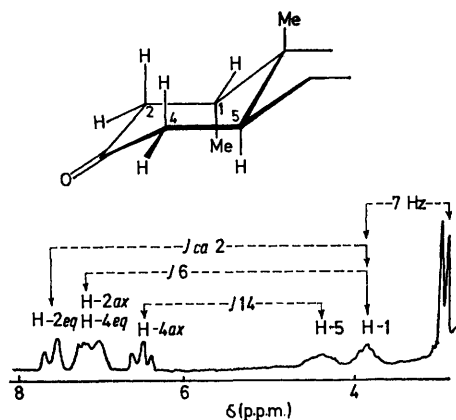
tris(dipivalomethanato)europium(III). By use of this reagent the n.m.r. spectrum was changed sufficiently to allow a complete coupling constant analysis of ring A.

Methyl resonances <sup>a</sup>

| 17-Acetate (2)  |      | Compound (3)    |              |
|-----------------|------|-----------------|--------------|
| 1 $\alpha$ -Me  | 0.89 | 1 $\alpha$ -Me  | 0.89         |
| 19-Me           | 1.14 | 19-Me           | 1.09         |
| 18-Me           | 0.85 | 17 $\alpha$ -Me | } 0.96, 0.97 |
| 17 $\alpha$ -Me | 1.40 | 17 $\beta$ -Me  |              |

<sup>a</sup> For ca. 0.1M-solutions in CCl<sub>4</sub>;  $\delta$  in p.p.m. from internal Me<sub>4</sub>Si.

The 17-acetate (2) was converted, *via* the 17-hydroxy-compound, into the unsaturated derivative (3) so that co-ordination with the shift reagent would occur only



Low-field portion of the 100 MHz spectrum of compound (3) (0.08M in CCl<sub>4</sub>) in the presence of 0.45 mol. equiv. of tris(dipivalomethanato)europium(III). Coupled resonances and the associated *J* values are indicated

at the 3-oxo-function. The reagent was then added in small portions to a solution of this derivative in carbon tetrachloride until the observed spectrum was suitable for extensive spin-decoupling experiments. This spectrum, together with the decoupling results and assignments, is shown in the Figure.

The assignment of the 1-proton signal follows from its coupling to the doublet methyl signal; the remaining resonances are readily assigned from their coupling (or lack of it) to the 1-proton signal and the known<sup>9</sup> shift characteristics of cyclohexanones. The magnitudes of the observed coupling constants clearly show that

ring A is in a chair conformation with the methyl group  $\alpha$ -oriented. The vicinal couplings to the 1-proton are 6 and ca. 2 Hz, showing that it cannot be axial, and the  $J_{4ax,5}$  value of 14 Hz precludes any significant distortion of the  $H_{ax}-C(4)C(5)-H$  angle from 180°, which would be necessary for the twist-boat suggested by Wechter *et al.*<sup>3</sup> for the  $\beta$ -methyl case. Further inspection of models reveals that the twist-boat conformation would give larger  $J_{1,2}$  values.

The observed couplings are apparently independent of shift reagent concentration; thus drastic conformational changes caused by co-ordination seem to be absent.

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian HA100 instrument operating at normal probe temperatures.

*Dehydrogenation of 17 $\beta$ -Acetoxy-1 $\alpha$ ,17 $\alpha$ -dimethyl-5 $\alpha$ -androst-3-one (2).*—(a) Compound (2) (100 mg; m.p. 197—199°<sup>7</sup>) and DDQ (75 mg) in dioxan (10 ml) were refluxed for 20 h. The product was extracted into ether; the extract was washed with sodium thiosulphate solution, sodium hydrogen carbonate solution, and water, and chromatographed on alumina (4 g; activity II). Elution with ether gave starting material (75 mg; from aqueous methanol). Methanol eluted a very polar material (5 mg). No compound with  $\lambda_{max}$  225—300 nm was detected in any of the fractions. A similar result was obtained when benzene was used instead of dioxan.

(b) Compound (2) (100 mg) and DDQ (130 mg) in dioxan (10 ml) were refluxed for 20 h. After similar work-up the material was chromatographed on alumina and gave starting material (35 mg) and a very polar material (25 mg).

*1 $\alpha$ ,17,17-Trimethyl-18-norandrost-13-en-3-one (3).*—The acetate (2) (90 mg) was refluxed in aqueous ethanolic sodium hydroxide for 2 h. On cooling, the 17 $\beta$ -hydroxy-compound (70 mg) crystallised; m.p. 183—185°.<sup>2</sup> This compound (50 mg) was dissolved in trifluoroacetic anhydride (1 ml) and set aside at room temperature for 48 h. The mixture was evaporated and the product purified by preparative t.l.c. [light petroleum-acetone (9:1)]. Crystallisation gave *compound (3)* (25 mg), m.p. 127—130° (from aqueous ethanol),  $M^+$  300 (Found: C, 83.7; H, 10.8. C<sub>21</sub>H<sub>32</sub>O requires C, 84.0; H, 10.7%).

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