Conformational Studies. Part 2.[1] Synthesis of 17β-Hydroxy-4,4-dimethyl-5α-androstan-3-one, and of the 19-Nor-analogue

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Prepared from 17β-hydroxy-5α-androstan-3-one by C-4 methylation of 17β-(tetrahydropyran-2-yloxy)-2,2-trimethylenedithio-5α-androstan-3-one. 17β-hydroxy-4,4-dimethyl-5α-androstan-3-one (1; R^1 = Me, R^2 = H), exhibited a negative o.r.d. curve, and was identical with the hydrogenation product of 17β-hydroxy-4,4-dimethylandrost-5-en-3-one (2; R^1 = Me, R^2 = H). 17β-Hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (1; R^1 = R^2 = H) was similarly synthesised from 17β-hydroxy-19-nor-5α-androstan-3-one and also had a negative o.r.d. curve. However, contrary to previous reports, hydrogenation of 17β-hydroxy-4,4-dimethyl-19-nor-androst-5-en-3-one (2; R^1 = R^2 = H) did not furnish the androstane (1; R^1 = R^2 = H) but a mixture of (1; R^1 = R^2 = H) and the 5β-diastereoisomer which was difficult to separate; both these products exhibit negative o.r.d. curves. The physical constants of various cognate derivatives of (1; R^1 = R^2 = H), reported values of which are probably those of mixtures, have been clarified.

B-Nortestosterone has been converted into 17β-hydroxy-4,4-dimethyl-B-nor-5α-androstan-3-one. The preparation of various steroidal 2-butylthiomethylene-3-ones is reported.

As part of a general investigation into conformational problems, particularly those relating to 4,4-dimethyl-3-oxo-5α-steroids and derivatives, we required authentic samples of 17β-hydroxy-4,4-dimethyl-5α-androstan-3-one (1; R^1 = Me, R^2 = H) and the 19-nor-analogue (1; R^1 = R^2 = H) for o.r.d. and *X*-ray crystallographic investigations.

It has been established [2] that hydrogenation of 4,4-dimethylcholest-5-en-3-one furnishes predominantly the corresponding 5α-derivative: hydrogenation of 17β-hydroxy-4,4-dimethylandrost-5-en-3-one (2; R^1 = R^2 = H) has been assumed [3] to proceed similarly to yield the

[1] Part 1, M. J. T. Robinson and W. B. Whalley, *Tetrahedron*, 1963, **19**, 2123.

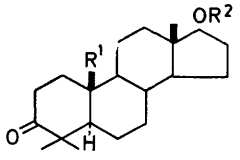
[2] J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 1957, 753.

[3] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 1957, **22**, 602.

5α-androstane (1; R^1 = Me, R^2 = H), and our present work confirms this conclusion.

The authenticity of the substance claimed [4] to be 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (1; $R^1 = R^2$ = H) is, however, uncertain. By analogy with the androstane series it has been assumed [4] (but not proven) that methylation of 19-nortestosterone yields 17β-hydroxy-4-4,dimethyl-19-norandrost-5-en-3-one (2; $R^1 = R^2$ = H), and that hydrogenation [4] of this gives 17β-hydroxy-4-4,dimethyl-19-nor-5α-androstan-3-one (1; $R^1 = R^2$ = H). Since the evidence for the structure (1; $R^1 = R^2$ = H) and hence for those of its various derivatives [4] is not beyond question, we have devised an unambiguous synthesis. Our results confirm the doubts which prompted our investigation.

Thus, the 2-hydroxymethylene derivative [5] of 17β-hydroxy-5α-androstan-3-one was converted by the action [2] of *SS*-trimethylene 1,3-bis(toluene-*p*-thiosulphonate) into the spiro-dithian (3; R^1 = H, R^2 = Me).



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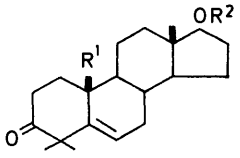

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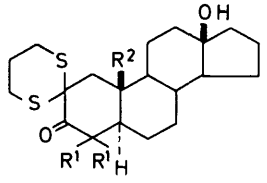

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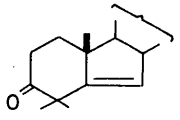

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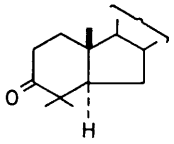

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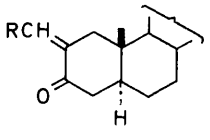

(6)

However, the rigorous conditions required for C-4 methylation caused *O*-methylation at the C-17 hydroxy-group: to avoid this complication the 17β-hydroxy-group was protected by forming the tetrahydropyranyl ether. Dimethylation of this tetrahydropyranyl ether with methyl iodide–potassium t-butoxide, followed by removal of the tetrahydropyranyl substituent with acid, gave the 4,4-dimethyl-2-dithioacetal (3; $R^1 = R^2$ = Me). The derived 17β-acetate was desulphurised with Raney nickel, and traces of 3-ols in the product were removed by oxidation (Jones reagent) to yield 17β-hydroxy-4,4-dimethyl-5α-androstan-3-one (1; R^1 = Me, R^2 = H) and the acetate (1; R^1 = Me, R^2 = Ac), which were identical with the corresponding derivatives prepared by hydrogenation of 17β-hydroxy-4,4-dimethylandrost-5-en-3-one (2; R^1 = Me, R^2 = H) and acetylation. We did not achieve the catalytic hydrogenation of (2; R^1 = Me, R^2 = H) to (1; R^1 = Me, R^2 = H) by the published method,[3] but a modification * with 1 : 1 acetic acid–cyclohexane containing a trace of perchloric acid as solvent functioned satisfactorily. Unequivocal, independent confirmation of the structure of compound (1; R^1 = Me, R^2 = H) has been provided by *X*-ray crystallography.[6]

The 19-nor-analogue was prepared similarly, from 19-nor-5α-androstan-3-one by way of the spirodithian (3; $R^1 = R^2$ = H). In this case methylation at C-4 proceeded more readily (in the absence of C-19) to yield substantial quantities of the 4,4-dimethyl-derivative (3; R^1 = Me, R^2 = H) with only minor amounts of *O*-methylation at C-17: hence protection of the 17β-hydroxy-group was unnecessary. Desulphurisation of the 17β-acetate of this dithian followed by oxidation of the product with Jones reagent furnished, after hydrolysis, 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (1; $R^1 = R^2$ = H), the structure of which was confirmed by *X*-ray crystallography.[6] The corresponding 17β-methyl ether was obtained similarly.

An alternative, more expeditious route to (1; $R^1 = R^2$ = H) commenced from 4-methyl-19-nortestosterone.[7] Reduction of this with lithium–liquid ammonia followed by trapping of the resultant enolate with methyl iodide furnished (1; $R^1 = R^2$ = H) in high yield. After the completion of our work, the same technique was reported by Stork *et al.*[8]

With authentic 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one-17β-ol available, we examined the published synthesis.[4] Thus, methylation of 19-nortestosterone gave 4,4-dimethyl-19-norandrost-5-en-3-one, τ 9.19 (3 H, s, H_3-18), 8.78 (3 H, s, H_3-4), 8.72 (3 H, s, H_3-4), 6.28 (1 H, t, *J* 8 Hz, H-17α), and 4.32 (1 H, t, vinylic H-6). As in the androstane series, the reported hydrogenation procedure [4] gave unsatisfactory results, but the modified technique * gave, after an extensive process of separation and purification (see Experimental section) 4,4-dimethyl-19-nor-5α-androstan-3-one, identical with that prepared by the alternative method, together with an isomeric compound which we formulate as the corresponding 5β-derivative (*cf.* ref. 9).

The product from this catalytic hydrogenation has previously [4] been purified by a combination of chromatography and crystallisation. These methods failed to

* We are grateful to Professor N. L. Allinger for this information.

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

[5] R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Amer. Chem. Soc.*, 1961, **83**, 1478.

[6] G. Ferguson, E. W. Macauley, J. M. Midgley, J. M. Robertson, and W. B. Whalley, *Chem. Comm.*, 1970, 944.

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

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

[9] G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1961, 2725.

separate our hydrogenation product or a synthetic 1 : 1 mixture of the 5α- and 5β-derivatives, though g.l.c. showed that each mixture consisted of two components in approximately equal proportions. These results, together with the differences between the physical constants of our specimen of (1; $R^1 = R^2 = H$) and those recorded [4] strongly suggest that the previous preparations, as already adumbrated, were of doubtful authenticity. This view was further confirmed by the oxidation of (1; $R^1 = R^2 = H$) to the corresponding 3,17-dione, which exhibits a characteristic double m.p., different from the single m.p. previously reported [10] Since the forms of both m.p.s gave the requisite elemental analysis they were not solvated.

However, depite these doubts, the o.r.d. curves of our (1; $R^1 = R^2 = H$) are negative as previously reported. Fortuitously, the difference between the amplitude reported [11] and our value, together with the negative o.r.d. and the similarity between the amplitudes of the curves of the 5α- and 5β-derivatives, combine to leave unchanged the general conclusions [10] concerning the conformation of (1; $R^1 = R^2 = H$).

17β-Hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (1; $R^1 = R^2 = H$) was converted by standard methods into 17β-hydroxy-4,4,17α-trimethyl-19-nor-5α-androstan-3-one. The amplitude of the o.r.d. curve of this authentic preparation (−9) differed substantially from that reported [11] (−15).

To provide comparative data, which will be discussed in a later publication, B-nortestosterone was methylated to yield 17β-hydroxy-4,4-dimethyl-B-norandrost-5-en-3-one (4). Hydrogenation of (4) gave a product which on general principles we formulate as the 5α-derivative (5).

During exploratory investigations relevant to this work we sought to use steroidal alkylthiomethylene derivatives of type (6; R = Bu^nS) as substrates for C-4 methylation.[12] Previously,[12] these alkylthiomethylene derivatives have been prepared by acid-catalysed condensation of the appropriate α-hydroxymethylene ketone with the requisite (usually n-butyl) thiol. This process failed with 2α-hydroxymethylene-3-oxo-5α-steroids of type (6; R = OH), but proceeded readily with the corresponding 2-methoxymethylene derivatives of type (6; R = OMe) with butane-1-thiol. However these derivatives failed to be of use for our purpose, since, in contrast to the derivatives from decalones,[12] *etc.*, they decomposed rapidly to intractable coloured products under the basic methylation conditions.

EXPERIMENTAL

Optical rotations and i.r. spectra were determined for solutions in chloroform unless otherwise stated; n.m.r. spectra were recorded for solutions in deuteriochloroform with a Varian A-60 spectrometer. Light petroleum refers to the fraction of b.p. 40—60 °C.

17β-*Hydroxy*-4,4-*dimethyl*-5α-*androstan*-3-*one* (1; R^1 = Me, R^2 = H).—Prepared by condensation of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one [5] (0.5 g) with *SS*-trimethylene 1,3-bis(toluene-*p*-sulphonate) (0.5 g) in boiling benzene during 2 h, 17β-*hydroxy*-2,2-*trimethylenedithio*-5α-*androstan*-3-*one* formed needles (0.4 g), m.p. 215° (from methanol–acetone), $[\alpha]_D^{20}$ +132° (*c* 2.5) (Found: C, 66.8; H, 9.0; S, 16.1. $C_{22}H_{34}O_2S_2$ requires C, 66.9; H, 8.7; S, 16.3%), $\nu_{max.}$ 3 470 (OH) and 1 700 cm^{-1} (C=O).

A solution of this dithian (0.5 g) in tetrahydrofuran (5 ml) containing 2,3-dihydropyran (0.3 g) and toluene-*p*-sulphonic acid (5 mg) was heated at 100 °C for 1.5 h. Next day the product was isolated and purified from aqueous acetone containing a trace of pyridine to yield the 17β-(*tetrahydropyran*-2-*yl*) *ether* in needles (0.37 g), m.p. 210—213°, $[\alpha]_D^{20}$ +106° (*c* 3.5) (Found: C, 67.7; H, 8.9; O, 10.1; S, 13.1. $C_{27}H_{42}O_3S_2$ requires C, 67.7; H, 8.8; O, 10.0; S, 13.4%), τ 9.23 (3 H, s, H_3-18) and 8.92 (3 H, s, H_3-19).

A solution of this pyranyl ether (1 g) in benzene (10 ml) was added to t-butyl alcohol (10 ml) containing potassium t-butoxide [from potassium (0.4 g)] in an atmosphere of nitrogen. Methyl iodide (0.3 ml) was added to the boiling solution and the refluxing continued for 0.25 h; further methyl iodide (0.3 ml) was then added. After refluxing for 15 min, more methyl iodide (0.6 ml) was introduced, and 15 min later the product was isolated and purified by chromatography from benzene–light petroleum (1 : 1) to yield 4,4-*dimethyl*-17β-(*tetrahydropyran*-2-*yloxy*)-2,2-*trimethylenedithio*-5α-*androstan*-3-*one* in needles (0.5 g), m.p. 166° (from methanol), $[\alpha]_D^{20}$ −68° (*c* 1.0) (Found: C, 68.9; H, 9.3; S, 12.5. $C_{29}H_{46}O_3S_2$ requires C, 68.8; H, 9.1; S, 12.7%), $\nu_{max.}$ 1 685 cm^{-1} (ααα′α′-tetrasubstituted C=O), τ 9.23 (3 H, s, H_3-18), 9.08 (3 H, s, H_3-19), 8.83 (3 H, s, 4-Me), and 8.60 (3 H, s, 4-Me).

A solution of this pyranyl ether (0.33 g) in ethanol (19 ml), water (1 ml), and concentrated hydrochloric acid (0.25 ml) was refluxed for 1.5 h. The product was purified from methanol–acetone to yield 17β-*hydroxy*-4,4-*dimethyl*-2,2-*trimethylenedithio*-5α-*androstan*-3-*one* (3; $R^1 = R^2$ = Me) in needles (0.23 g), m.p. 207°, $[\alpha]_D^{20}$ −43° (*c* 1.3) (Found: C, 68.8; H, 9.2; S, 15.0. $C_{24}H_{38}O_2S_2$ requires C, 68.2; H, 9.0; S, 15.2%), $\nu_{max.}$ 3 550 and 3 430 (OH) and 1 685 cm^{-1} (C=O), τ 9.27 (3 H, s, H_3-19), 9.08 (3 H, s, H_3-18), 8.83 (3 H, s, 4-Me), and 8.60 (3 H, s, 4-Me). Prepared quantitatively with pyridine–acetic anhydride the derived 17β-*acetate* formed needles, m.p. 206° (from methanol–acetone), $[\alpha]_D^{20}$ −50° (*c* 1.6) (Found: C, 66.7; H, 8.6; S, 13.7. $C_{26}H_{40}O_3S_2$ requires C, 67.2; H, 8.7; S, 13.8%).

A solution of this acetate (0.8 g) in ethanol (70 ml) containing W-2-type Raney nickel (8 g) was refluxed for 6 h, and the product isolated and oxidised with Jones reagent to yield 17β-acetoxy-4,4-dimethyl-5α-androstan-3-one, which formed plates (0.4 g), m.p. 152—153° (from methanol), $[\alpha]_D^{20}$ −16.3° (*c* 2.0) (Found: C, 77.0; H, 10.3. Calc. for $C_{23}H_{36}O_3$: C, 76.7; H, 10.1%), $\nu_{max.}$ 1 735 (ester) and 1 703 cm^{-1} (C=O), τ 9.18 (3 H, s, H_3-19), 8.92 (9 H, s, H_3-18 and 4-Me_2), and 7.95 (3 H, s, Ac) (lit.,[13] m.p. 150—152.5° for a specimen prepared by an alternative process).

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

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

[12] R. E. Ireland and J. A. Marshall, *J. Amer. Chem. Soc.*, 1959, **81**, 6336; *J. Org. Chem.*, 1962, **27**, 1615, 1620; D. C. Aldridge, J. F. Grove, P. McCloskey, and W. Klyne, *J. Chem. Soc.*, 1963, 2569.

[13] E. Kaspar and M. Schenck, Schering Akt-Ger., Ger. P., 1,023,765 (*Chem. Abs.*, 1960, **54**, 5756a).

Hydrolysis of this acetate (0.5 g) in boiling methanol containing potassium hydroxide (0.1 g) during 15 h gave 17β-hydroxy-4,4-dimethyl-5α-androstan-3-one (0.4 g) in needles, m.p. 149° (from acetone–light petroleum), $[\alpha]_D^{20}$ −16.3° (*c* 2.0), identical with a specimen prepared by catalytic hydrogenation of 4,4-dimethylandrost-5-en-3-one {lit.,[3] m.p. 145—147°, $[\alpha]_D^{20}$ −13.7° (*c* 2.0)} (Found: C, 78.9; H, 10.7. Calc. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.7%). Regenerated from this alcohol by way of the unstable 2-hydroxymethylene derivative, 17β-hydroxy-4,4-dimethyl-2,2-trimethylenedithio-5α-androstan-3-one (3; $R^1 = R^2 = Me$) was identical with an authentic specimen.

17β-(*Tetrahydropyran-2-yloxy*)-5α-*androstan-3-one*.— Prepared from 17β-hydroxy-5α-androstan-3-one (0.5 g) and 2,3-dihydropyran (0.3 g) in boiling tetrahydrofuran (5 ml) containing toluene-*p*-sulphonic acid (5 mg) during 1.5 h, the *tetrahydropyranyl ether* (0.5 g) formed plates, m.p. 146° (from aqueous acetone), $[\alpha]_D^{20}$ +97° (*c* 1.1) (Found: C, 76.8; H, 10.2. $C_{24}H_{38}O_3$ requires C, 77.0; H, 10.2%).

17β-*Methoxy*-4α-*methyl*-2,2-*trimethylenedithio*-5α-*androstan*-3-*one*.—This compound was the only identified product from the methylation of 17β-hydroxy-2,2-trimethylenedithio-5α-androstan-3-one under various conditions. The following illustrates the method. A solution of the dithian (1 g) in benzene (10 ml) was added to t-butyl alcohol (10 ml) containing potassium t-butoxide [from potassium (0.5 g)]. After addition of methyl iodide (0.4 ml) the mixture was refluxed for 3 h. The crude product was purified from benzene by chromatography on alumina to yield the 4α-*methyl*-17β-*methoxy-derivative* which formed needles (0.25 g), m.p. 148°, $[\alpha]_D^{20}$ +81° (*c* 0.9) [Found: C, 68.8; H, 9.3; S, 15.1; OMe, 7.9. $C_{23}H_{35}OS_2$(OMe) requires C, 68.0; H, 9.2; S, 15.1; OMe, 7.3%], devoid of OH i.r. absorption, $\nu_{max.}$ 1 700 cm^{-1} (C=O), τ 9.24 (3 H, s, H_3-18), 8.92 (3 H, s, H_3-19), 8.80 (3 H, d, *J* 7 Hz, 4-Me), and 6.66 (3 H, s, OMe).

17β-*Hydroxy*-4,4-*dimethyl*-2,2-*trimethylenedithio*-19-*nor*-5α-*androstan*-3-*one* (3; R^1 = Me, R^2 = H).—A mixture of 17β-hydroxy-2-hydroxymethylene-19-nor-5α-androstan-3-one (1 g), *SS*-trimethylene 1,3-bis(toluene-*p*-sulphonate) (1.2 g), and sodium acetate (2.5 g) in ethanol (30 ml) was refluxed for 0.5 h under nitrogen. After 4 days the product was isolated in the usual manner and purified by chromatography from benzene on alumina to yield 17β-*hydroxy*-2,2-*trimethylenedithio*-19-*nor*-5α-*androstan*-3-*one* (3; $R^1 = R^2$ = H) in prisms (0.65 g), m.p. 225—229°, $[\alpha]_D^{20}$ +245° (*c* 2.0) (Found: C, 66.9; H, 8.6; S, 16.6. $C_{21}H_{32}O_2S_2$ requires C, 66.3; H, 8.4; S, 16.9%). A solution of this dithian (1 g) in benzene (12 ml) was added to a warm solution of potassium t-butoxide [from t-butyl alcohol (15 ml) and potassium (0.5 g)] under nitrogen. The mixture was refluxed while methyl iodide (1.2 ml) was introduced during 15 min. Isolated in the usual manner, the product was purified by chromatography on alumina to yield [by elution with benzene–light petroleum (3 : 7)] 17β-*methoxy*-4,4-*dimethyl*-2,2-*trimethylenedithio*-19-*nor*-5α-*androstan*-3-*one*, which formed needles (0.07 g), m.p. 156° (from methanol), $[\alpha]_D$ +138° (*c* 2.8) [Found: C, 68.5; H, 8.8; S, 14.8; OMe, 7.4. $C_{23}H_{35}OS_2$(OMe) requires C, 68.2; H, 9.1; S, 15.2; OMe, 7.3%], $\nu_{max.}$ 1 690 cm^{-1} (ααα′α′-tetrasubstituted C=O), τ 9.20 (3 H, s, H_3-18), 8.81 (3 H, s, 4-Me), 8.74 (3 H, s, 4-Me), and 6.63 (3 H, s, OMe).

A solution of the foregoing dithian (0.5 g) in ethanol (40 ml) containing W-2-type Raney nickel (6 g) was refluxed for 5 h. After isolation a solution of the product in acetone was oxidised with Jones reagent to yield 17β-*methoxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-3-*one*, which separated from aqueous methanol in needles (0.3 g), m.p. 130°, $[\alpha]_D^{20}$ −20.9° (*c* 1.1), o.r.d. (*c* 0.26 in MeOH) $[\phi]_{500}$ −100°, $[\phi]_{400}$ −180°, $[\phi]_{313}$ −1 000°, $[\phi]_{269}$ +680°, $[\phi]_{214}$ +250° [Found: C, 79.2; H, 10.8; OMe, 9.8. $C_{20}H_{31}O$(OMe) requires C, 79.2; H, 10.8; OMe, 9.8%], τ 9.21 (3 H, s, H_3-18), 8.94 (6 H, s, 4-Me_2), 6.64 (3 H, s, OMe).

Further elution of the column with benzene–ether (9 : 1) gave a semi-crystalline product (0.4 g) which could not be adequately purified and was acetylated. Chromatography of the crude acetate gave two major fractions. The first crystallised from ethanol–acetone to yield 17β-*acetoxy*-4,4-*dimethyl*-2,2-*trimethylenedithio*-19-*nor*-5α-*androstan*-3-*one* in plates (0.2 g), m.p. 185°, $[\alpha]_D^{20}$ +120° (*c* 2.8) (Found: C, 66.7; H, 8.2; S, 14.2. $C_{25}H_{38}O_3S_2$ requires C, 66.6; H, 8.5; S, 14.2%), $\nu_{max.}$ 1 735 (acetate) and 1 690 cm^{-1} (C=O), τ 9.16 (3 H, s, H_3-18), 8.81 (3 H, s, 4-Me), 8.75 (3 H, s, 4-Me), and 7.95 (3 H, s, Ac). Hydrolysis of this acetate gave the 17β-*ol* (3; R^1 = Me, R^2 = H) in needles, m.p. 214—216° (from acetone—light petroleum), $[\alpha]_D^{20}$ +144° (*c* 2.0) (Found: C, 68.2; H, 8.8; S, 15.6. $C_{23}H_{36}O_2S_2$ requires C, 67.6; H, 8.9; S, 15.9%), $\nu_{max.}$ 1 690 cm^{-1} (C=O), τ 9.21 (3 H, s, H_3-18), 8.82 (3 H, s, 4-Me), and 8.76 (3 H, s, 4-Me). Purification of the second fraction from alcohol–acetone gave 17β-*acetoxy*-4α-*methyl*-2,2-*trimethylenedithio*-19-*nor*-5α-*androstan*-3-*one* in needles (0.2 g), m.p. 209° $[\alpha]_D^{20}$ +197° (*c* 2.5) (Found: C, 65.7; H, 8.2; S, 14.7. $C_{24}H_{36}O_3S_2$ requires C, 66.0; H, 8.3; S, 14.7%), $\nu_{max.}$ (CCl_4) 1 735 (acetate C=O) and 1 700 cm^{-1} (C=O), τ 9.17 (3 H, s, H_3-18), 8.94 (3 H. d, *J* 6.5 Hz, 4-Me), and 7.96 (3 H, s, Ac). Hydrolysis of this acetate gave the 17β-*ol* in needles (0.2 g), m.p. 228° (from acetone–light petroleum), $[\alpha]_D^{20}$ +226° (*c* 1) (Found: C, 66.8; H, 8.5; S, 16.0. $C_{22}H_{34}O_2S_2$ requires C, 66.9; H, 8.7; S, 16.3%), $\nu_{max.}$ 1 700 cm^{-1} (C=O), τ 9.21 (3 H, s, H_3-18), and 8.94 (3 H, d, *J* 6.5 Hz, 4-Me).

Further methylation of this 4α-methyl derivative (3.3 g) by the same process gave 17β-hydroxy-4,4-dimethyl-2,2-trimethylenedithio-19-nor-5α-androstan-3-one (1.3 g) and starting material (0.7 g).

17β-*Hydroxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-3-*one* (1; $R^1 = R^2$ = H).—(*a*) Desulphurisation of 17β-acetoxy-4,4-dimethyl-2,2-trimethylenedithio-19-nor-5α-androstan-3-one (0.25 g) occurred in boiling alcohol (20 ml) containing W-2-type Raney nickel (5 g) during 5 h. A solution of the crude product in acetone (20 ml) was oxidised with Jones reagent. Purification from acetone–light petroleum gave 17β-*acetoxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-3-*one* (0.15 g) in needles, m.p. 167°, $[\alpha]_D^{20}$ −25.5° (*c* 2.0) (Found: C, 76.5; H, 10.1. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%), $\nu_{max.}$ (CCl_4) 1 735 (acetate) and 1 705 cm^{-1}, (C=O) τ 9.17 (3 H, s, H_3-18), 8.94 (6 H, s, 4-Me_2), and 7.95 (3 H, s, Ac). Hydrolysis of this acetate with potassium hydroxide in methanol gave (quantitatively) the 17β-*ol* (1; $R^1 = R^2$ = H), in needles, m.p. 161—162° (from acetone–light petroleum) (Found: C, 79.4; H, 10.5. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%), $[\alpha]_D^{20}$ −20.4° (*c* 1.6), o.r.d. (*c* 0.28 in methanol) $[\phi]_{550}$ −110°, $[\phi]_{440}$ −200°, $[\phi]_{313}$ −1 050°, $[\phi]_{270}$ +670°, $[\phi]_{265}$ +500—600° (steep portion of curve), $[\phi]_{213}$ −310°. {lit. o.r.d. (*c* 0.125 in MeOH) $[\phi]_{700}$ −76°, $[\phi]_{315}$ −974°, $[\phi]_{272.5}$ +1 070°, $[\phi]_{265}$ +790°}. $\nu_{max.}$ 1 700 cm^{-1} (C=O), τ 9.21 (3 H, s, H_3-18), 8.94 (6 H, s. 4-Me_2) (lit.,[4] m.p. 150—152°, $[\alpha]_D$ −22°).

(*b*) A solution of 4-methyl-19-nortestosterone [8] (1.5 g) in ether (150 ml) was added to a solution of lithium (0.6 g) in liquid ammonia (450 ml) during 3 min. The blue solution was stirred for 2 min, and then methyl iodide (30 g) in

ether (50 ml) was added. After stirring under reflux for 1 h, the ammonia was allowed to evaporate. Isolated in the normal manner, the product was purified by chromatography from benzene on alumina; elution with benzene–ether (3 : 1) gave 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (0.7 g) in needles, m.p. 159° (from acetone–light petroleum), identical (i.r. and n.m.r. spectra, $[\alpha]_D$, m.p., and mixed m.p.) with the product prepared by method (*a*).

Oxidation of this alcohol (0.25 g) with Jones reagent gave (quantitatively) 4,4-*dimethyl*-19-*nor*-5α-*androstane*-3,17-*dione* in needles, m.p. 128° and (after resolidification) 143° (from light petroleum) (lit.,[10] m.p. 156—158°), $[\alpha]_D^{20}$ +48° (*c* 1.0), $\nu_{max.}$ 1 740 (five-membered ring C=O) and 1 705 cm^{-1} (six-membered ring C=O), μ 2.86 ± 0.02 D (Found: C, 79.0; H, 10.0. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%).

Hydrogenation of 17β-*Hydroxy*-4,4-*dimethyl*-19-*norandrost*-5-*en*-3-*one*.—The following conditions are illustrative of the various processes investigated. Prepared by the method of Bowers and Ringold,[4] a solution of 17β-acetoxy-4,4-dimethyl-19-norandrost-5-en-3-one (4.5 g) in acetic acid (120 ml) was added to platinic oxide (0.6 g) which had been prehydrogenated in cyclohexane (120 ml), and the mixture was shaken in hydrogen for 5 h (uptake *ca.* 750 ml). The product was isolated and oxidised with Jones reagent; a sample was removed and the remainder rehydrogenated in acetic acid (80 ml) containing platinic oxide (0.5 g) and 60% perchloric acid (0.1 ml). Absorption of 300 ml of hydrogen occurred during 3 h. The mixture was separated by an extensive application of chromatography and fractional crystallisation into the 3-ols, which were then oxidised with Jones reagent to yield (i) 17β-acetoxy-4,4-dimethyl-19-nor-5α-androstan-3-one (0.8 g), identical (m.p., mixed m.p., rotation, i.r., and n.m.r.) with the previously prepared specimen and (ii) 17β-*acetoxy*-4,4-*dimethyl*-19-*nor*-5β-*androstan*-3-*one* (0.6 g), which separated from light petroleum in needles, m.p. 102°, $[\alpha]_D^{20}$ −8.1° (*c* 1.3) (Found: C, 75.9; H, 10.0 $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%), $\nu_{max.}$ (CCl_4) 1 735 (acetate) and 1 705 cm^{-1} (C=O), τ 9.16 (3 H, s, H_3-18), 8.90 (3 H, s, 4-Me), 8.80 (3 H, s, 4-Me), and 7.95 (3 H, s, Ac). Saponification of this acetate gave the 17β-*ol* in needles, m.p. 125°, $[\alpha]^{20}$ −5.5° (*c* 1.2), o.r.d. (*c* 0.17 in MeOH) $[\phi]_{400}$ −60°, $[\phi]_{309}$ −1 065°, $[\phi]_{268}$ +1 480°, $[\phi]_{265}$ +1 480, $[\phi]_{242}$ +1 180°, $[\phi]_{208}$ +1 780° (Found: C, 78.9; H, 10.8. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.5%), $\nu_{max.}$ 1 700 cm^{-1} (C=O), τ 9.21 (3 H, s, H_3-18), 8.90 (3 H, s, 4-Me), and 8.80 (3 H, s, 4-Me). Oxidation with Jones reagent gave 4,4-*dimethyl*-19-*nor*-5β-*androstane*-3,17-*dione*, which formed needles, m.p. 105° (from light petroleum), $[\alpha]_D$ +65° (*c* 1.0) (Found: C, 79.0; H, 9.8. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%), $\nu_{max.}$ 1 740 (C=O in five-membered ring) and 1 705 cm^{-1} (C=O in six-membered ring), μ 3.06 ± 0.02 D.

A mixture of equal quantities of 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one and the 5β-isomer could not be separated on t.l.c. under a wide variety of conditions. The sample from the hydrogenation was saponified with methanolic potassium hydroxide: both the product and the 'synthetic' mixture were separable by g.l.c. [10 ft column of GaschromeP containing 1% SE-30; column temperature 180 °C; argon (8 lb in^{-2}) as carrier gas] into two components having retention times (unassigned) of 31.4 and 33.0 min.

17β-*Hydroxy*-4,4,17α-*trimethyl*-19-*nor*-5α-*androstan*-3-*one*.—A solution of 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one (0.5 g) in benzene (60 ml) containing ethylene glycol (5.0 ml) and toluene-*p*-sulphonic acid (30 mg) was refluxed during 5.5 h with continuous removal of water. 3,3-*Ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-17β-*ol* formed needles (0.5 g), m.p. 148° (from acetone–methanol), $[\alpha]_D^{20}$ +5° (*c* 0.1) (Found: C, 75.2; H, 10.2. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%).

Oxidation of this alcohol (0.36 g) with chromic oxide (0.4 g) in pyridine (10 ml) gave 3,3-*ethylenedioxy*-4,4-*dimethyl*-19-*nor*-5α-*androstan*-17-*one* (0.31 g) in needles, m.p. 174° (from acetone), $[\alpha]_D^{20}$ +14° (*c* 0.27), $\nu_{max.}$ 1 740 cm^{-1} (five-membered C=O) (Found: C, 76.8; H, 10.0. $C_{22}H_{34}O_3$ requires C, 76.2; H, 9.9%).

A solution of this ketone (0.3 g) in anisole (10 ml) was added to methylmagnesium iodide [from magnesium (0.2 g) in ether (25 ml)] and the mixture refluxed during 5 h. The resultant 17β-*hydroxy*-4,4,17α-*trimethyl*-19-*nor*-5α-*androstan*-3-*one* (0.23 g) formed prisms (from aqueous acetone), m.p. 168°, o.r.d. (*c* 0.107 in MeOH) $[\phi]_{500}$ −130°, $[\phi]_{400}$ −260°, $[\phi]_{310}$ −920°, $[\phi]_{225}$ −1 000°, *a* − 9 (Found: C, 79.0; H, 10.7. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%) (lit.,[4] m.p. 178°, *a* − 15 for product of doubtful authenticity).

Methylation of 17β-*Hydroxy*-B-*norandrost*-4-*en*-3-*one*.—Methylation of a solution of the title compound (0.5 g) in t-butyl alcohol (25 ml) containing potassium t-butoxide [from potassium (0.3 g)] and methyl iodide (0.9 ml) during 5 h at room temperature followed by purification of the product by chromatography from alumina and elution with benzene–ether gave (i) 17β-*hydroxy*-4,4-*dimethyl*-B-*norandrost*-5-*en*-3-*one* in needles (0.15 g), m.p. 144° (from light petroleum–acetone), $[\alpha]_D^{20}$ −20.4° (*c* 1.7) (Found: C, 79.7; H, 10.1. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%), $\nu_{max.}$ 3 625 (OH) and 1 705 cm^{-1} (C=O), τ 9.18 (3 H, s, H_3-18), 8.87 (3 H, s, H_3-19), 8.87 (3 H, s, 4-Me), and 8.73 (3 H, s, 4-Me); and (ii) 17β-*hydroxy*-4-*methyl*-B-*norandrost*-4-*en*-3-*one* (0.18 g) in needles, m.p. 140° (from light petroleum–acetone), $[\alpha]_D^{20}$ −20.7° (*c* 1.8) (Found: C, 78.5; H, 9.7. $C_{19}H_{28}O_2$ requires C, 78.5; H, 10.1%), τ 9.18 (3 H, s, H_3-18), 8.93 (3 H, s, H_3-19), and 8.32 (3 H, s, 4-Me).

Prepared with pyridine–acetic anhydride, 17β-*acetoxy*-4,4-*dimethyl*-B-*norandrost*-5-*en*-3-*one* formed needles, m.p. 95° (from aqueous methanol), $[\alpha]_D^{20}$ −22.7° (*c* 1.6) (Found: C, 76.9; H, 9.4. $C_{22}H_{32}O_3$ requires C, 76.8; H, 9.4%). Hydrogenation of this acetate (0.3 g) in acetic acid (15 ml) and cyclohexane (15 ml) containing 60% perchloric acid (0.1 ml) and platinic oxide (0.1 g) occurred during 18 h, to yield (after oxidation with Jones reagent) 17β-*acetoxy*-4,4-*dimethyl*-B-*nor*-5α-*androstan*-3-*one* (0.2 g), which formed needles, m.p. 116° (from aqueous methanol), $[\alpha]_D^{20}$ +62° (*c* 1.1), o.r.d. (*c* 0.10 in MeOH) $[\phi]_{400}$ +470°, $[\phi]_{313}$ +1 850°, $[\phi]_{283}$ −350°, $[\phi]_{215}$ +2 220° (Found: C, 76.0; H, 10.0%; M^+ 346. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%; *M*, 346), $\nu_{max.}$ (CCl_4) 1 735 (acetate) and 1 710 cm^{-1} (C=O), τ 9.19 (3 H, s, H_3-18), 8.98 (6 H, s, 2 Me), 8.79 (3 H, s, Me), and 7.95 (3 H, s, OAc).

2-(*Butylthiomethylene*)-17β-*hydroxy*-5α-*androstan*-3-*one*.—A solution of 17β-hydroxy-2-methoxymethylene-5α-androstan-3-one (1 g) in benzene (120 ml) containing butane-1-thiol (1 ml) and toluene-*p*-sulphonic acid (0.01 g) was refluxed, with removal of water azeotropically, during 5 h. Purification of the product from ether–light petroleum gave 2-(*butylthiomethylene*)-17β-*hydroxy*-5α-*androstan*-3-*one* in needles (0.8 g), m.p. 98°, $[\alpha]_D^{20}$ −15.9° (*c* 1.0) (Found: C, 73.2; H, 9.9; S, 7.7. $C_{24}H_{38}O_2S$ requires C, 73.8; H, 9.8; S, 8.2%). Prepared with pyridine–acetic anhydride, the 17β-*acetate* formed needles, m.p. 147° (from methanol), $[\alpha]_D^{20}$ −35.1° (*c* 1.3) (Found: C, 72.6; H, 9.4; S, 7.5. $C_{26}H_{40}O_3S$ requires C, 72.2; H, 9.3; S, 7.4%).

2-(*Butylthiomethylene*)-17β-*hydroxy*-19-*nor*-5α-*androstan*-3-*one*.—Prepared as previously from 17β-hydroxy-2-hydroxymethylene-19-nor-5α-androstan-3-one [5] (1 g), 2-(*butylthiomethylene*)-17β-*hydroxy*-19-*nor*-5α-*androstan*-3-*one* (1.1 g) formed needles, m.p. 153° (from ether–light petroleum) $[\alpha]_D$ +85.9° (*c* 2.0) (Found: C, 73.5; H, 9.4; S, 8.7. $C_{23}H_{36}O_2S$ requires C, 73.3; H, 9.6; S, 8.5%).

2-(*Butylthiomethylene*)-5α-*cholestan*-3-*one*.—A suspension of 2-hydroxymethylene-5α-cholestan-3-one (0.5 g) in methanol (8 ml) containing 60% perchloric acid (0.1 ml) was refluxed for 2 h. 2-*Methoxymethylene*-5α-*cholestan*-3-*one* formed plates (0.4 g), m.p. 155° (from methanol), $[\alpha]_D$ +47.0° (*c* 1.0) [Found: C, 81.8; H, 11.1; OMe, 7.2. $C_{28}H_{45}O(OMe)$ requires C, 81.3; H, 11.3; OMe, 7.2%]. Condensation of this methoxy-derivative (0.5 g) with butane-1-thiol (0.5 ml) in benzene (60 ml) gave 2-(*butylthiomethylene*)-5α-*cholestan*-3-*one* (0.5 g) in plates, m.p. 77°, $[\alpha]_D$ −9.9° (*c* 1.0) (Found: C, 78.6; H, 11.3; S, 6.6. $C_{32}H_{54}OS$ requires C, 78.9; H, 11.2; S, 6.6%).

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