[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CIV.[1] Synthesis of 4,4-Dimethyl and 2,2-Dimethyl 19-nor-Hormone Analogs

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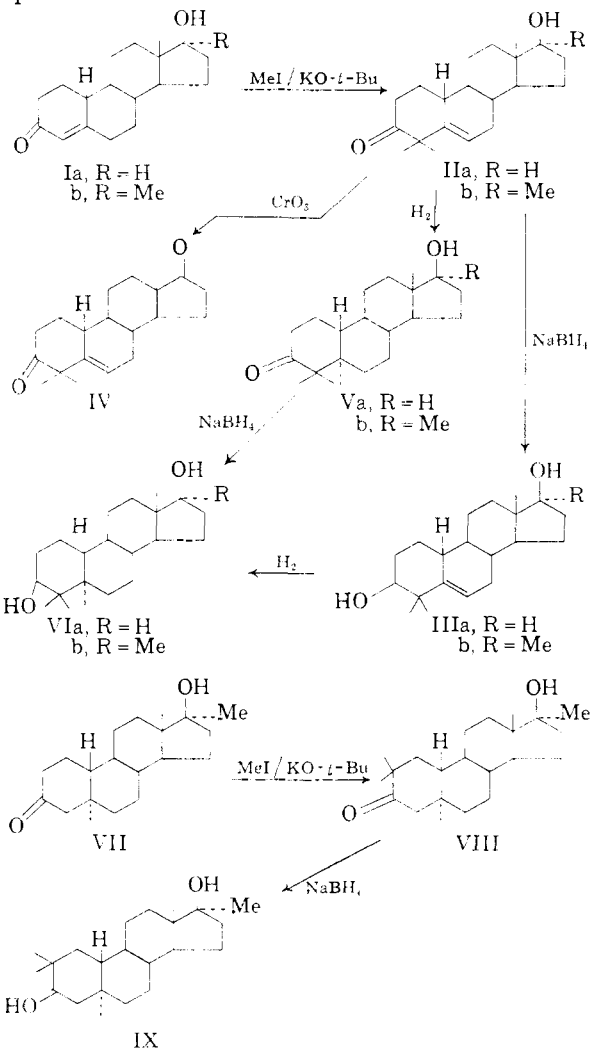
Methylation of 19-nortestosterone (Ia) and 17α-methyl-19-nor-testosterone (Ib) smoothly afforded the 4,4-dimethyl-Δ^5-3-ketones (IIa and IIb). The corresponding dihydroallo compounds were obtained by catalytic hydrogenation. Sodium borohydride reduction of the saturated and unsaturated ketones afforded the corresponding 3β-alcohols. Methylation of dihydroallo-17α-methyl-19-nortestosterone afforded the 2,2-dimethyl derivative which gave the corresponding 3β-alcohol on reduction with sodium borohydride.

As part of a broad program being carried out in these laboratories directed toward the synthesis of methylated steroid hormones[2] it was of interest in connection with a search for new androgenic, anabolic or tumor inhibitory agents to extend this work to the synthesis of 4,4-dimethyl and 2,2-dimethyl hormone analogs in the 19-norandrostane series.[3] Interest in 4,4-dimethyl steroids as distinct from the naturally occurring 4,4,14-trimethyl steroids[4] was stimulated when Woodward and Barton and their colleagues unequivocally showed that direct methylation of Δ^4-cholestene-3-one in *t*-butyl alcohol with excess methyl iodide in the presence of potassium *t*-butoxide smoothly gave Δ^5-4,4-dimethylcholestene-3-one.[5,6]

Using this methylation procedure 4,4-dimethyl steroids have been prepared in the ergostane,[7] pregnane[3a] and androstane series.[3a,3b] Methylation of 19-nortestosterone (Ia) and 17α-methyl-19-nortestosterone (Ib) using the original technique of Woodward and Barton and their colleagues[5] readily gave the corresponding 4,4-dimethyl-Δ^5-3-ketones (IIa and IIb).

Although it is known that 4,4,10β-trimethyl-Δ^5-3-ketones are stable to further methylation at C-2 under our experimental conditions, it was not immediately apparent that a 19-nor-steroid would not methylate further at C-2. Should the mechanism for further methylation require the approach of the entering group to be along the line of the axial bond (β-face approach) then replacement of the 10β-methyl group by hydrogen (1,3-diaxially situated with respect to an incoming methyl group) may reduce the non-bonded interactions in the transition state[8] sufficiently to make the reaction feasible.

On the other hand, hindrance to equatorial attack (α-face approach) is virtually the same in both series and thus by analogy no reaction should take place at C-2 in the 19-nor series if this steric course operated.



Although the direction of alkylation of cyclic ketones has not been clearly defined, sufficient evidence is now available[9] to suggest that alkylation

(1) Part CIII, A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958).

(2) Previous paper relating to the synthesis of methylated steroid hormones: A. Bowers and H. J. Ringold, *ibid.*, **80**, 3091 (1958).

(3) For the synthesis of these compounds in the C-10 methyl series see: (a) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956); (b) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

(4) For excellent reviews on these compounds see: (a) E. R. H. Jones and T. G. Halsall, *Fortsch. Chem. Org. Naturstoffe*, **12**, 44 (1955); (b) R. M. Gascoigne and J. J. H. Simes, *Quart. Revs. Chem. Soc.*, **9**, 328 (1955).

(5) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(6) It was pointed out recently, *cf.* E. J. Corey, H. J. Burke and W. A. Remers, THIS JOURNAL, **78**, 180 (1956), that highly specific α-alkylation of extended enolate ions (—C—C—C—C—C—) has been observed in numerous instances and can now be accepted as a characteristic of such systems; *cf.* A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957), and references cited therein.

(7) G. Cooley, B. Ellis and V. Petrow, *ibid.*, 2998 (1955).

(8) Only the non-bonded interactions in the transition state need to be considered. Subsequent inversion to the equatorial epimer is possible by enolization and reprotonation in the alkaline reaction medium.

(9) See for example (a) W. S. Johnson, *Chemistry & Industry*, 167 (1956); (b) M. J. T. Robinson, *Tetrahedron*, **1**, 49 (1957), (c) J. L. Beton, T. G. Halsall, E. R. H. Jones and D. C. Phillips, *J. Chem. Soc.*, 753 (1957); (d) R. Howe and F. J. McQuillin, *ibid.*, 1194 (1958).

of a cyclic ketone proceeds axially.[10] Thus, *a priori* one may have tended to predict that a 19-nor-4,4-dimethyl-3-keto compound in contrast to a 4,4,10-trimethyl steroid would undergo further methylation at C-2 β, since alkylation would probably proceed axially. The groups 1,3-diaxially situated with respect to an entering 2β-methyl group in the 19-nor case are reduced from two methyl groups to a methyl and hydrogen. In actuality, however, no methylation did occur at C-2 as was readily demonstrated by condensation of IIa with ethyl formate yielding a 2-hydroxymethylene derivative with characteristic ultraviolet maximum at 290 mμ and it can only be concluded that even in the 19-nor series steric hindrance is great enough to prevent facile alkylation at C-2β.

Oxidation of IIa with 8 *N* chromic acid[11] gave the 3,17-diketone IV in high yield. Reduction of the 4,4-dimethyl-3-ketones IIa and IIb with sodium borohydride gave the 3β-alcohols IIIa and IIIb. The equatorial 3β-conformation of the hydroxyl groups follows from the known stereochemical course of the reduction of a 4,4-dimethyl-3-ketone.[12] Catalytic hydrogenation at atmospheric pressure of the Δ^5-3-ketones IIa and IIb in methanol solution over a palladium–carbon catalyst afforded the dihydroallo ketones Va and Vb. The *trans* arrangement of rings A and B in the saturated compounds followed from the work of Jones and Halsall and their co-workers[9c,13] who proved rigorously that hydrogenation of a 4,4-dimethyl-Δ^5-3-ketone led to the dihydroallo compound. In addition, Va and Vb had the highly characteristic rotatory dispersion curves of 4,4-dimethyl-3-keto dihydroallo steroids.[14]

Reduction of the dihydroallo-3-ketones Va and Vb with sodium borohydride gave the dihydroallo-3β-alcohols VIa and VIb. Alternatively VIa was prepared by the catalytic hydrogenation of the corresponding Δ^5-compound IIIa. This reduction proceeded only with difficulty and required a longer reaction time and a greater ratio of catalyst than the analogous reduction of the corresponding 3-ketone (IIa → Va). However, even under these conditions we were not able to effect complete hydrogenation of the 17α-methyl compound IIIb. In general reduction of a 4,4-dimethyl-Δ^5-steroid is a relatively slow reaction due to the hindered nature of the double bond.[15]

It recently has been established that dihydroallo-3-ketones in the 10-methyl series are readily dimethylated at C-2[16] and on applying this reaction to 17α-methyl-19-norandrostane-17β-ol (VII) we obtained the 2,2-dimethyl-3-ketone VIII. However in this case also the steric requirements for methylation are not analogous to those in the 10-methyl series and it was necessary to establish that further methylation had not occurred at C-4. Similar to the 4,4-dimethyl-3-ketone, VIII readily condensed with ethyl formate to give a hydroxymethylene derivative λ_{max} 294–296 mμ, demonstrating the presence of a methylene group α to the C-3 ketone. Sodium borohydride reduction of VIII gave the corresponding 3β-alcohol IX.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Rotations were measured in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. We are grateful to Dr. L. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. We are indebted to Miss M.E. Barba for skilled technical assistance. The elemental analyses were carried out by A. Bernhardt, Mulheim, Ruhr, Germany.

4,4-Dimethyl-19-nor-Δ^5-androstene-17β-ol-3-one (IIa).[17]—Methyl iodide (3.5 cc.) was added to a solution of 19-nortestosterone[18] (Ia) (2.0 g.) in *t*-butyl alcohol (30 cc.) containing potassium (1.1 g.) and cooled to 0° in a nitrogen atmosphere. After stirring for 2.5 hours at room temperature the bulk of the solvent was removed under vacuum and the product was precipitated with water. Isolation with ether gave a product which was adsorbed from benzene (100 cc.) onto alumina (100 g.). Elution with benzene–ether (80:20, 1 l.) afforded 4,4-dimethyl-19-nor-Δ^5-androstene-17β-ol-3-one (IIa) (1.25 g.), m.p. 130–136°, raised by crystallizations from acetone-hexane to 144–146°, $[\alpha]_D$ +2°; IIa did not exhibit selective absorption in the ultraviolet and gave a yellow color with tetranitromethane.

Condensation of IIa with ethyl formate in benzene in the presence of sodium hydride[19] afforded a semi-solid derivative; λ_{max}^{EtOH} 288–292, log ϵ 3.82

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.61; H, 10.29.

4,4,17α-Trimethyl-19-nor-Δ^5-androstene-17β-ol-3-one (IIb).—Methylation of 17α-methyl-19-nortestosterone[20] (Ib) exactly as described in the previous experiment afforded 4,4,17α-trimethyl-19-nor-Δ^5-androstene-17β-ol-3-one (IIb) in 76% yield. It exists in two polymorphic forms having m.p.'s. 160–162° (needles) and 168–170° (rhombs), $[\alpha]_D$ −15°; IIb did not exhibit selective absorption in the ultraviolet and gave a yellow color with tetranitromethane.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.46; H, 10.20.

4,4-Dimethyl-19-nor-Δ^5-androstene-3β,17β-diol (IIIa).—Sodium borohydride (200 mg.) in aqueous dioxane (4:1, 5 cc.) was added to a solution of 4,4-dimethyl-19-nor-Δ^5-androstene-17β-ol-3-one (IIa) (300 mg.) in dioxane (15 cc.). After 1 hour at room temperature addition of water and isolation with ether afforded a product which was adsorbed from benzene (200 cc.) onto alumina (20 g.). Elution with benzene–ether (70:30, 500 cc.) afforded 4,4-dimethyl-19-nor-Δ^5-androstene-3β,17β-diol (IIIa) (260 mg.), m.p. 190–194°, raised by several crystallizations from aqueous methanol to 192–194°, $[\alpha]_D$ +4°.

(10) *Cf.* ref. 9a where it was suggested that axial alkylation may be the rule for unhindered ketones and refs. 9c and 9d where the alkylation of ketones has been compared with the bromination and deuteration of enolates.

(11) See for example: A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(12) For a detailed argument of the stereochemical course of hydride reductions of 4,4-dimethyl-3-ketones, saturated or unsaturated in ring B, see ref. 3a and references cited therein.

(13) See also ref. 3a for a stereochemical argument leading to the same conclusion.

(14) We are grateful to Professor Carl Djerassi of Wayne State University, Detroit, Mich., for the determination of the rotatory dispersion curves of these compounds. For a description of this useful technique see C. Djerassi, *Bull. soc. chim. France*, 741 (1957), and references cited therein.

(15) For example see ref. 9c where the hydrogenation of 4,4-dimethyl-Δ^5-cholestene-3-one had to be carried out in acetic acid at 80° with a platinum oxide catalyst.

(16) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(17) After the completion of this work N. W. Atwater, THIS JOURNAL, **79**, 5315 (1957), described the isolation of a compound (m.p 149.5–150°, $[\alpha]_D$ +33°), to which he ascribed structure IIa as a by-product from a modified methylation procedure designed to afford the 4-monomethyl compound as the major product.

(18) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(19) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(20) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

Anal. Calcd. for $C_{20}H_{32}O_2 \cdot 1/2CH_3OH$: C, 76.73; H, 10.68. Found: C, 76.36; H, 10.50.

4,4,17α-Trimethyl-19-nor-Δ⁵-androstene-3β,17β-diol (IIIb).—Sodium borohydride reduction of 4,4,17α-trimethyl-19-nor-Δ⁵-androstene-17β-ol-3-one (IIb) exactly as described in the previous experiment afforded 4,4,17α-trimethyl-19-nor-Δ⁵-androstene-3β-17β-diol (IIIb) in 77% yield, m.p. 170–172°, $[\alpha]_D$ −21°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.38; H, 10.44.

4,4-Dimethyl-19-nor-Δ⁵-androstene-3,17-dione (IV).—A solution of 4,4-dimethyl-19-nor-Δ⁵-androstene-17β-ol-3-one (IIa) (500 mg.) in acetone (20 cc.) at 0–5° was treated with an excess of 8 *N* chromic acid.[11] After 2–3 minutes addition of water and isolation with ether afforded a product which was adsorbed from benzene–hexane (50:50, 50 cc.) onto alumina (30 g.). Elution with benzene (500 cc.) afforded 4,4-dimethyl-19-nor-Δ⁵-androstene-3,17-dione (IV) (380 mg.), m.p. 139–145°, raised by several crystallizations from aqueous acetone to 142–144°, $[\alpha]_D$ +66°.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.93; H, 9.39. Found: C, 80.01; H, 9.40.

4,4-Dimethyl-19-norandrostane-17β-ol-3-one (Va).—A suspension of 10% palladium-on-carbon (100 mg.) in methanol (10 cc.) was stirred under an atmosphere of hydrogen for 1 hour. A solution of 4,4-dimethyl-19-nor-Δ⁵-androstene-17β-ol-3-one (IIa) (500 mg.) in methanol (40 cc.) was then added and stirring under the hydrogen atmosphere was continued at room temperature for 6 hours when the uptake of hydogen had ceased. After filtration and removal of the solvent, the product, in benzene (50 cc.), was adsorbed onto alumina (30 g.). Elution with benzene–ether (80:20, 300 cc.) afforded 4,4-dimethyl-19-norandrostane-17β-ol-3-one (Va) (410 mg.), m.p. 135–143°, raised by several crystallizations from acetone–hexane to 150–152°, depressed on admixture with starting material, $[\alpha]_D$ −22°; Va gave no color with tetranitromethane.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.61; H, 10.45.

4,4,17α-Trimethyl-19-norandrostane-17β-ol-3-one (Vb).—A suspension of 10% palladium-on-carbon (500 mg.) in methanol (20 cc.) was prereduced for 1 hour in an atmosphere of hydrogen. A solution of 4,4-17α-trimethyl-Δ⁵-19-norandrostene-17β-ol-3-one (IIb) (1.5 g.) in methanol (60 cc.) was added and hydrogenated at room temperature and atmospheric pressure for 24 hours. After filtration and evaporation of the solvent the product in benzene (100 cc. was adsorbed onto alumina (75 g.). Elution with benzene–ether (80:20, 500 cc.) and (70:30, 300 cc.) afforded a product (1.31 g.), m.p. 160–166°, which gave a strong yellow color with tetranitromethane. The hydrogenation was repeated with this product for a further 24 hours in the presence of the palladium–carbon catalyst (1.5 g.) and then isolated in the manner described above. Chromatography over alumina (75 g.) afforded 4,4,17α-trimethyl-19-norandrostane-17-β-ol-3-one (Vb) (850 mg.), m.p. 159–163°, which gave no color with tetranitromethane. After several crystallizations from aqueous acetone it had m.p. 178–180°, $[\alpha]_D$ −43°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.41; H, 10.63.

4,4-Dimethyl-19-norandrostane-3β,17β-diol (VIa). (a) **By Hydrogenation of IIIa.**—A suspension of 10% palladium-on-carbon (175 mg.) in methanol (10 cc.) was prereduced for 1 hour in an atmosphere of hydrogen. A solution of 4,4-dimethyl-19-nor-Δ⁵-androstene-3β,17β-diol (400 mg.) in methanol (40 cc.) was added and hydrogenated at room temperature and atmospheric pressure for 18 hours. After filtration and evaporation of the solvent the product in benzene (100 cc.) was adsorbed onto alumina (30 g.). Elution with benzene–ether (70:30, 500 cc.) afforded 4,4-dimethyl-19-norandrostane-3β-17β-diol (VIa) (240 mg.), m.p. 200–206°, raised by several crystallizations from acetone to 212–214°, $[\alpha]_D$ +9°; VIa gave no color with tetranitromethane.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.44; H, 11.21.

(b) **By Sodium Borohydride Reduction of Va.**—A solution of sodium borohydride (150 mg.) in aqueous dioxane (4:1, 5 cc.) was added to a solution of 4,4-dimethyl-19-norandrostane-17β-ol-3-one (Va) (190 mg.) in dioxane (10 cc.). After 1 hour at room temperature, addition of water and isolation with ether afforded a product which was adsorbed from benzene (30 cc.) onto alumina (15 g.). Elution with benzene–ether (70:30, 300 cc.) afforded 4,4-dimethyl-19-norandrostane-3β,17β-diol (VIa) (150 mg.) m.p. 205–209°, raised by several crystallizations from aqueous acetone to 213–215°, undepressed on admixture with a sample prepared as in (a). $[\alpha]_D$ +11°. The infrared spectra of the two compounds were identical.

4,4,17α-Trimethyl-19-norandrostane-3β,17β-diol (VIb).—A solution of sodium borohydride (30 mg.) in water (0.5 cc.) was added to a solution of 4,4,17α-trimethyl-19-norandrostane-17β-ol-3-one (Vb) (100 mg.) in dioxane (7.5 cc.). After 3 hours at room temperature addition of water and filtration afforded 4,4,17α-trimethyl-19-norandrostane-3β,-17β-diol (VIb) (80 mg.) m.p. 200–205°, raised by several crystallizations from acetone-hexane to 206–208°, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 10.09. Found: C, 78.49; H, 11.27; O, 9.82.

2,2,17α-Trimethyl-19-norandrostane-17β-ol-3-one (VIII).—Methyl iodide (7.0 cc.) was added to a solution of 17α-methyl-19-norandrostane-3-one[21] (4.0 g.) in *t*-butyl alcohol (75 cc.) containing potassium (2.2 g.) and cooled to 0° in an atmosphere of nitrogen. After stirring at room temperature for 3 hours addition of water and isolation with ether afforded a product which was adsorbed from benzene–hexane (50:50, 300 cc.) onto alumina (200 g.). Elution with benzene (1 l.) gave 2,2,17α-trimethyl-19-norandrostane-3-one (VIII) (3.4 g.), m.p. 128–131°, raised by several crystallizations from acetone–hexane to 140–142°, $[\alpha]_D$ +102°. With ethyl formate in benzene in the presence of sodium hydride[19] it afforded a crude hydroxymethylene derivative, λ_{max}^{EtOH} 294–296 mμ, log ε 3.78.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.19. Found: C, 79.43; H, 10.36.

2,2,17α-Trimethyl-19-norandrostane-3β,17β-diol (IX).—A solution of sodium borohydride (500 mg.) in aqueous dioxane (4:1, 5 cc.) was added to a solution of 2,2,17α-trimethyl-19-norandrostane-17β-ol-3-one (VIII) (750 mg.). After 3 hours at room temperature addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene (100 cc.) onto alumina (30 g.). Elution with benzene–ether (80:20, 400 cc.) afforded 2,2,17α-trimethyl-19-norandrostane-3β,17β-diol (X) (680 mg.), m.p. 171–173°, raised by several crystallizations from acetone–hexane to 178–179°, $[\alpha]_D$ +28°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 10.09. Found: C, 78.61; H, 11.22; O, 9.89.

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(21) (a) A. Bowers, H. J. Ringold and R. I. Dorfman, THIS JOURNAL, **79**, 4556 (1957); (b) A. Bowers, H. J. Ringold and E. Denot, *ibid.*, **80**, 6115 (1958).