6,16-Dimethylated Steroids. IV. 4,4-Dimethyl Analogs[1]

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Alkylation of the 3-pyrrolidyl enamines of 6α,16α-dimethyl-17α-hydroxyprogesterone and 6α,16α-dimethylprogesterone has provided the corresponding 4,4-dimethyl-5-pregnene analogs. The former was also obtained by direct alkylation of 17α,20β-isopropylidenedioxy-6α,16α-dimethyl-4-pregnen-3-one followed by hydrolysis to the 17α,20β-diol (**7**) and oxidation to the 20-ketone (**4b**). The 17α-acetate (**4c**) gave an unexpectedly high response in the Clauberg assay for oral progestational activity.

In previous papers of this series,[1,3] we have described a series of 6,16α-dimethylprogesterones variously substituted at positions 17 and 21. The 6,16α-dimethyl-17α-acetoxyprogesterones and their 21-fluoro derivatives were shown to possess unusually high oral progestational activity.

We now wish to report the synthesis of several 4,4,-6,16α-tetramethyl-5-pregnene analogs, one of which, 4,4,6,16α-tetramethyl-5-pregnen-17α-ol-3,20-dione 17-acetate (**4c**), showed an unexpectedly high response in the oral Clauberg assay. This latter substance constitutes the first reported example of a 4,4-dialkylated 5-pregnen-3-one exhibiting significant biological activity.

Numerous reports have been issued describing syntheses of 4,4-dimethyl-5-androsten-3-ones and 4,4-dimethyl-19-nor-5-androsten-3-ones.[4] In the pregnane series, only 4,4-dimethyl-5-pregnene-3,20-dione[4a] and 4,4-dimethyl-9α-fluoro-11β,17α,21-trihydroxy-5-pregnene-3,20-dione[5] have been described.

Although significant biological activity is reported for various of the 4,4-dimethyl-5-androsten-3-ones,[4f,h,6,6] no biological activity has yet been reported for any 4,4-dimethyl-5-pregnen-3-ones. In all instances, the 4,4-dimethyl-5-en-3-one compounds were prepared by direct methylation of the parent 4-en-3-ones by the method first described by Woodward, *et al.*[7]

The initial preparations of the 4,4-dimethyl steroids reported herein proceeded by way of alkylation of the appropriate 3-pyrrolidyl enamines. 6α,16α-Dimethylprogesterone (**1a**) on treatment with pyrrolidine in methanol[8] gave excellent yields of the 3,5-dien-3-amine (**2a**). Alkylation with methyl iodide in absolute methanol afforded a mixture of 4,6α,16α-trimethylprogesterone and 4,4,6,16α-tetramethyl-5-pregnene-3,-20-dione (**4a**) from which the latter was separated readily by chromatography. This alkylation to a 4,4-dimethyl-5-en-3-one is analogous to the perchloryl fluoride 4,4-difluorination of enamines reported by Nakanishi, *et al.*[3]

Treatment of 6α,16α-dimethyl-17α-hydroxyprogesterone (**1b**) or its 17α-acetate (**1c**) with pyrrolidine in methanol gave mixtures of the corresponding 3-enamines (**2b** or **2c**) and starting material from which separation of the enamine was difficult. The desired 3-enamine (**2b**) was prepared in excellent yield, however, by treatment of 6β,16α-dimethylpregnane-5α,-17α-diol-3,20-dione (**3a**) or its 5α-acetate (**3b**)[3] with pyrrolidine in methanol. Concomitant rapid elimination of the 5α-oxygen functions occurred under the basic reaction conditions.

Direct alkylation of the 3-enamine (**2b**) with methyl iodide in methanol gave the 4,4,6,16α-tetramethyl-5-pregnen-17α-ol-3,20-dione (**4b**) admixed with 4,6α,-16α-trimethyl-17α-hydroxyprogesterone. Separation proved to be difficult. The mixture was, therefore, acetylated in the usual manner[10] and chromatographed. The tetramethyl 17α-acetate (**4c**) was isolated in a pure state but the trimethyl 17α-acetate could not be freed of impurities.

An alternate route to the tetramethyl-17-oxygenated compounds proceeded from 17α,20β-isopropylidenedioxy-6α,16α-dimethyl-4-pregnen-3-one (**5**).[3] Direct alkylation with methyl iodide in *t*-butyl alcohol containing potassium *t*-butoxide[11] again gave a mixture of the trimethyl and tetramethyl compounds. The tetramethyl compound (**6**), however, predominated and was separated readily. Hydrolysis of the 17α,20β-isopropylidenedioxy group was accomplished by treatment with refluxing aqueous acetic acid. The 17α,20β-

(1) Previous paper of the series: M. B. Meyers, R. P. Graber, and D. N. Jones, *J. Med. Chem.*, **7**, 548 (1964).

(2) Searle Chemicals, Inc., Chicago 80, Ill.

(3) R. P. Graber, M. B. Meyers, L. G. Hickman, E. H. Boeckhoff, and A. D. Odell, *J. Med. Chem.*, **7**, 540 (1964).

(4) (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); (c) N. W. Atwater, *J. Am. Chem. Soc.*, **79**, 5315 (1957); (d) A. Bowers and H. J. Ringold, *ibid.*, **81**, 424 (1959); (e) N. W. Atwater, *ibid.*, **82**, 2847 (1960); (f) 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, *ibid.*, **83**, 1478 (1961); (g) N. W. Atwater, R. F. Bible, Jr., E. A. Brown, R. B. Portner, J. S. Mildna, L. N. Nysted, and P. B. Sollmann, *J. Org. Chem.*, **26**, 3077 (1961); (h) H. J. Ringold and G. Rosenkranz, German Patent 1,100,-621 (Sept. 6, 1961); (i) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, **15**, 669 (1962); *J. Am. Chem. Soc.*, **84**, 3402 (1962); (j) E. Batres and H. J. Ringold, U. S. Patent 3,067,216 (Dec. 4, 1962).

(5) W. S. Allen, C. C. Pidacks, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **26**, 5036 (1961).

(6) Although ref. 4f, h, and j allege significant activity in various bioassay procedures, see ref. 4a in which a series of 4,4-dimethyl compounds are described as inactive. See also "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Ed., Pergamon Press, New York, N. Y., 1961, pp. 209–219, in which H. J. Ringold has presented a stereochemical rationale for the inactivity of 4,4-dimethylandrostan-17β-ol-3-one.

(7) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954); *J. Chem. Soc.*, 1131 (1957).

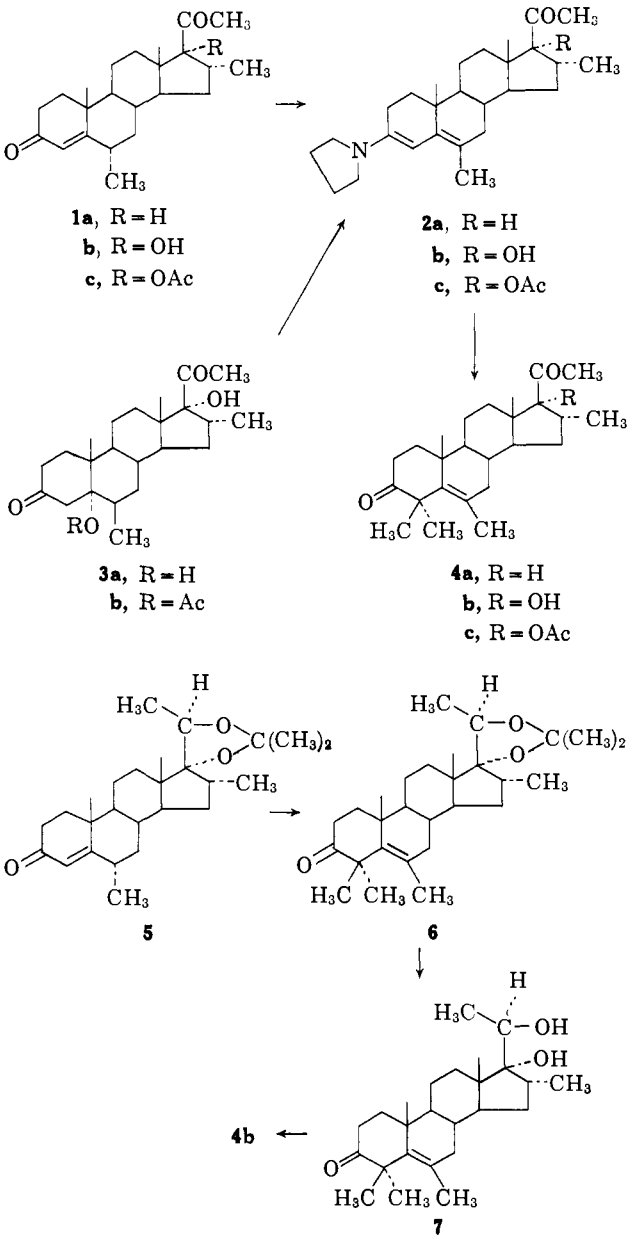
(8) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953); M. E. Herr and F. W. Heyl, *ibid.*, **75**, 5927 (1953). The procedures described in this paper represent modifications of the original procedure cited. Undoubtedly, crystallization of the enamine from the reaction mixture sufficed to shift the equilibrium in favor of the product thus obviating the necessity of using a water-immiscible solvent such as benzene for azeotropic separation of the water formed.

(9) S. Nakanishi, R. L. Morgan, and E. V. Jensen, *Chem. Ind.* (London), 1136 (1960).

(10) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 4220 (1952); **75**, 3489 (1953); Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *ibid.*, **74**, 5394 (1952).

(11) See particularly ref. 4i for a lucid discussion of the mechanism of this reaction.

glycol (**7**) was then oxidized in good yield with either 8 *N* chromic acid–sulfuric acid reagent[12] or with N-bromosuccinimide in acetone[3,13] to 4,4,6,16α-tetramethyl-5-pregnen-17α-ol-3,20-dione (**4b**). Acetylation of the tetramethyl-5-pregnene afforded the 17α-acetate (**4c**) identical with that prepared *via* alkylation of the enamine.



The oral progestational activity of **4c** was estimated by the Clauberg method on immature estrogen-primed rabbits.[14] The data obtained are as follows.

Level, mg.	Response
0.075	0.8+
0.75	1.5+
7.5	3.8+

Since the data do not give the normal response curve, no meaningful comparison of the activity of **4c** with any standard substance, *e.g.*, ethisterone, can be given. The response at the 0.075-mg. level, however, is particularly interesting for a compound of this structure.

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(13) E. W. Cantrall and S. Bernstein, U. S. Patent 3,019,219 (Jan. 30, 1962).

(14) Bioassays by Endocrine Laboratories, Madison 1, Wis.

Experimental[15]

3-(N-Pyrrolidyl)-6α,16α-dimethylpregna-3,5-dien-20-one (2a).—A solution of 3.42 g. of 6α,16α-dimethylprogesterone (**1a**) in 20 ml. of absolute methanol containing 1 drop of pyrrolidine was heated to boiling and then 1.5 ml. of pyrrolidine was added. The mixture was boiled gently for 5 min. during which a crystalline solid separated. The mixture was cooled in ice; the solid was separated by filtration, washed with cold methanol, and dried *in vacuo* at room temperature to give 3.665 g. (92.7%), m.p. 144–146° dec., $[\alpha]^{25}D$ −24.9°; λ_{max}^{KBr} 5.87, 6.11, and 6.23 μ.[16]

Anal. Calcd. for $C_{27}H_{41}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.25; H, 10.22; N, 3.14.

4,4,6,16α-Tetramethyl-5-pregnene-3,20-dione (4a).—The enamine (**2a**) (2.85 g.) in 250 ml. of absolute methanol was treated with 50 ml. of methyl iodide and the solution heated under reflux for 40 hr. The mixture was concentrated *in vacuo* to *ca.* one-half the original volume, 10 ml. of 10% aqueous sodium hydroxide solution added, and this mixture heated under reflux for 10 min. The solution was then concentrated *in vacuo* to about 50 ml. and diluted with water (2000 ml.). The crystalline solid which separated was removed by filtration, washed to neutrality with water, and dried *in vacuo* to give 2.15 g., m.p. 78–84°. A 1.84-g. portion was chromatographed over 60 g. of Florisil (column prepared in hexane). The fractions eluted with methylene chloride were combined, 450 mg., m.p. 112–115°, no selective absorption in the ultraviolet. Recrystallization from methanol afforded 223 mg., m.p. 114–115°, $[\alpha]^{25}D$ +10°, λ_{max}^{KBr} 5.84 and 5.87 μ.

Anal. Calcd. for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 80.12; H, 10.03.

Further elution of the column with methylene chloride–ether (8:2) gave 972 mg. of solid, m.p. 70–86°, λ_{max} 250–251 mμ (ε 900). Attempts to separate the 4,6α,16α-trimethylprogesterone from this mixture failed.

3-(N-Pyrrolidyl)-6α,16α-dimethylpregna-3,5-dien-17α-ol-20-one (2b).—A suspension of 5 g. of 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione (**3a**) in 30 ml. of absolute methanol was heated to boiling and 1.5 ml. of pyrrolidine added. The solid quickly dissolved. The mixture was heated for 2 min., then quickly cooled in ice, and the crystalline solid separated by filtration. After washing with cold methanol and drying *in vacuo* the product weighed 5.726 g., m.p. 151–160° dec. Recrystallization from absolute methanol afforded 3.102 g. (56.8%), m.p. 188–190° dec., $[\alpha]^{25}D$ −148°; λ_{max}^{KBr} 2.86, 5.89, 6.08, and 6.22 μ.

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.24; H, 9.95; N, 3.50.

Treatment of the 5α-acetate (**3b**) with pyrrolidine in methanol under the above conditions gave material identical in all respects with that prepared above. Treatment of **1b** with pyrrolidine in benzene in the presence of *p*-toluenesulfonic acid[8] gave only recovered starting material. Treatment of 6α,16α-dimethyl-17α-acetoxyprogesterone (**1c**) with pyrrolidine in methanol also gave a mixture of the 3-enamine 17-acetate (**2c**) and starting material.

4,4,6,16α-Tetramethyl-5-pregnen-17α-ol-3,20-dione 17-Acetate (4c). A. From the Enamine 2b.—A solution of 3.0 g. of the enamine (**2b**) in 250 ml. of absolute methanol and 50 ml. of methyl iodide was heated under reflux for 64 hr. The solution was evaporated *in vacuo* to *ca.* 100 ml., poured into ice–water, and the resulting suspension acidified to pH 2 with hydrochloric acid. After standing for 1.5 hr., the product was extracted with methylene chloride. The extracts were washed to neutrality with water, dried, and evaporated to dryness *in vacuo* to give 2.510 g. (89%), m.p. 135–148°; λ_{max} 250–251 mμ (ε 300); λ_{max}^{KBr} 2.98, 5.88, 6.04, and 6.18 μ.

The crude product (2.5 g.) was dissolved in 20 ml. of glacial acetic acid and the solution treated with 4 ml. of acetic anhydride

(15) All melting points were determined in capillaries on a Hershberg apparatus (Eck and Krebs, Inc., New York) using Anschütz thermometers. Rotations were observed in chloroform at *ca.* 1% concentration, ultraviolet spectra in 95% ethanol. Infrared spectra were determined using a Beckmann Model IR-5 spectrophotometer.

(16) Attempts to recrystallize this material resulted in partial decomposition. Therefore, the physical data above are on the "crude" product. The material was also carried on without further purification.

and 0.50 g. of *p*-toluenesulfonic acid monohydrate. The mixture was stored at room temperature for 16 hr., then diluted with water, and the product extracted with methylene chloride. The combined extracts were washed with water, 5% aqueous sodium bicarbonate solution, saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* to give 2.875 g. of solid product, m.p. 90–110°. Chromatography over 100 g. of Florisil (column prepared in hexane) and elution with methylene chloride–ether (9:1) gave 478 mg., m.p. 96–107°, no selective absorption in the ultraviolet. Rechromatography of this material over 30 g. of Florisil (column prepared in benzene) and elution with benzene–ethyl acetate (19:1) gave 184 mg., m.p. 150–155.5°. Crystallization (3 times) from aqueous methanol provided the sample for analysis, m.p. 154–155.5°, no selective absorption in the ultraviolet, λ_{max}^{KBr} 5.75, 5.85, and 8.01 μ, $[\alpha]^{25}D$ −42°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 75.66; H, 9.41. Found: C, 75.62; H, 9.39.

B. From the 17α,20β-Diol (7).—To a solution of 1.0 g. of the tetramethyl diol (**7**) in 120 ml. of acetone and 35 ml. of water was added 2.0 g. of N-bromosuccinimide and the mixture stored at room temperature for 17 hr. Dilution with water gave crystalline material which was removed by filtration, washed thoroughly with water, and dried *in vacuo* to 986 mg. (97%) of crude **4b**, m.p. 91–103°; λ_{max}^{KBr} 2.87, 5.85, 5.99, and 6.26 μ.

Acetylation of 900 mg. of this crude product was carried out by treatment with 30 ml. of acetic acid, 9 ml. of acetic anhydride, and 360 mg. of *p*-toluenesulfonic acid monohydrate at room temperature for 18 hr. Dilution with water afforded 978 mg. (98%) of crude acetate, m.p. 98–104°. This material was chromatographed over 30 g. of silica gel (column prepared in benzene). The fractions eluted with benzene–ethyl acetate (19:1 and 9:1) were combined, yield, 792 mg. (79.5%). Recrystallization of a 100 mg. portion from aqueous methanol gave 80 mg., m.p. 154–155°, undepressed on admixture with the material prepared from the 3-enamine, and with identical infrared spectra in KBr. In addition, the mass spectrum[17] showed a parent peak at m/e = 428 corresponding to $C_{27}H_{40}O_4$.

17α,20β-Isopropylidenedioxy-4,4,6,16α-tetramethyl-5-pregnen-3-one (6).—A 12-g. portion of 17α,20β-isopropylidenedioxy-6α,16α-dimethyl-4-pregnen-3-one (**5**) (m.p. 167–169°, $[\alpha]^{26}D$ −5.7°) was dissolved with stirring in 360 ml. of *t*-butyl alcohol containing 7 g. of potassium. The mixture was stirred for 5 hr. in a nitrogen atmosphere and then 30 ml. of methyl iodide was added. Stirring under nitrogen was continued for 10 min. and the mixture stored at room temperature for 16 hr. After dilution with 300 ml. of water, the excess methyl iodide was removed *in vacuo*. Further dilution with water followed by extraction with ether gave 12.31 g. (96%) of crude **6**, m.p. 144–155°, no selective absorption in the ultraviolet. The mass spectrum[17] showed a strong parent peak at m/e = 428 corresponding to $C_{28}H_{44}O_3$.

A 1.5-g. portion was chromatographed over 30 g. of silica gel (column prepared in benzene). The fractions eluted with benzene–ethyl acetate (19:1) were crystallized from hexane–acetone to give the sample for analysis, 906 mg., m.p. 190–191°, $[\alpha]^{25}D$ −78.8°; λ_{max}^{KBr} 5.86, 6.82, 6.91, 7.26, 7.87, 8.25, 8.45, 9.12, 9.25, 9.66, 9.92, and 11.52 μ, no selective absorption in the ultraviolet. The mass spectrum[17] again showed the strong parent peak at m/e = 428.

Anal. Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.22; H, 10.32.

4,4,6,16α-Tetramethyl-5-pregnene-17α,20β-diol-3-one (7). A suspension of 10.0 g. of **6** in 350 ml. of acetic acid and 200 ml. of water was heated under reflux for 2 hr. During this time the solid slowly dissolved. The solution was diluted with water and the solid which separated was removed by filtration, washed thoroughly with water, and dried *in vacuo* to give 8.56 g. (93.5%), m.p. 96–107°. Chromatography over silica gel (elution with 9:1 benzene–ethyl acetate) followed by crystallization from methanol (twice) gave the sample for analysis, m.p. 142–143°, $[\alpha]^{23}D$ −41°; λ_{max}^{KBr} 2.85, 5.88, 6.85, 7.22, 9.00, 9.75, 9.98, and 10.23 μ, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 77.27; H, 10.38. Found: C, 77.10; H, 10.51.

4,4,6,16α-Tetramethyl-5-pregnen-17α-ol-3,20-dione (4b). A solution of 300 mg. of the 17α,20β-diol (**7**) in 40 ml. of acetone was cooled to 10° and dry nitrogen passed through the solution for several minutes. Then under a nitrogen atmosphere, 0.3 ml. of 8 *N* chromic acid reagent (5.4 g. of chromium trioxide, 18 ml. of water, and 4 ml. of concentrated sulfuric acid) was quickly added and the mixture stirred for 3 min. The excess oxidizing agent was destroyed by quickly adding a slurry of 400 mg. of sodium bisulfite in 7 ml. of water. After 1 min. additional, the mixture was poured into ice–water and the product extracted with ether. The extracts were washed with water, dried, and evaporated to dryness *in vacuo* to give 285 mg. (95.5%) of crude **4b**, m.p. 177–180°. Recrystallization from hexane–acetone gave 208 mg. (69.7%), m.p. 181–182°, $[\alpha]^{28}D$ −73°, no selective absorption in the ultraviolet, λ_{max}^{KBr} 2.87, 3.00, 5.94, 6.05, and 6.19 μ.[18] The mass spectrum[17] showed a strong peak at m/e = 386 corresponding to 4,4,6,16α-tetramethyl-5-pregnen-17α-ol-3,20-dione (**4b**).

Anal. Calcd. for $C_{25}H_{38}O_3 \cdot H_2O$: C, 74.21; H, 9.97. Found: C, 74.27; H, 9.85.[18]

Chromatography of the mother liquors of the preceding sample gave a small amount of additional material. The presence of a small amount of 4,4,6,16α-tetramethyl-5-androstene-3,17-dione was also indicated by infrared analysis.

Acknowledgments.—The authors wish to thank Mr. Robert D. Fisher and Mr. Harold M. Boyd and their associates for determination of the ultraviolet and rotational data, and Dr. L. E. Peterson and Mr. L. G. Hickman for the mass spectrographic analyses.

(17) For a description of the apparatus and procedures used for the mass spectrographic analyses, see L. Peterson, *Anal. Chem.*, **34**, 1781 (1962).

(18) The infrared spectrum together with the analysis indicate that this material is the 3-ketone hydrate. This same phenomenon has been noted by others in the 4,4-difluoro series. See E. V. Jensen, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960, p. 25M; also S. Nakanishi, unpublished work on 4,4-difluoro-19-nor-5-androsten-3-ones.