[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

Synthesis of 7-Methyl Steroid Hormones. I. 7β-Methylprogesterone

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The synthesis of 7β-methylprogesterone is described, starting from 7-keto-5-pregnene-3β,20β-diol diacetate.

In recent years, nuclear alkylated homologs of steroid hormones have been described, bearing methyl groups at the 1-,[1,2] 2-,[3,4] 4-,[5] 6-,[6,7a,7b] 11-,[8,9] 14-,[10a,10b,11] 16-[12–14a,14b] and 17-[15] positions.

In view of the interesting physiological activity shown by some of these substances,[16] we essayed the synthesis of 7-alkylated steroids, among them 7β-methylprogesterone (V), the subject of this paper.

The work stems from the observation made in 1937 by both Heilbron[17] and Kharasch[18] that 7-ketocholesterol when treated with Grignard reagent, furnished the Δ^5-7-alkyl-7-hydroxy compound in good yield. These workers also described the dehydration of this system, leading to a conjugated diene, the ultraviolet absorption (λ_{max} 236 mμ)[18] of which precluded a 5,7-diene and suggested the 7-methylene-Δ^5-system. An obvious route to 7-methylprogesterone, therefore, would start from 7-keto-5-pregnene-3β,20β-diol diacetate (I).[19]

When this 7-ketone I was treated with methylmagnesium iodide or, preferably, lithium methyl in ether–tetrahydrofuran mixtures, a crystalline methyl triol resulted, showing no selective ultraviolet absorption between 220 and 350 mμ. This compound is formulated as 7α-methyl-5-pregnene-3β,7β,20β-triol (II). The 7α-configuration for the methyl group is assigned on the following grounds.

First, this compound is the major reaction product (69% yield) and the general rule of preferred attack from the α-face[20] would favor this assignment. Further support stems from the fact that dehydration of the methyl triol-diacetate with phosphorus oxychloride in pyridine at room temperature, followed by saponification gives, in fair yield, the 7-methylene compound (III). The structure of the latter follows from its ultraviolet absorption (λ_{max} 237 mμ,ε 20,000) and infrared (6.03, 6.19 μ) spectra, and from its formation when 7-keto-5-pregnene-3β,20β-diol-diacetate (I) was subjected to the Wittig reaction[21,22] followed by alkaline hydrolysis.

Now if the methyl group in the methyl triol II were equatorially disposed (7β) then a *trans* diaxial relationship would exist between the 7α-hydroxyl group and the hydrogen at C(8), a relationship known to favor smooth elimination.[23] The 7α-methyl-7β-hydroxy-Δ^5- system, however, would be expected to yield an exocyclic methylene group on dehydration, since the hydroxyl can now only achieve a suitable coplanar *trans* relationship with a hydrogen from the methyl group.[24]

The conjugated diene III, on hydrogenation in ethanol with palladium–charcoal catalyst, rapidly absorbed 1 mole of hydrogen to yield a compound which had no selective ultraviolet absorption, and gave a positive tetranitromethane test. This compound is formulated as 7β-methyl-5-pregnene-3β,20β-diol (IV) on the bases of preferred hydrogenation from the α-face and molecular rotation data. The molecular rotation increments associated with 7α-and 7β-substitution in 5-allo and

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(16) See A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. and Pharmacol.*, **9**, 929 (1957), who describe the activity of 6α-methylethisterones. These authors found that (administered orally, and using the McPhail–Clauberg test) 6α-methylethisterone was six times as active as ethisterone, while 6α,21-dimethylethisterone showed eleven times the activity of ethisterone. Even more striking were the data presented recently by Hogg and co-workers (see ref. 7b) showing that 6α-methyl-17α-acetoxyprogesterone possesses fifty to sixty times the activity of progesterone (subcutaneous administration in the McPhail–Clauberg test) and one hundred to three hundred times the activity of ethisterone when administered orally (again in the McPhail–Clauberg test).

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(22) F. Sondheimer and R. Mechoulam, THIS JOURNAL, **79**, 5029 (1957), describe the conversion of a Δ^5-7-ketone to the $\Delta^{5,7}$-7-methylene compound by the Wittig reaction.

(23) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(24) *Cf.* D. H. R. Barton, A. S. Campos-Neves and R. C. Cookson, *ibid.*, 3500 (1956); see also E. J. Corey and R. R. Sauers, THIS JOURNAL, **79**, 3925 (1957).

Δ^5-compounds have recently been tabulated by Shoppee, *et al.*[25]

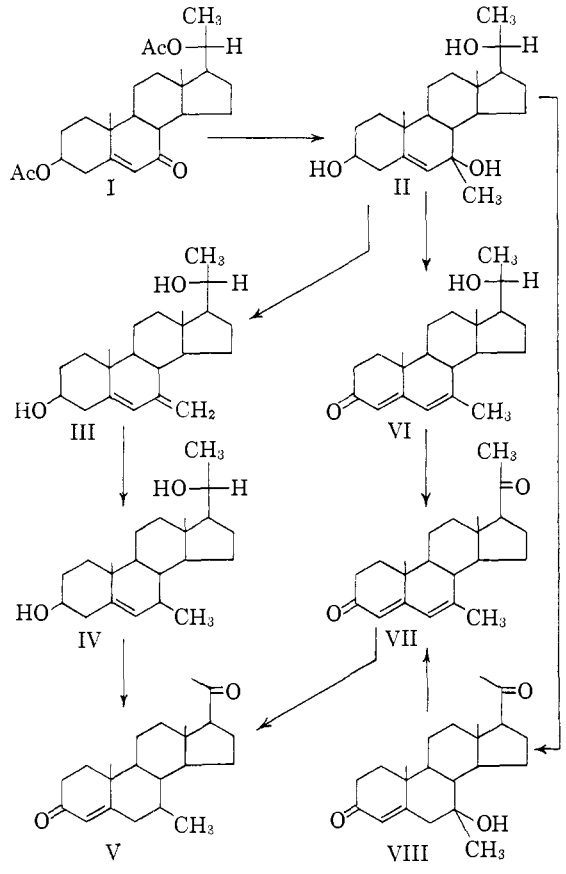
The figures indicate that when the groups OH, OAc, NH_2 and NHAc are introduced at the 7α-position a large negative [M]D increment results, whereas such groups, when introduced as 7β-substituents, cause a large positive [M]D increment. The molecular rotation difference between our 7-methyl-5-pregnene-3β,20β-diol and 5-pregnene-3β,20β-diol is +121°, while the Δ[M]D values associated with the introduction of 7α- and 7β-hydroxyl groups into cholesterol are, respectively, −231° and +180°.

Finally, Oppenauer oxidation of 7β-methyl-5-pregnene-3β,20β-diol (IV), followed by oxidation of the resulting crude 7β-methyl-4-pregnene-20β-ol-3-one with the chromium trioxide–sulfuric acid reagent[26] led, in modest yield, to 7β-methylprogesterone (V).

An alternative route to V involved the following reaction sequence. When 7α-methyl-5-pregnene-3β,7β,20β-triol (II) underwent the Oppenauer oxidation, a compound showing λ_{max} 297 (ε 28,000) was formed. We formulate this substance as 7-methyl-4,6-pregnadiene-20β-ol-3-one (VI) on the bases of its ultraviolet and infrared spectra and subsequent reactions. Small quantities of another substance showing the same ultraviolet absorption spectrum, but less polar (as evidenced by paper chromatography) were also formed in this reaction. This latter material proved to be the 20-ketone VII corresponding to VI, and was obtained in good yield by chromic acid oxidation of the 20β-ol (VI).

In passing it should be noted that the 7α-methyl-7β-hydroxy-Δ^4-3-ketone system was not present in the Oppenauer product because of the lack of ultraviolet absorption maxima in the 240 mμ region. This is not surprising since such a system if formed, would be expected to yield the $\Delta^{4,6}$-diene-3-one under acidic or basic conditions, without difficulty. Indeed, 7α-methyl-7β-hydroxyprogesterone (VIII), prepared directly from 7α-methyl-5-pregnene-3β,7β,20β-triol (II) by microbiological oxidation using *Flavobacterium dehydrogenans*,[27,28] was smoothly converted to 7-methyl-4,6-pregnadiene-3,20-dione (VII) on treatment with perchloric acid in methanol or with alcoholic alkali. The ultraviolet (λ_{max} 244 mμ) and infrared spectra of 7α-methyl-7β-hydroxyprogesterone (VIII) are fully in accord with the proposed structure.

Finally, hydrogenation of 7-methyl-4,6-pregnadiene-3,20-dione (VIII) in benzene with palladium–strontium carbonate catalyst[29] until one mole of hydrogen was absorbed gave in poor yield, after chromatography, 7β-methylprogesterone (V) identified by melting point, mixed melting point and paper chromatographic behavior when compared with a sample prepared by the first route described above.



After this paper was submitted, two articles appeared (R. A. Sneen, THIS JOURNAL, **80**, 3971, 3982 (1958)) assigning a 6β-orientation to the 6-alkyl (and aryl) substituents in a series of compounds prepared by the action of Grignard reagents on cholestan-3β-ol-6-one acetate. These assignments were made largely on the basis of an unpublished method of molecular rotation analysis. Pending a full description of this method, we shall continue to assign the 7α-configuration to the methyl group in compounds II and VIII.

Experimental[30]

7α-Methyl-5-pregnene-3β,7β,20β-triol (II).—To an ethereal solution of lithium methyl (from 2.29 g. of lithium and 9.4 ml. of methyl iodide, in 200 ml. of ether) was added dropwise, with stirring, a solution of 5-pregnene-3β,20β-diol-7-one-3-20-diacetate (I, 2.08 g.) in tetrahydrofuran (60 ml.) during a period of 20 minutes, and under nitrogen. The stirred reaction mixture was left at 25° for 12 hours under nitrogen and was then cautiously added to iced 5% ammonium sulfate solution (400 ml.). After 8 hours at room temperature the mixture was extracted three times with methylene chloride, the combined extracts washed with water and evaporated *in vacuo*. The gelatinous residue (1.7 g.) was chromatographed on Florisil, the benzene–ether (1:2) eluates giving the **7α-methyltriol II** (1.4 g.) as prisms (from ethyl acetate–methanol), m.p. 186–189°, $[\alpha]_D$ −56°, λ_{max}^{Nujol} 3.0 μ.

Anal. Calcd. for $C_{22}H_{36}O_3$ (348.5): C, 75.81; H, 10.41. Found: C, 76.10; H, 10.16.

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(30) Melting points were obtained on the Kofler block, unless otherwise stated. Rotations were measured at 25° in dioxane solution, and at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corporation, for measurement of ultraviolet and infrared spectra and rotations. Microanalyses were performed by Mr. Conner (Microanalytical Laboratory, Schering Corporation) and the Schwarzkopf Microanalytical Laboratory, Woodside, L. I.

7-Methylene-5-pregnene-3β,20β-diol (III). (A).—The above 7α-methyl-5-pregnene-3β,7β,20β-triol (II, 6.0 g.) was acetylated (pyridine and acetic anhydride at steam-bath temperature for 1 hour) and the crude product was dissolved in pyridine (300 ml.) and phosphorus oxychloride (9 ml.) and left at 25° for 53 hours. The reaction mixture was then poured into ice and water, and the crude product (isolated by methylene chloride extraction in the usual manner) was saponified by refluxing 10% methanolic potassium hydroxide solution (0.5 hour). Chromatography on Florisil furnished, in the benzene–ether eluates, 1.74 g. of 7-methylene-5-pregnene-3β-20β-diol (III) as prisms (from ethyl acetate), m.p. 202–205°, $[\alpha]D$ −251°, λ_{max}^{MeOH} 237 mμ (ε 20,000); λ_{max}^{Nujol} 3.03, 6.03, 6.19 μ.

Anal. Calcd. for $C_{22}H_{34}O_2$ (330.5): C, 79.95; H, 10.37. Found: C, 79.70; H, 9.98.

B.—To a stirred ethereal solution of *n*-butyllithium (prepared from 1.4 g. of lithium and 10.6 ml. of *n*-butyl chloride in 140 ml. of ether) was added triphenylmethylphosphonium bromide (35.4 g.), under nitrogen, and the suspension was stirred for 8 hours at room temperature. A solution of 5-pregnene-3β,20β-diol-7-one-3,20-diacetate (I, 8.0 g.) in tetrahydrofuran (120 ml.) was then added, and the mixture was stirred under nitrogen for 17 hours. Ice and water were added and the steroid isolated by ether extraction. The resulting oil was chromatographed on Florisil, elution with benzene–ether (4:1) affording the 7-methylene compound (II, 296 mg.) as prisms (from ethyl acetate), m.p. 200–206° (m.p. undepressed on admixture with III (obtained in A above); λ_{max}^{MeOH} 237 (ε 20,000).

7β-Methyl-5-pregnene-3β,20β-diol (IV).—The 7-methylene compound III (2.97 g.) was hydrogenated in ethanol (150 ml.) using palladium-on-charcoal (5%, 900 mg.) as catalyst at 25°. The reaction was stopped as soon as 1 mole of hydrogen had been taken up (4 minutes) and the crude product was chromatographed on Florisil. The benzene–ether eluates gave, after crystallization from acetone–hexane, 7β-methyl-5-pregnene-3β,20β-diol (IV, 1.81 g.) as needles, m.p. 170–173°, $[\alpha]D$ −25°, λ_{max}^{Nujol} 3.1 μ.

Anal. Calcd. for $C_{22}H_{36}O_3$ (332.5): C, 79.46; H, 10.92. Found: C, 79.32; H, 11.29.

7β-Methylprogesterone (V). A.—7β-Methyl-5-pregnene-3β,20β-diol (IV, 500 mg.) in cyclohexanone (7.5 ml.) was added dropwise under nitrogen to a refluxing mixture of toluene (50 ml.) and cyclohexanone (5 ml.) from which 5 ml. had been distilled previously. Aluminum isopropoxide (1.0 g.) in toluene (10 ml.) was then added dropwise over 25 minutes, while 12 ml. of the reaction mixture was removed by distillation. The mixture was then refluxed for 3.5 hours under nitrogen, and then steam distilled until the organic solvents had been removed. After acidification with 2 *N* hydrochloric acid, the mixture was extracted with ether, and the combined ethereal extracts washed successively with 2 *N* hydrochloric acid and water, then dried over sodium sulfate. Evaporation *in vacuo* yielded an oil (490 mg.) showing λ_{max}^{MeOH} 241 mμ (ε 9,500). This material was dissolved in acetone (40 ml.) cooled to 10°, and chromium trioxide–sulfuric acid reagent[26] (0.4 ml.) added dropwise. After 0.5 hour at 25°, methanol was added to the mixture followed by a large quantity of water. Isolation of the product with ether, followed by chromatography on Florisil furnished in the benzene–ether eluates, 7β-methylprogesterone (V, 130 mg.) as prisms from acetone–hexane, m.p. 94–97°, $[\alpha]D$ +123°, λ_{max}^{MeOH} 242 mμ (ε 16,500); λ_{max}^{Nujol} 5.87, 6.03, 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$ (328.5): C, 80.44; H, 9.83. Found: C, 80.79; H, 10.00.

B.—7-Methyl-4,6-pregnadiene-3,20-dione (VII, 33 mg.) was hydrogenated in benzene solution (5 ml.), using palladium-on-strontium carbonate catalyst (16 mg.), at room temperature, until 1 mole of hydrogen was absorbed. Chromatography of the crude product (showing λ_{max}^{MeOH} 241, 296; ε 9,300, 6000) on Florisil gave in the benzene-ether (4:1) eluates, a solid, m.p. 90–94° (m.p. undepressed on admixture with an authentic specimen of V prepared by route A above). On paper chromatography in the propylene glycol–ligroin system the material migrated as one spot, at the same rate as authentic V.

7-Methyl-4,6-pregnadien-20β-ol-3-one (VI).—A mixture of toluene (220 ml.) and cyclohexanone (20 ml.) was distilled until 20 ml. had been removed. To this refluxing mixture, under nitrogen, was then added 7α-methyl-5-pregnene-3β,7β,20β-triol (II, 2.20 g.) in cyclohexanone (30 ml.) followed by aluminum isopropoxide (4.40 g.) in toluene (40 ml.). The latter was added dropwise over 30 minutes, while 50 ml. was distilled from the reaction mixture. After 3.5 hours reflux under nitrogen, the mixture was steam distilled, acidified with 2 *N* hydrochloric acid and the steroid isolated with ether in the usual manner. Chromatography over Florisil, and elution with benzene–ether mixtures gave 7-methyl-4,6-pregnadien-20β-ol-3-one (VI, 650 mg.) as prisms from acetone–hexane, m.p. 174–176° (Fisher–Johns block), $[\alpha]D$ +194°, λ_{max}^{MeOH} 297 mμ (ε 28,000); λ_{max}^{Nujol} 2.93, 6.08, 6.21, 6.33 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$ (328.5): C, 80.44; H, 9.83. Found: C, 80.57; H, 9.72.

7-Methyl-4,6-pregnadiene-3,20-dione (VII). A.—A solution of 7-methyl-4,6-pregnadien-20β-ol-3-one (VI, 600 mg.) in acetone (40 ml.) was cooled to 10°, and chromium trioxide–sulfuric acid reagent[26] (0.8 ml.) was added dropwise with shaking. After 0.5 hour at 25°, methanol was added, then water, and the steroid was isolated by ether extraction. Chromatography on Florisil yielded, in the benzene–ether (9:1) eluates, 7-methyl-4,6-pregnadiene-3,20-dione (VII, 402 mg.), flat needles (from acetone-hexane), m.p. 112–113° (Fisher–Johns block), $[\alpha]D$ +319°, λ_{max}^{MeOH} 297 mμ (ε 28,000); λ_{max}^{Nujol} 5.85, 6.03, 6.20, 6.27 μ.

Anal. Calcd. for $C_{22}H_{30}O_2$ (326.5): C, 80.93; H, 9.26. Found: C, 80.68; H, 9.45.

B.—A solution of 7α-methyl-7β-hydroxyprogesterone (VIII, 20 mg.) in methanol (2 ml.), containing 2 drops of 70% perchloric acid, was left at 25° for 17 hours. Water was added and the product (isolated with ether) crystallized on trituration with hexane, m.p. 108–110° (m.p. undepressed on admixture with an authentic specimen of VII prepared as in A, λ_{max}^{MeOH} 296 mμ (ε 28,000). On paper chromatography, in the propylene glycol–ligroin system, this material migrated as one spot, at the same rate as authentic VII.

7α-Methyl-7β-hydroxyprogesterone (VIII).—*Flavobacterium dehydrogenans* was grown in a 1% Difco yeast buffered solution (10 g. of Difco yeast, 4.68 g. of $Na_2HPO_4 \cdot 7H_2O$ and 4.48 g. of KH_2PO_4 per liter) with shaking and light for 20 hours. The methyltriol II (1.0 g.) in methanol (40 ml.) was added, and the transformation was allowed to proceed for 44 hours, with shaking and light. Extractions with ethyl acetate and evaporation of the dried (Na_2SO_4) solution yielded an oil.

Chromatography on Florisil gave, on elution with benzene-ether mixtures, 7α-methyl-7β-hydroxyprogesterone (VIII, 350 mg.) as prisms (from acetone–hexane), m.p. 154–157°, $[\alpha]D$ +121°, λ_{max}^{MeOH} 244 mμ (ε 15,700); λ_{max}^{Nujol} 2.92, 5.8, 5.99, 6.18 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$ (344.5): C, 76.70; H, 9.36. Found: C, 76.96; H, 9.06.

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