6,16-Dimethylated Steroids. III. Synthesis of 21-Substituted 6,16α-Dimethyl-17α-hydroxyprogesterones[1]

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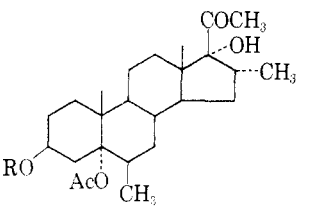
The preparation of several 21-fluoro-6,16α-dimethyl-17α-hydroxyprogesterones is described. In addition, facile syntheses of both 6α,16α- and 6β,16α-dimethyl Reichstein's Substance S acetates (**4a** and **b**) are presented. Both 21-fluoro-6α,16α-dimethyl-17α-acetoxyprogesterone (**3b**) and its 6-dehydro analog (**3d**) showed marked potency in the oral Clauberg assay for progestational activity.

In earlier papers of this series, the synthesis of various 6,16α-dimethylprogesterones[2,3] and 6,16α-dimethyl-17α-hydroxyprogesterones[4] was described. The former demonstrated the validity of the hypothesis that 6,16-dimethyl substitution of the progesterone nucleus greatly enhanced oral progestational activity as determined by the Clauberg assay. The latter series constituted one of the most active groups of orally active compounds known to date.

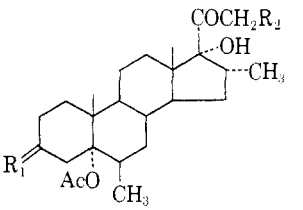
The work described presently is an extension of this series of compounds to include several 21-substituted analogs. A number of reports have been issued describing various 21-fluorinated progesterones which in preliminary tests showed potent biological activity.[5] Particularly active was the 21-fluoro-6-methyl-6-dehydro-17α-acetoxyprogesterone. Thus, in view of the availability of 6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one 3-monoacetate (**1a**) from our work on 6,16α-dimethyl-17α-hydroxyprogesterone,[3,4] it seemed of interest to prepare several 21-fluoro-6,16α-dimethyl-17α-acyloxyprogesterones.

Direct iodination of the dimethyltriolone 3-monoacetate (**1a**)[4] at C-21 proceeded in nearly quantitative yield by the excellent procedure of Rothman, *et al.*[6] The crude 21-iodo compound (**2a**) was notably unstable and was generally carried on to the next step immediately. In contrast, purified crystalline material stored at 0° retained stability for periods up to 2 months. Iodination of the dimethyltriolone 3,5-diacetate (**1b**) led unexpectedly to the same product (**2a**), loss of the readily hydrolyzed 3-ester function presumably having occurred by methanolysis catalyzed by the calcium oxide present in the reaction mixture.

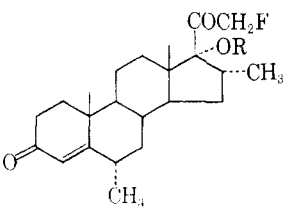
Replacement of the 21-iodine by fluorine was accomplished by the procedures described by Dodson, *et al.*[5] As reported by the Searle group, it was observed that replacement of 21-iodine by fluorine in 17α-hydroxy-20-ketosteroids was always accompanied by formation of small amounts of the 17α,21-oxide.



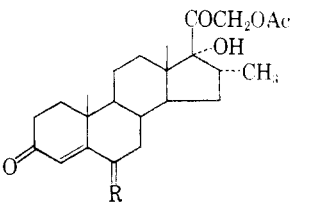
1a, R = H
b, R = Ac



2a, R_1 = 17α-OH; R_2 = I
b, R_1 = 17α-OH; R_2 = F
c, R_1 = 17α-OAc; R_2 = F
d, R_1 = =O; R_2 = F
e, R_1 = 17α-OH; R_2 = OAc
f, R_1 = =O; R_2 = OAc



3a, R = H
b, R = Ac
c, R = H, 6-dehydro
d, R = Ac, 6-dehydro



4a, R = 6α-H
b, R = 6β-CH_3

Separation of the desired 21-fluorinated dimethyltriolone 3-monoacetate (**2b**) was readily accomplished, however, by chromatography over Florisil.

Oxidation of **2b** with 8 *N* chromic acid–sulfuric acid in acetone[7] provided the 3-ketone (**2d**). Treatment with hydrochloric acid in absolute ethanol[8] readily eliminated acetic acid and effected epimerization of the 6β-methyl group to the more stable α-configuration to give 21-fluoro-6α,16α-dimethyl-17α-hydroxyprogesterone (**3a**).

Acetylation of the 17α-hydroxyl in the usual manner[9] afforded the 17α-acetate (**3b**). Dehydrogenation of **3a** with chloranil in *t*-butyl alcohol[10] gave the 6-dehydro

(1) Previous paper of the series: R. P. Graber, M. B. Meyers, L. G. Hickman, E. H. Borgerhoff, and A. D. Odell, *J. Med. Chem.*, **7**, 540 (1964).

(2) R. P. Graber and M. B. Meyers, *Chem. Ind.* (London), 1478 (1960).

(3) R. P. Graber, M. B. Meyers, and V. A. Lamberson, *J. Org. Chem.*, **27**, 2534 (1962).

(4) R. P. Graber and M. B. Meyers, *ibid.*, **26**, 1774 (1961); see also ref. 1.

(5) P. Tamhanser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956); R. L. Elton, *Proc. Soc. Exptl. Biol. Med.*, **101**, 677 (1959); R. L. Elton, R. A. Edgren, and D. W. Calhoun, *ibid.*, **103**, 175 (1960); C. G. Bergstrom, P. B. Sollmann, B. T. Nicholson, and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 2322 (1960).

(6) E. S. Rothman, T. Perlstein, and M. E. Wall, *J. Org. Chem.*, **25**, 1993 (1960); see also H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, **80**, 250 (1958); G. Stork, H. J. Ringold, F. Sondheimer, and G. Rosenkranz, U. S. Patent 2,874,154 (1959); *cf.* Syntex Corp., British Patent 778,858 (1957).

(7) 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).

(8) D. Burn, G. Cooley, V. Petrow, and G. O. Weston, *ibid.*, 3808 (1959).

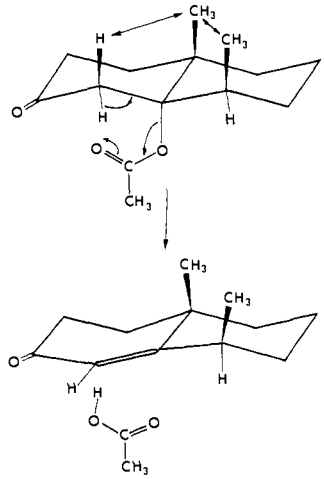
(9) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 4220 (1952); **75**, 3489 (1953); Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *ibid.*, **74**, 5394 (1952).

(10) E. J. Agnello and G. D. Laubach, *ibid.*, **82**, 4293 (1960).

compound (**3c**) which in turn was converted to its 17α-acetate (**3d**).

Replacement of the 21-iodine of **2a** by acetate proceeded smoothly by the triethylamine–acetic acid procedure of Rothman, *et al.*,[6] to give 6β,16α-dimethylpregnane-3β,5α,17α,21-tetrol-20-one 5,21-diacetate (**2e**). Oxidation with 8 *N* chromic acid in acetone[7] afforded the 3-ketone (**2f**). Treatment of **2f** with hydrochloric acid in absolute ethanol[8] or better with hydrogen chloride in chloroform effected elimination of the 5-acetoxyl group and epimerization of the 6β-methyl to the α-configuration to afford 6α,16α-dimethyl Reichstein's Substance S acetate[11] (6α,16α-dimethyl-4-pregnene-17α,21-diol-3,20-dione 21-acetate) (**4a**). This substance has been hydroxylated microbiologically[11a,d] at C-11 to provide 6α,16α-dimethylhydrocortisone, one of the most potent corticoid analogs known to date.[11a]

The previously unknown 6β,16α-dimethyl Substance S acetate (**4b**) was prepared in high yield from **2f** by thermal elimination of acetic acid *in vacuo* under mild conditions. This elimination is undoubtedly a *cis* elimination involving the C_4-α hydrogen atom and would appear to be assisted by 1,3-diaxial interaction between the C_4-β hydrogen and the C_{10} methyl group as well as by the release of 1,3-diaxial interaction between the methyls at C_{10} and C_6-β as they assume pseudo-axial configuration α to the double bond in the product.



Preliminary biological evaluation by the Clauberg method in estrogen-primed rabbits[12] showed that 21-fluoro-6α,16α-dimethyl-17α-acetoxyprogesterone (**3b**) had *ca.* 25 times the oral progestational activity of ethisterone. The 6-dehydro-17α-acetoxy compound (**3d**) showed *ca.* 100 times the oral activity of ethisterone. Thus, in these preliminary assays, the 21-fluoro analogs show somewhat less activity than the corresponding unfluorinated compounds.[4]

Experimental[13]

21-Iodo-6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one 5-Acetate (2a). A. From the 5-Monoacetate (1a).—To a solution of 64.35 g. of **1a** and 3.53 g. of azobisisobutyronitrile in 635 ml. of purified tetrahydrofuran and 320 ml. of methanol was added 111 g. of powdered calcium oxide. This mixture was stirred and a solution of 69.7 g. of iodine in 320 ml. of tetrahydrofuran and 195 ml. of methanol added in portions. The temperature of the reaction mixture was maintained at *ca.* 25° by means of a cooling bath; the mixture was also protected from exposure to direct light.[14]

The iodination reaction was initiated by addition of sufficient iodine solution to produce a distinct brown coloration. The mixture was allowed to stir until iodine absorption had definitely begun as evidenced by partial decolorization. (In various runs, this induction period ranged from a few minutes to 1 hr. or more.) Then the remainder of the iodine solution was added dropwise at a rate such that a slight excess of iodine was always present; this portion of the addition required 2.25 hr. The red-brown mixture was allowed to stir 1 additional hr. and then filtered through a bed of Supercel to remove the calcium oxide. The residue on the filter was washed several times with small portions of 2:1 tetrahydrofuran–methanol.

The clear, red-brown filtrate was stirred and 5% aqueous sodium thiosulfate solution added until the iodine color was discharged. After further dilution with 3.0 l. of water, the product was extracted with three 500-ml. portions of ethyl acetate. The extracts were combined, washed with 150-ml. portions of 5% aqueous sodium thiosulfate solution and saturated sodium chloride solution (twice), dried, and concentrated *in vacuo* (below 30°). As the concentration proceeded, a crystalline solid separated. The concentration was stopped at a residual volume of *ca.* 75 ml., and the slurry was cooled briefly in an ice bath and filtered. The product was washed once with a small volume of ethyl acetate and dried *in vacuo* at room temperature, 57.37 g., m.p. 156° dec.[15]; $\lambda_{max}^{CCl_4}$ 2.74, 2.83, 5.72 (sh), 5.77, 5.83, and 7.97 μ (IR-4).

B. From the 3,5-Diacetate (1b).—A 0.464-g. sample of **1b** was dissolved in a mixture of 3.4 ml. of purified tetrahydrofuran and 2.7 ml. of methanol. Calcium oxide (1.03 g.) and azobisisobutyronitrile (30 mg.) were added and the suspension was stirred under illumination from a 60-w. blue tungsten filament bulb.[14] A solution of 0.525 g. of iodine in 2.7 ml. of tetrahydrofuran and 1.7 ml. of methanol was then added dropwise. Initially, 4 drops of the iodine solution was added and the mixture allowed to stir at room temperature for 15 min. until definite absorption of iodine was apparent. The remainder of the solution was then added dropwise over a 33-min. period. After stirring for an additional 32 min., the mixture was filtered to remove the calcium oxide which was rinsed several times with *ca.* 1:1 tetrahydrofuran–methanol. The filtration flask contained 20 ml. of 5% aqueous sodium thiosulfate solution and the filtrate was immediately decolorized. The colorless solution was extracted 3 times with ethyl acetate; the extracts were washed with saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* at 20–25° to give a foam, 0.527 g. (96%). The infrared spectrum of this material was superimposable with that prepared by iodination of the 5-monoacetate (**1a**). For further proof that this material had indeed suffered hydrolysis of the 3-ester function, the 0.527-g. sample above was carried on to the 21-acetoxy compound (*vide infra* under preparation of **2c**).

21-Fluoro-6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one 5-Acetate (2b).—A 10.76-g. sample of crude **2a** (prepared from 9.10 g. of **1a**) was dissolved in 500 ml. of acetonitrile, and 10.0 g. of silver fluoride (Harshaw Chemical Co.) was added. The mixture was heated under reflux for 80 min., then cooled, and filtered through a layer of Supercel. The filtrate was evaporated to a small volume *in vacuo*, diluted with 500 ml. of ethyl acetate, and refiltered through Supercel. This filtrate was evaporated

(11) (a) W. F. Schneider and H. C. Murray, *Chem. Ind.* (London), 1163 (1960); (b) J. Iriarte and M. L. Franco, *J. Org. Chem.*, **26**, 2047 (1961); (c) M. Sletzinger, U. S. Patent 2,929,815 (1950); (d) M. Sletzinger and W. A. M. Sletzinger, U. S. Patent 2,929,815 (1960); (d) M. Sletzinger and W. A. Gaines, U. S. Patent 2,940,968 (1960); (e) F. H. Lincoln and W. P. Schneider, U. S. Patent 3,030,360 (1962).

(12) Bioassays performed by Endocrine Laboratories, Madison 1, Wis.

(13) Unless otherwise specified, melting points are capillary melting points taken on a Hershberg apparatus and are corrected, rotations were observed in chloroform at *ca.* 1% concentration, ultraviolet spectra were determined in 95% ethanol, and infrared spectra were determined using a Beckman Model IR-5 spectrophotometer. Solvent extracts were dried routinely by filtration through anhydrous magnesium sulfate.

(14) In the early work, the iodination was carried as described above but under illumination from a tungsten filament bulb. Later comparison runs however, showed that not only was illumination not necessary but that it was, in fact, detrimental.

(15) Various attempts were made to prepare a sample of **2a** for analysis. Sharp melting samples were obtained with melting points ranging from 115–116.5° dec. to 156° dec. Analytical data were low in C and H and high in I.

to dryness *in vacuo* to give an amorphous product, 8.74 g.; $\lambda_{max}^{CCl_4}$ 2.77, 2.85, 5.51, 5.78, and 8.07 μ.

The **21-fluoro 3,5-diacetate (2c)** was prepared by acetylation of a portion of crude material from another run carried out exactly as above. The acetylation was performed in the usual manner with acetic anhydride and pyridine and the product chromatographed over neutral alumina. The material eluted with 9:1 benzene–ether was recrystallized twice from ether–Skellysolve B, m.p. 203–207°; $[\alpha]^{25}D$ +6.0°; λ_{max}^{KBr} 2.93, 5.78, 5.85, 7.88, and 8.04 μ.

Anal. Calcd. for $C_{27}H_{41}FO_6$: C, 67.47; H, 8.60. Found: C, 67.45, 67.61; H, 8.71, 8.78.

The earlier fractions from the chromatogram showed λ_{max}^{KBr} 5.50, 5.80, and 8.05 μ, and probably represented the **17α,21-oxido 20-ketone structure** related to **2c**. This material was not further investigated.

21-Fluoro-6α,16α-dimethyl-17α-hydroxyprogesterone (3a). A. Oxidation of the 21-Fluorotriolone 5-Acetate (2b).—The 8.74-g. sample of crude **2b** prepared above was dissolved in 350 ml. of acetone and, with vigorous stirring, 12 ml. of 8 *N* chromic acid solution was added (5.4 g. of chromium trioxide, 18 ml. of water, and 4 ml. of concentrated sulfuric acid). The addition was completed in 55 sec. After 3 min. total time, a slurry of 10 g. of sodium bisulfite in 10 ml. of water was added. The mixture was poured into saturated sodium chloride solution and extracted with ethyl acetate. The combined extracts were washed with water and saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* to give **3d** as an amorphous solid, 8.42 g.; $\lambda_{max}^{CCl_4}$ 2.78, 2.85, 2.92, 5.52, 5.76, 8.10, and 8.23 μ.

A purified sample was prepared by chromatography over neutral alumina and crystallization from ether–Skellysolve B, m.p. 147–150° (microblock); λ_{max}^{KBr} 5.79, 5.83, 7.90, 8.01, and 8.20 μ. After drying *in vacuo* at 96°, this material melted at 188–196°; λ_{max}^{KBr} 5.79, 5.86, 6.03, and 6.23 μ indicating loss of acetic acid to produce the 4-ene-3-one conjugated system.

B. Acid-Catalyzed Elimination of Acetic Acid.—The 8.42 g. of crude **2d** prepared above was dissolved in 400 ml. of absolute ethanol and treated with 2 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for 1 hr., cooled, evaporated *in vacuo* to a small volume, and diluted with 500 ml. of water. The gummy solid was extracted with ethyl acetate and the combined extracts were washed with water and saturated sodium chloride solution. After drying, the solvent was removed *in vacuo* to give an amorphous solid, 6.81 g.; $\lambda_{max}^{CCl_4}$ 2.78, 2.88, 5.52, 5.7, 5.86 (sh), 5.96, and 6.22 μ. This material was chromatographed over Florisil and 500-ml. fractions were taken. The column was developed with 4:1 and 1:1 Skellysolve B–benzene mixtures. These latter fractions gave material which was not further purified but showed $\lambda_{max}^{CCl_4}$ (no hydroxyl) 5.52, 5.96, and 6.22 μ ascribable to **6α,16α-dimethyl-17α,21-oxido-4-pregnene-3,20-dione.**

The material eluted next with 9:1 benzene–ether and 3:1 benzene–ether was combined and crystallized from ether, 2.58 g.; m.p. 197–205°; λ_{max}^{KBr} 5.79, 5.88, 6.05, and 6.24 μ. A sample prepared for analysis by recrystallization from ether melted at 202–208.5°; $[\alpha]D$ +89.8°; λ_{max} 242 mμ (ε 15,750); $\lambda_{max}^{CCl_4}$ 5.77, 5.82, 6.00, and 6.21 μ.

Anal. Calcd. for $C_{23}H_{33}FO_4$: C, 73.37; 8.83. Found: C, 72.77; H, 8.91.

21-Fluoro-6α,16α-dimethyl-17α-hydroxyprogesterone Acetate (3b).—A solution of 1.51 g. of **3a** in 40 ml. of glacial acetic acid and 40 ml. of acetic anhydride was flushed with nitrogen. A solution of 1.2 g. of *p*-toluenesulfonic acid monohydrate in 40 ml. of glacial acetic acid was added with stirring and the mixture stored at room temperature for 18 hr. It was then poured into 1.0 l. of ice water, with stirring, and the product extracted with ethyl acetate. The extracts were washed with water (twice), 5% aqueous sodium bicarbonate solution, and with saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* to give a partially crystalline residue, 1.75 g. This was dissolved in 100 ml. of methanol was flushed with nitrogen, and the solution was treated with 1.5 ml. of concentrated hydrochloric acid in 50 ml. of methanol. After 2.5 hr. at room temperature, 600 ml. of water was added and the gummy precipitate extracted with ethyl acetate. The extracts were washed with water and saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* to give an amorphous residue, 1.68 g.; $\lambda_{max}^{CCl_4}$ (no hydroxyl) 5.76, 5.84, 5.96, 6.21, 7.95, and 8.04 μ.

The product could not be crystallized and was therefore chromatographed over Florisil. The column was developed with mixtures of Skellysolve B–benzene (19:1, 9:1, and 3:1). The material eluted with 1:1 Skellysolve B–benzene and with benzene was combined (593 mg.) and crystallized from methylene chloride–Skellysolve B to give 394 mg. of **3b**; m.p. 177–189.5°; λ_{max} 241 mμ (ε 13,860) and 290 (28200); λ_{max}^{KBr} 5.79, 6.00, 6.23, 6.34 (sh), 7.91, and 8.03 μ. The absorption in the ultraviolet at 290 mμ (confirmed by the shoulder at 6.34 μ in the infrared) indicated the presence of *ca.* 12% of 4,6-dien-3-one (**3d**). A further crystallization from the same solvents raised the melting point to 189–194° but did not change the ultraviolet spectrum materially.

Anal. Calcd. for $C_{25}H_{35}FO_5$: C, 71.74; H, 8.43; F, 4.54. Found: C, 71.45, 71.70; H, 8.05, 8.21; F, 4.60.

21-Fluoro-6,16α-dimethyl-6-dehydro-17α-hydroxyprogesterone (3c).—A solution of 0.460 g. of **3a** in 35 ml. of *t*-butyl alcohol was treated with 1.4 g. of chloranil and the mixture heated under reflux for 4.25 hr. The mixture was cooled to room temperature and filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was taken up in ethyl acetate and the solution washed with water, 5% aqueous sodium hydroxide solution (twice), water (twice), and saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo*, 0.45 g. The infrared spectrum indicated that only about 50% of the product was the 4,6-dien-3-one (**3c**). The product was therefore retreated with 1.4 g. of chloranil in 50 ml. of *t*-butyl alcohol containing 0.5 ml. of glacial acetic acid under reflux for 22.5 hr. Work-up as above gave a solid product, 0.422 g.; λ_{max}^{KBr} 5.77, 5.84 (sh), 6.05, 6.16, and 6.33 μ. Three recrystallizations from Skellysolve B gave 198 mg. of needles, m.p. 213.5–224°; $[\alpha]^{25}D$ +67.8°; λ_{max} 290 mμ (ε 23,600).

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 73.76; H, 8.35; F, 5.07. Found: C, 74.14, 74.06; H, 8.27, 8.34; F, 4.76, 4.83.

21-Fluoro-6,16α-dimethyl-6-dehydro-17α-hydroxyprogesterone Acetate (3d).—A solution of 208 mg. of **3c** in 20 ml. of glacial acetic acid and 10 ml. of acetic anhydride was treated with 0.2 g. of *p*-toluenesulfonic acid monohydrate at room temperature with stirring for 48 hr. The mixture was then poured into 250 ml. of ice water and the product extracted with ethyl acetate. The extracts were washed with water, sodium bicarbonate solution, and sodium chloride solution, dried, and evaporated *in vacuo* to a foam. This material was dissolved in 20 ml. of methanol and treated with 0.2 ml. of concentrated hydrochloric acid for 3.5 hr. at room temperature. Dilution with 200 ml. of water and extraction with ethyl acetate gave 236 mg. of an amorphous product; $\lambda_{max}^{CCl_4}$ 5.76, 5.84, 6.02, 6.14, 7.96 (sh), and 8.06 μ.

The crude product was dissolved in a mixture of Skellysolve B–benzene (1:1) and placed on a column of Florisil. The material eluted with benzene was combined and crystallized from methylene chloride–Skellysolve B, 54 mg., m.p. 207–217° (microblock); $[\alpha]^{25}D$ +16.0°; λ_{max} 291 mμ (ε 23,000); λ_{max}^{KBr} 5.79, 6.02, 6.17, 6.33, 7.91, and 8.03 μ.

Anal. Calcd. for $C_{25}H_{33}FO_5$: C, 72.09; H, 7.99; F, 4.56. Found: C, 72.17; H, 8.14; F, 4.40.

6β,16α-Dimethylpregnane-3β,5α,17α,21-tetrol-20-one 3,21-Diacetate (2e).—A 57.0-g. portion of the crude crystalline 21-iodo compound (**2a**) was dissolved in 585 ml. of acetone. To this solution was added a mixture of 306 ml. of triethylamine and 235 ml. of glacial acetic acid.[16] The resulting mixture was heated under reflux for 65 min., cooled to *ca.* 25°, and poured into 5.3 l. of water with stirring. The semisolid product which separated was extracted with one 500-ml. and three 300-ml. portions of ethyl acetate. The combined extracts were washed with 200-ml. portions of water, 1 *N* aqueous hydrochloric acid, 5% sodium bicarbonate solution (twice), water, and saturated sodium chloride solution, then dried, and evaporated *in vacuo* to *ca.* 75–100 ml. The resulting slurry of crystalline material was cooled briefly to 10° and filtered. The solid product was washed twice with small portions of ethyl acetate and dried *in vacuo*, 35.4 g., m.p. 141–145°; $\lambda_{max}^{CCl_4}$ 2.79, 5.74, 5.79, and 8.11 μ. A second crop was obtained by concentration of the mother liquor, 4.27 g., m.p. 142–154°; the infrared spectrum was substantially identical with that of the first crop.

A sample for analysis was prepared by crystallization from ether–Skellysolve B, needles, m.p. 159–161°; $[\alpha]^{23}D$ +8.6°; λ_{max}^{KBr} 5.71, 5.80, 7.88, 7.98, and 8.11 μ; positive reaction with triphenyltetrazolium chloride.

[16] The preparation of the triethylamine–acetic acid mixture was attended by considerable evolution of heat. It was found best, therefore, to prepare the mixture with external cooling and to cool it to *ca.* 25° before addition to the solution of the 21-iodo compound.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.59, 67.61; H, 9.14, 9.10.

The 0.527-g. sample of **2a** (*vide supra*) prepared by iodination of the 3,5-diacetate (**1b**) was treated with triethylamine–acetic acid in acetone exactly as described above. The crude product was crystallized twice from ether–Skellysolve B, m.p. 161–163°, undepressed on admixture with the material above, m.p. 159–161°. The infrared spectra were substantially identical.

6β,16α-Dimethylpregnane-5α,17α,21-triol-3,20-dione 5,21-Diacetate (2f).—A solution of 35.2 g. of the tetralone (**2e**) (m.p. 141–145°) in 2.1 l. of acetone was stirred vigorously (5.0-l. Morton flask) and cooled to *ca.* 10°. In 30 sec., 42.3 ml. of an 8 *N* chromic acid solution was added. Stirring was continued for an additional 3 min. and then the mixture was quickly diluted with a solution of 58.5 g. of sodium bisulfite in 220 ml. of water. After stirring for another 15 min., the mixture was poured into 7 l. of saturated sodium chloride solution and extracted with ethyl acetate. The combined extracts were washed thoroughly, then dried, and evaporated *in vacuo* to an amorphous solid, 36.3 g. Crystallization from ether–hexane afforded 33.41 g. of the triketone (**2f**), $[\alpha]^{28}D$ +10.5°; λ_{max}^{KBr} 5.74 (sh), 5.79, 5.84 (sh), 7.89 (sh), 8.07, and 8.17 (sh) μ. A sample prepared for analysis by recrystallization from ether–Skellysolve B melted at 90–96° (evolution of gas), resolidifying, and melting again at 112–121° (microblock), $[\alpha]^{27}D$ +9.5°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.13, 68.21; H, 8.66, 8.36.

Other samples showed the following melting point behavior: foaming at *ca.* 95°, melting 136–146°, resolidification above 165°, and final melting at 211–217°. This behavior is undoubtedly due to elimination of acetic acid to form the 6β-methyl-4-en-3-one (**4b**) (*vide infra*).

6α,16α-Dimethyl-4-pregnene-17α,21-diol-3,20-dione 21-Acetate (4a). A. With Hydrochloric Acid in Ethanol.—A solution of 1.10 g. of **2f** in 100 ml. of absolute ethanol was treated with 0.5 ml. of concentrated hydrochloric acid and the mixture heated under reflux for 110 min. After cooling, the solution was concentrated *in vacuo* to a small volume and diluted with water; the oil which separated was extracted with ethyl acetate. The extracts were washed with saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo*, 0.92 g.; $\lambda_{max}^{CCl_4}$ 2.79, 2.88, 5.71, 5.80, 5.86, 5.96, 6.22, 7.89, and 8.13 μ. This crude material appeared to have lost a considerable portion of the 21-ester function on the basis of the infrared spectrum, and was therefore reacetylated with 5.0 ml. of pyridine and 1.0 ml. of acetic anhydride at room temperature overnight. Dilution with water and extraction with ethyl acetate gave an amorphous product containing only slightly more 21-ester material.

The material was therefore chromatographed over 50 g. of neutral alumina.[17] The material brought through with 1:1 benzene–ether and 9:1 ether–acetone was combined (375 mg.) and recrystallized twice from methylene chloride–Skellysolve B to give stubby needles, m.p. 172–175°; $[\alpha]^{28}D$ +95.3° (lit.[11a] m.p. 174–176°; $[\alpha]D$ +100°; λ_{max}^{EtOH} 241 mμ (ε 16,100); lit.[11b] m.p. 191–192°; $[\alpha]D$ +102.5°; λ_{max}^{EtOH} 240–242 mμ (ε 17,000); λ_{max}^{KBr} 2.94, 5.71, 5.81, 6.10, 6.29, and 8.13 μ).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.92, 72.12; H, 8.44, 8.63.

From the earlier fractions of the chromatogram (9:1 Skellysolve B–benzene), a crystalline solid was isolated, $\lambda_{max}^{CCl_4}$ (no hydroxyl bands) 5.86, 5.97, 6.23, 9.08, and 9.42 μ (no bands for acetate ester in the 8.0 μ region). This was not investigated further but very probably was the rearranged product, **21,21-diethoxy-6α,16α-dimethyl-4-pregnene-3,20-dione.**

B. With Hydrogen Chloride in Chloroform.—A solution of 78.7 g. of **2f** in 875 ml. of chloroform was cooled to 10° and gaseous hydrogen chloride passed slowly through the solution for 90 min. with stirring. Stirring was continued for an additional 90 min. while the solution warmed to room temperature. The solution was then washed with 100-ml. portions of water (twice), 5% sodium bicarbonate solution (3 times), water, and saturated sodium chloride solution, dried, and evaporated to dryness *in vacuo* to give a solid, 64.7 g. Crystallization from acetone–hexane afforded a first crop of 44.3 g., m.p. 191.5–193.5°[18]; λ_{max}^{KBr} 5.72, 5.80, 6.04, 6.22, and 8.1 μ. A second crop was obtained by concentration of the mother liquor, 12.20 g., m.p. 188.5–191°. The two crops were combined and crystallized again from acetone–hexane, m.p. 192–194°; $[\alpha]^{29}D$ +97.8°; λ_{max} 242 mμ (ε 16,600); $\lambda_{max}^{CCl_4}$ 2.74, 2.84, 5.69, 5.75, 5.91, 5.97 (sh), 6.20, and 8.09 μ (IR-4).

6β,16α-Dimethyl-4-pregnene-17α,21-diol-3,20-dione 21-Acetate (4b).—A 10.06-g. sample of **2f** was placed in a round-bottomed flask and heated *in vacuo* at *ca.* 0.1 mm. in an oil bath at 136–144° for 45 min. The solid initially melted slowly with gas evolution to a light orange oil. After *ca.* 20–25 min., the oil slowly crystallized to a cream-colored solid. The cake was cooled to room temperature *in vacuo* at 56° for 16 hr., 8.72 g.; m.p. 211–214°; $\lambda_{max}^{CCl_4}$ 2.79, 2.86, 5.71, 5.78, 5.96, 6.22, and 8.13 μ. Recrystallization from acetone gave 5.92 g. (67.3%) of **4b**; m.p. 219–220.5°; $[\alpha]D$ +68.4°[19]; λ_{max} 243 mμ (ε 16,200); $\lambda_{max}^{CCl_4}$ 2.74, 2.83, 5.69, 5.75, 5.92, 5.98 (sh), 6.20, and 8.09 μ (IR-4).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.14, 72.03; H, 8.64, 8.65.

A second crop was obtained by concentration of the mother liquor, 1.19 g., m.p. 216–218.5°, raising the yield to 80.8%.

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(17) See footnote 38 of ref. 1.

(18) A discrepancy in melting points exists among the various publications describing the preparation of this compound. Reference 11a gives m.p. 174–176°, whereas ref. 11b gives m.p. 191–192°. We have observed that our earlier preparations showed the lower m.p. and later preparations the higher m.p.; the lower melting material did not depress the m.p. of the higher melting sample. In fact, remelting the former material after the preparation of the latter showed melting at 178–179°, resolidification, and remelting at 191–195°. These two forms are thus undoubtedly polymorphic modifications of the same substance (**4a**).

(19) The ΔMD for **4a** and **4b** (6α-6β) is +122.5°. The ΔMD for 6α,16α-dimethylprogesterone and its 6β-epimer (6α-6β) is +106°, see ref. 3.