2,2-Dimethyl-4-bromotestosterone Acetate (XIII).—Dibromo compound XII (820 mg.) was heated in boiling γ-collidine (5 ml.) for 40 minutes. The cooled mixture was diluted with ethyl acetate, washed with dilute sulfuric acid and the solution evaporated. Methanol–acetone crystallization of the residue yielded 2,2-dimethyl-4-bromotestosterone acetate (XIII), m.p. 151–153°, $[\alpha]D$ +82°, λ_{max} 262 mμ, log ε 4.07

Anal. Calcd. for $C_{23}H_{33}BrO_3$: Br, 18.27. Found: Br, 17.92.

2,2-Dimethyl-4-bromoandrostan-17β-ol-3-one Acetate (XIV).—IIc acetate (700 mg.) in glacial acetic acid (10 ml.) was brominated with one equivalent of bromine (310 mg. in 3.1 ml. of acetic acid), uptake being complete in 5 minutes. Water precipitation gave the crude 4-bromo compound XIV which was crystallized from acetone–hexane to yield 470 mg. (55%) of XIV, m.p. 142–144° dec.; analytical sample, m.p. 146–148° dec., $[\alpha]D$ +13° (ethanol).

Anal. Calcd. for $C_{23}H_{35}BrO_3$: C, 62.87; H, 8.02; Br, 18.19. Found: C, 62.59; H, 7.86; Br, 18.47.

2,2-Dimethyltestosterone Acetate (XV).—Treatment of 420 mg. of XIV with 2 ml. of boiling γ-collidine for 1.5 hours followed by ethyl acetate dilution and sulfuric acid wash yielded an oil with λ_{max} 240 mμ, log ε 4.03. The product, in hexane (25 ml.), was absorbed on 20 g. of neutral alumina and then eluted with 50-ml. portions of hexane. Fractions 6 to 13 were recrystallized from acetone–hexane, furnishing XV, m.p. 171–173°, $[\alpha]D$ +44°, λ_{max} 240 mμ, log ε 4.19.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.23; H, 9.81.

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

Steroids. CVI.[1] Synthesis of 7β-Methyl Hormone Analogs

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The preparation of 7β-methylcortisone *via* addition of methyl Grignard reagent to 7-ketocortisone bisethylene ketal acetate is described. The resulting addition product after hydrolysis and dehydration provided the corresponding 7-methyl-$\Delta^{4,6}$-dienone which upon hydrogenation was converted to 7β-methylcortisone. Alternately 7β-methylcortisone was prepared by hydrolysis of the coupling product of methyl Grignard reagent with 7-bromocortisone bisethylene ketal acetate. Hydride reduction of the Grignard coupling product followed by acid hydrolysis led to 7β-methylhydrocortisone. The synthesis of 7β-methyltestosterone by addition of methyl Grignard to 7-ketotestosterone ethylene ketal acetate is also described.

Previous reports from this Laboratory and others have described the substitution of methyl groups at position 2,[2] 4,[3] 6[4] and 11[5] of the steroid nucleus as well as position 1[6] in the 19-norsteroid series.

In continuation of the general program directed toward the relationship of structural modification to biological activity we now report the preparation of some 7-methyl analogs in the testosterone and cortical hormone series.

Although no 7-methyl-Δ^4-3-ketones have been previously reported, the 7-methylene and 7-methyl-7-hydroxy derivatives of cholesterol have been prepared[7] by the addition of methyl Grignard reagent to the corresponding 7-ketone. In our present work this general method was utilized, but as will be seen the method became impractical in the preparation of the 7-methylcorticoids, forcing employment of an alternate route.

Starting with cortisone bisethylene ketal acetate (Ia) the Lenhard and Bernstein procedure[8] was used to prepare the unstable 7-bromo compound Ib which was then hydrolyzed and oxidized to form 7-ketocortisone bisethylene ketal acetate (Ic) in overall yields of 50 to 60% based on Ia. Reaction of this 7-keto compound with methylmagnesium bromide proceeded in tetrahydrofuran solvent at room temperature and after 5–6 hours appeared almost complete on the basis of ultraviolet spectroscopy.

Treatment of the resulting 7-methyl-7-hydroxy compound Id with a methanolic acetone solution of perchloric acid directly yielded 7-methyl-Δ^6-dehydrocortisone (IIa). The use of perchloric acid catalyst for hydrolysis of the two ethylene ketal groups with concomitant dehydration of the 7-hydroxy groups invariably gave better yields of the dienone IIa than the methanol–sulfuric acid ketal hydrolysis method.[9]

The hydrogenation of the dienone IIa to 7β-methylcortisone (IIIa) was carried out under a variety of conditions, but in no case could a completely selective reduction of the Δ^6-double bond be achieved. When the reductions were stopped after one mole of hydrogen had been consumed, the product was a three-component mixture of IIa, IIIa and presumably 7β-methyldihydroallocortisone which we did not attempt to obtain pure. Only by using 1.2 moles of hydrogen for the reduction was the dienone totally reduced and even so chromatography and recrystallization did not yield a completely pure sample of 7β-methylcortisone. On the basis of the ultraviolet maximum the above product was estimated to be only 80% pure.

The preparation of pure 7β-methylcortisone (IIIa) was accomplished by our second general route which involved the coupling of methylmagnesium bromide and 7-bromocortisone bisethylene ketal acetate (Ib). The product of this reaction

(1) Paper CV, H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, THIS JOURNAL, **81**, 427 (1959).

(2) (a) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955); (b) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

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(4) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (c) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957), and preceding papers; (d) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958).

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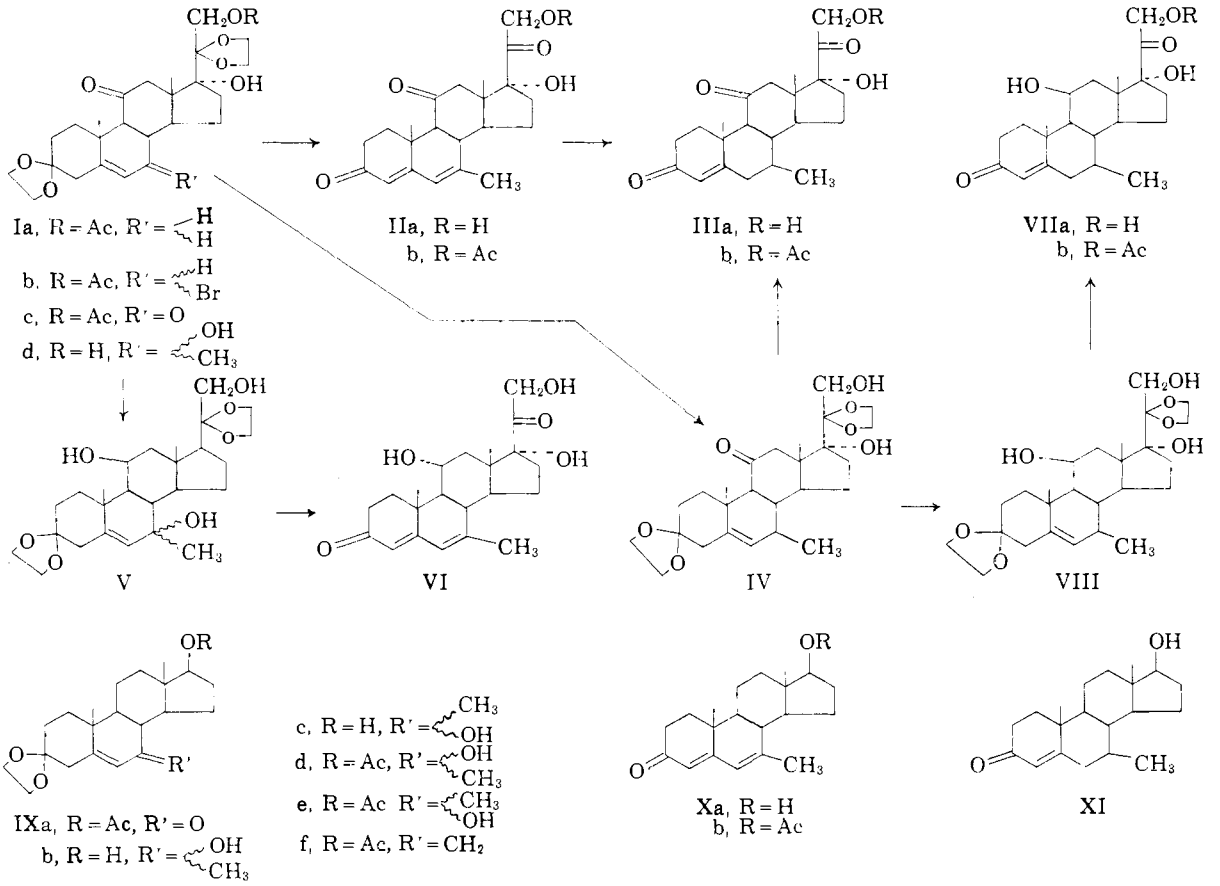
(6) (a) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2477 (1956); (b) C. Djerassi, A. E. Lippman and J. Grossman, *ibid.*, **78**, 2479 (1956).

(7) B. Bonn, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 1274 (1936).

(8) R. H. Lenhard and S. Bernstein, THIS JOURNAL, **78**, 990 (1956).

(9) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).



was usually a dark colored gum which could be crystallized to furnish a low yield of 7β-methylcortisone bisethylene ketal (IV). Treatment of this compound under the above perchloric acid hydrolysis conditions then yielded 7β-methylcortisone (IIIa) which was further purified as its 21-acetate. Comparison by mixture melting point and infrared spectra showed this acetate and that obtained from the hydrogenation product to be the same.

Similar routes were followed to obtain 7β-methylhydrocortisone (VIIa). Thus Id upon treatment with lithium aluminum hydride in tetrahydrofuran under reflux led to the 11β-hydroxy compound V which after perchloric acid hydrolysis provided 7-methyl-Δ^6-dehydrohydrocortisone (VI). The selective reduction of this dienone proved to be even more difficult than the 7-methyl-Δ^6-dehydrocortisone case and for this reason the method was abandoned.

We again turned to the product of the Grignard coupling reaction, IV, and upon reduction of its 11-ketone, followed by ketal hydrolysis we obtained 7β-methylhydrocortisone (VIIa) which was further purified as its 21-acetate.

For the preparation of 7β-methyltestosterone (XIa), the method of Grignard addition was quite satisfactory. Thus 7-ketotestosterone ethylene ketal acetate (IXa)[10] upon treatment with methylmagnesium bromide led to a mixture from which two crystalline compounds were obtained. Since elemental analysis of these compounds, as well as that of their respective acetates IXd and IXe, indicated isomerism, and since neither possessed any high selective ultraviolet absorption, they were assigned the epimeric C-7 structures IXb and IXc. In addition to these two compounds, a small amount of 7-methylenetestosterone ethylene ketal (IXf) was isolated as its acetate. The structure of IXf followed from its analytical data, ultraviolet maximum, λ_{max}^{EtOH} 238 mμ, log ε 4.25, and facile acid-catalyzed conversion to Xb.

When the total crude crystalline product of the Grignard reaction was treated with hot aqueous acetic acid, 7-methyl-Δ^6-dehydrotestosterone (Xa) was obtained in excellent yield. Once more extensive studies of the hydrogenation of this dienone did not lead to any satisfactory selective method for reduction of the Δ^6-bond. The best results were obtained using 1.2 moles of hydrogen; however, in contrast to the corticoid cases 7β-methyltestosterone could be readily obtained pure by direct crystallization or in a somewhat improved yield by chromatography.

The assignment of the 7-β-configuration to the above analogs has been made on the basis of the catalytic hydrogenations of the dienones II and X which would be expected to proceed by α-face adsorption.

Experimental[10a]

3,20-Bisethylenedioxy-Δ^5-pregnene-17α,21-diol-7,11-dione 21-Acetate (7-Ketocortisone Bisethylene Ketal Acetate) (Ic).—A solution of 19.5 g. of Ia in 2300 ml. of carbon

(10) P. N. Rao and P. Kurath, THIS JOURNAL, **78**, 5660 (1956).

(10a) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet spectra in 95% ethanol unless otherwise specified. The infrared spectra of all compounds have been recorded

tetrachloride under reflux was treated with one portion of 7.8 g. of finely powdered N-bromosuccinimide and allowed to boil for 10 minutes using a G. E. photoflood lamp as the heat source. The solution was chilled, filtered and the filtrate stirred with 200 g. of neutral alumina for 3 hours at room temperature. The mixture was again filtered and the alumina cake washed with 2 liters of acetone. The combined filtrates were then evaporated to dryness and the residue, dissolved in 75 ml. of pyridine, slowly added to a stirred mixture of 15 g. of chromium trioxide in 150 ml. of pyridine. After stirring overnight at room temperature the slurry was diluted with 500 ml. of ethyl acetate and filtered first through a small pad of filter-aid, then through a short column containing 100 g. of neutral alumina. Both filter cakes were washed with ethyl acetate and the combined filtrates evaporated to dryness. The residue readily crystallized from acetone to provide 9.2 g., m.p. 244–246°, which after one further crystallization gave 8.2 g., m.p. 254–256°. Further recrystallization from the same solvent provided the analytical sample of Ic, m.p. 257–258°, $[\alpha]_D$ −21°, λ_{max} 238–240 mμ, log ε 4.03.

Anal. Calcd. for $C_{27}H_{36}O_9$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.24.

7-Methyl-3,20-bisethylenedioxy-Δ⁵-pregnene-7,17α,21-triol-11-one (7-Methyl-7-hydroxycortisone Bisethylene Ketal) (Id).—To 200 ml. of anhydrous tetrahydrofuran containing 2.0 g. of Ic was added 40 ml. of 4 *N* ethereal methylmagnesium bromide. The solution was kept chilled by an ice-bath throughout the addition (3–5 min.) and for about 5 min. thereafter. The solution was then stirred at room temperature for 5 to 6 hours and finally decomposed by pouring onto 200 g. of crushed ice containing excess ammonium chloride. The resulting solution was extracted with ethyl acetate and the combined extracts were washed neutral with water, dried over sodium sulfate and evaporated to leave 1.6 g. of oil and crystals. Upon the addition of ethyl acetate most of the oil solidified to leave a crystalline mass, λ_{max} 240 mμ, log ε 2.4. By recrystallization, first from methylene chloride–ethyl acetate, followed by treatment with carbon in ethyl acetate, approximately 1 g. of pure white crystals, m.p. *ca.* 260°, was obtained. Further recrystallization from ethyl acetate yielded the analytical sample of Id, m.p. 268–269°, $[\alpha]_D$ −23°, no selective absorption in the ultraviolet above 220 mμ.

Anal. Calcd. for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00; O, 26.75. Found: C, 65.77; H, 8.07; O, 26.40.

7-Methyl-Δ⁴,⁶-pregnadiene-17α,21-diol-3,11,20-trione (7-Methyl-Δ⁶-dehydrocortisone) (IIa).—Approximately 1.45 g. of crude crystalline Id was heated for 50 minutes in a boiling solution consisting of 30 ml. of methanol, 30 ml. of acetone and 1.5 ml. of perchloric acid. After this time, 1.3 ml. of pyridine was added and the solution evaporated under reduced pressure almost to dryness. Water (10 ml.) was added and the resulting crystals were collected. These were dissolved in 20 ml. of acetone which was then slowly evaporated until the solution began to crystallize. At this point 10 ml. of water was added and the mixture was chilled, yielding 0.61 g. of crystals, m.p. 210–216°. By extracting the mother liquors with chloroform an additional 0.16 g., m.p. 207–213°, was obtained. After several recrystallizations either from ethyl acetate or acetone, the pure dieneone IIa was obtained, m.p. 224–225°, $[\alpha]_D$ +390°, λ_{max} 294 mμ, log ε 4.45.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58; O, 21.48. Found: C, 70.92; H, 7.63; O, 21.36.

7-Methyl-Δ⁴,⁶-pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (7-Methyl-Δ⁶-dehydrocortisone Acetate) (IIb).—The acetate was prepared from IIa by 3-hour treatment with excess pyridine, acetic anhydride at 25° followed by water precipitation. After three recrystallizations from methanol the sample exhibited m.p. 213–214°, $[\alpha]_D$ +359°, λ_{max} 292–294 mμ, log ε 4.41.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30; O, 23.16. Found: C, 69.32; H, 7.20; O, 23.14.

7β-Methyl-Δ⁴-pregnene-17α,21-diol-3,11,20-trione 21-Acetate. (7β-Methylcortisone 21-Acetate) (IIIb) *via* **the Dienone IIa.**—To 100 ml. of methanol containing 0.4 g. of pre-reduced 2% palladium-on-strontium carbonate catalyst, was added 1.48 g. of IIa dissolved in 150 ml. of methanol and the compound hydrogenated at 25° and 570 mm. After 40 minutes, 150 ml. of hydrogen (1.2 moles) had been consumed and the reduction was stopped. Following filtration, the solution was concentrated to yield 875 mg. of white crystals. Further concentration produced a second crop of slightly colored crystals, 446 mg. The main fraction was crystallized several times from methanol without any appreciable change in m.p. or ultraviolet absorption intensity, m.p. 238–242°, $[\alpha]_D$ +155° (dioxane), λ_{max} 240 mμ, log ε 4.08. The acetate IIIb was prepared from this material in the usual manner and after 4 recrystallizations from ethyl acetate exhibited m.p. 213–215°, $[\alpha]_D$ +180° (methanol), λ_{max} 240 mμ, log ε 4.13.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75; O, 23.04. Found: C, 69.18; H, 8.08; O, 23.16.

7-Bromo-3,20-bisethylenedioxy-Δ⁵-pregnene-17α,21-diol-11-one 21-Acetate (7-Bromocortisone Bisethylene Ketal Acetate) (Ib).—Under the conditions previously described, 4.5 g. of Ia was allylically brominated and the carbon tetrachloride solution evaporated to dryness under high vacuum keeping the temperature at or only slightly above room temperature. Without such precautions the product undergoes rapid decomposition. A small portion of the resulting white powder was recrystallized three times from benzene–carbon tetrachloride to obtain m.p. 93–96° dec., $[\alpha]_D$ −144°. Due to the rapid decomposition of this compound at room temperature, no analytical specimen was obtained.

7β-Methyl-3,20-bisethylenedioxy-Δ⁵-pregnene-17α,21-diol-11-one. (7β-Methylcortisone Bisethylene Ketal) (IV).—The main portion of the above product Ib was dissolved in 225 ml. of anhydrous tetrahydrofuran and was treated with 120 ml. of 4 *N* ethereal methylmagnesium bromide. During the addition which was made over 4–7 minutes, the reaction was chilled by the use of an ice-bath. After the reaction had proceeded for 15–20 minutes the ice-bath was removed and the solution stirred at room temperature for 18 hours. It was then poured onto crushed ice containing excess ammonium chloride. After extraction with ethyl acetate the extracts were washed neutral with water, dried over sodium sulfate and evaporated to leave 4 g. of dark gum. Adsorption of this gum on 60 g. of Florisil followed by elution with benzene–acetone (4:1) yielded 0.52 g. of product, m.p. 207–210°. Recrystallization from acetone and then ethyl acetate provided the analytical sample of IV, m.p. 223–225°, $[\alpha]_D$ ±0°, λ_{max} 290–298 mμ, log ε 1.65.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28; O, 24.21. Found: C, 67.55; H, 8.32; O, 24.65.

7β-Methylcortisone IIIa *via* **the Grignard Coupling Product IV.**—To 80 ml. of methanol–acetone (1:1) containing 1.5 ml. of perchloric acid was added 2.88 g. of the total crude gum obtained from a Grignard coupling reaction. After being heated at reflux temperature for 50 min., 1.5 ml. of pyridine was added and the solution was concentrated to *ca.* 20 ml. Following dilution with water and extraction with ethyl acetate (4 × 50 ml.), the organic extracts were washed neutral with water, then dried over sodium sulfate and evaporated to leave 2.0 g. of gum. This gum was chromatographed on 80 g. of silica. Elution with ether–ethyl acetate (4:1) provided 230 mg. of crystals, m.p. 208–210°. After one recrystallization from ethyl acetate the melting point was raised to 233–235°. Three further recrystallizations from the same solvent provided the analytical sample m.p. 236–238°, $[\alpha]_D$ +172° (dioxane), λ_{max} 240 mμ, log ε 4.23.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; O, 21.36. Found: C, 70.59; H, 7.97; O, 21.41.

The acetate IIIb was prepared as follows. Seventy mg. of the above analytical sample m.p. 236–238° was heated on the steam-bath for one hour with 0.5 ml. of pyridine and 0.2 ml. of acetic anhydride. The solution was then diluted with 4 ml. of water and chilled and the resultant crystals filtered. Recrystallization once from ethyl acetate yielded 60 mg. of IIIb, m.p. 212–213°, $[\alpha]_D$ +194° (methanol), λ_{max} 240 mμ, log ε 4.23.

Comparison of this acetate as well as its precursor by infrared spectra and mixed melting point determination with the samples obtained by reduction of the 7-methyldienone IIa showed the compounds to be the same. Comparison of the rotary dispersion curves was quantitatively similar ex-

and are in accord with the reported structures. All ethylene ketals were recrystallized in the presence of a few drops of pyridine. Analytical samples were dried for 40 hours at 100° in high vacuum. We are indebted to Dr. L. Throop and staff for the rotation and spectral measurements.

cept that the pure sample exhibited a slightly more complex fine structure in the 350–380 mμ region.

7-Methyl-3,20-bisethylenedioxy-Δ⁵-pregnene-7,11β,17α,-21-tetrol (7-Methyl-7-hydroxyhydrocortisone Bisethylene Ketal) (V).—Two hundred ml. of tetrahydrofuran containing 1 g. of lithium aluminum hydride and 1 g. of crude crystalline Id was allowed to reflux for 12 hours, after which time the excess hydride was decomposed with ethyl acetate and saturated aqueous sodium sulfate. After filtration the solution was evaporated to dryness leaving a frothy gum whose infrared spectrum showed only negligible absorption in the carbonyl region.

The total residue, 0.7 g., was then chromatographed on 30 g. of silica. Elution with benzene–acetone (1:1) provided 0.52 g. of crystals which were recrystallized 7 times from benzene to provide V, m.p. 223–227°, $[\alpha]_D$ −27°, λ_{max} 244–248 mμ, 294–298 mμ, log ε 2.48, 2.77.

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39. Found: C, 65.58; H, 8.48.[11]

7-Methyl-Δ⁴,⁶-pregnadiene-11β,17α,21-triol-3,20-dione. (7-Methyl-Δ⁶-dehydrohydrocortisone) (VIa).—Twenty ml. of methanol–acetone (1:1) containing 0.1 ml. of perchloric acid and 500 mg. of crude V obtained from the preceding experiment was boiled for one hour, pyridine (0.2 ml.) was added and the solution concentrated to a small volume. Approximately 20 ml. of water was added and the mixture extracted 4 times with 50 ml. of chloroform. The extracts were washed with water, dried and evaporated to leave 0.5 g. of gummy crystals which were chromatographed on 15 g. of Florisil. The benzene–acetone (4:1 and 1:1) eluates were recrystallized from ethyl acetate yielding 200 mg. of VIa, m.p. 245–250°. Three further recrystallizations from the same solvent led to the analytical sample, m.p. 248–253°, $[\alpha]_D$ +315° (pyridine), λ_{max} 296–298 mμ, log ε 4.48.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; O, 21.36. Found: C, 70.68; H, 8.07; O, 21.37.

Attempted Preparation of 7β-Methyl-Δ⁴-pregnene-11β,-17α,21-triol-3,20-dione (7β-Methylhydrocortisone) (VII) *via* the Dienone, VIa.—To 50 ml. of dioxane containing 105 mg. of 5% palladium-on-carbon was added 800 mg. of VI dissolved in 125 ml. of dioxane. The hydrogenation was allowed to proceed for 1.5 hours (25°, 570 mm.) after which time 81 ml. of hydrogen (1.2 moles) had been consumed. Upon isolation there was obtained 771 mg. of crude VII, λ_{max} 244–246, 296–298 mμ, log ε 3.68, 4.03. Because of the large amount of dienone remaining, the hydrogenation was repeated until 27 additional ml. of hydrogen had been absorbed. The resulting product then showed λ_{max} 244, 296 mμ, log ε 3.73, 3.59. Chromatography on 35 g. of Florisil provided with benzene–acetone (4:1) elution, 175 mg. of crystalline material which by its ultraviolet spectrum was shown still to be a grossly contaminated mixture. This was then submitted to paper chromatography using Whatman No. 1 filter paper impregnated with methanol–formamide (1:1). Elution with benzene–hexane (1:1) was allowed to continue for 2.5 hours after which time three bands could be observed by the use of TPTZ reagent. The middle band was separated and eluted from the paper with methanol to provide 30 mg. of gummy crystals, which were dissolved in ethyl acetate and passed through 400 mg. of Florisil. The resulting 20 mg. of crystals exhibited m.p. 235–240°, λ_{max} 244 mμ, log ε 3.97, but no further purification was attempted.

7β-Methyl-3,20-bisethylenedioxy-Δ⁵-pregnene-11β,17α,-21-triol (7β-Methylhydrocortisone Bisethylene Ketal) (VIII).—One hundred ml. of tetrahydrofuran containing 0.5 g. of lithium aluminum hydride and 200 mg. of IV was allowed to reflux for 6.5 hours. Work-up in the manner previously described led to a gum which showed no carbonyl absorption in the infrared. By crystallization from ethyl acetate there was obtained 100 mg. of VIII, m.p. 179–183°, which by further recrystallization was raised to m.p. 194–195°, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68; O, 24.11. Found: C, 67.52; H, 8.79; O, 23.73.

7β-Methylhydrocortisone (VIIa).—Twenty ml. of acetone containing 210 mg. of VIII, m.p. 180–185°, 4 drops of water and 0.1 ml. of perchloric acid, was boiled for one hour. Approximately 0.15 ml. of pyridine was added and the solution worked up as described for the previous hydrolyses There remained 160 mg. of gum which crystallized from ethyl acetate to provide 105 mg. of VIIa, m.p. 224–227°. Repeated recrystallization from the same solvent furnished material with m.p. 237–238°, $[\alpha]_D$ +30° (dioxane), λ_{max} 244, 292–294 mμ, log ε 4.22, 2.66.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.15; H, 8.67.

7β-Methylhydrocortisone Acetate (VIIb).—The acetate was prepared in the usual manner and was recrystallized from acetone–ether, m.p. 206–207°, $[\alpha]_D$ +134°, λ_{max} 244 mμ, log ε 4.18.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; O, 22.94. Found: C, 68.61; H, 8.19; O, 22.54.

Preparation of the Epimeric 7-Methyl-7-hydroxytestosterone Ethylene Ketals IXb and IXc.—To 125 ml. of anhydrous tetrahydrofuran containing 5.0 g. of 7-ketotestosterone ketal acetate (IXa)[10] was added 35 ml. of 4 *N* methylmagnesium bromide. Because IXa was slightly insoluble in this medium at room temperature, the reaction was allowed to proceed at 40°. After 3 hours of stirring the mixture was poured into aqueous ammonium chloride and then extracted with ethyl acetate. The combined extracts were washed neutral with water, dried over sodium sulfate and evaporated yielding 4.2 g. of gummy crystals, λ_{max} 240 mμ, log ε 2.51.

When 2.0 g. of this gum was absorbed on 60 g. of neutral alumina, elution with benzene–hexane (7:1) and benzene provided 0.82 g. of crystals, m.p. 180–185°. After several recrystallizations from acetone–hexane, the analytical sample of IXb was obtained, m.p. 200–202°, $[\alpha]_D$ −29°, no high selective ultraviolet absorption.

Anal. Calcd. for $C_{22}H_{34}O_4 \cdot 1/2C_3H_6O$: C, 72.09; H, 9.53; O, 18.39. Found: C, 72.17; H, 9.47; O, 18.53.

Further elution of the column with benzene–ether (4:1) provided 0.58 g. of crystals which were recrystallized repeatedly from acetone–hexane to obtain pure IXc, m.p. 142–143°, $[\alpha]_D$ −38°, no high selective ultraviolet absorption.

Anal. Calcd. for $C_{22}H_{34}O_4 \cdot 1/2C_3H_6O$: C, 72.09; H, 9.53; O, 18.39. Found: C, 71.82; H, 9.55; O, 18.44.

The Epimeric 7-Methyl-7-hydroxytestosterone Ethylene Ketal Acetates (IXd and IXc).—These acetates were prepared by 18-hour treatment with acetic anhydride–pyridine at room temperature. Thus IXb led to the acetate IXd which was recrystallized from acetone, m.p. 203–205°, $[\alpha]_D$ −53°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 71.25; H, 8.80; O, 19.63.

From IXc there was obtained the acetate IXe which was recrystallized from ether–hexane, m.p. 173–175°, $[\alpha]_D$ −8°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 71.36; H, 8.91; O, 19.45.

7-Methylenetestosterone Ethylene Ketal Acetate (IXf).—In one case the total crude product of a Grignard coupling reaction, λ_{max} 240 mμ, log ε 2.55, was acetylated in pyridine–acetic anhydride for 20 hours at room temperature. The resulting 4 g. of gum, obtained *via* the usual procedure, was then chromatographed on 160 g. of neutral alumina. In addition to the isolation of the above acetates, hexane–benzene (1:1) elution also provided 50 mg. of crystals which were recrystallized several times from acetone to provide the analytical sample, m.p. 191–193°, $[\alpha]_D$ −158°, λ_{max} 238 mμ, log ε 4.25.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.28; H, 8.72.

Conversion of IXf to 7-Methyl-Δ⁶-dehydrotestosterone Acetate (Xb).—Fifty mg. of IXf was allowed to stand at room temperature overnight in 1 ml. of acetone containing 5 mg. of *p*-toluenesulfonic acid. Water then was added and after chilling in ice, the solution was filtered to provide 30 mg. of product, m.p. 125–130°. After several recrystallizations from hexane the analytical sample of Xb was obtained, m.p. 139–141°, $[\alpha]_D$ −197°, λ_{max} 294–296 mμ, log ε 4.34.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.03; H, 8.72.

This same dienone acetate was also obtained directly from Xa by acetylation with pyridine–acetic anhydride.

(11) Repeated attempts to obtain a satisfactory analysis indicate that V is strongly solvated by benzene. Our analytical results have usually been in agreement for approximately 0.25 mole of benzene.

7-Methyl-Δ^6-dehydrotestosterone (Xa).—Approximately 1.6 g. of the crude product obtained by the addition of methyl Grignard reagent to IXa was heated for 80 minutes on the steam-bath in 65 ml. of 80% aqueous acetic acid. The solution was then poured into excess water and the resultant crystals (1.05 g., m.p. 188–191°) collected. After two recrystallizations from ether–hexane, pure Xa was obtained, m.p. 196–197°, $[\alpha]D$ +249°, λ_{max} 296–298 mμ, log ε 4.43.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.66. Found: C, 79.64; H, 9.80; O, 10.28.

7β-Methyltestosterone (XI).—A suspension of 112 mg. of 5% palladium–carbon catalyst in 50 ml. of methanol containing 78 mg. of potassium hydroxide was prehydrogenated. To this mixture 1.4 g. of Xa in 200 ml. of methanol was added and the compound hydrogenated at 25° and 570 mm. After 60 minutes, 164 ml. of hydrogen (1.2 moles) had been consumed. The mixture was filtered, acetic acid (0.5 ml.) added and the solution evaporated to dryness and water added. The residual crystalline product, 1.1 g., λ_{max} 242–244 mμ, log ε 3.99, was chromatographed on 40 g. of unwashed alumina. Elution with benzene–ether (9:1) provided 500 mg. of crystals which after six recrystallizations from acetone provided the analytical sample, m.p. 183–185°, λ_{max} 244 mμ, log ε 4.21, $[\alpha]D$ +112° (ethanol).

Anal. Calcd. for $C_{20}H_{30}O_2 \cdot C_3H_6O$: C, 76.62; H, 10.07; O, 13.31. Found: C, 76.92; H, 9.95; O, 13.12.

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

Steroids. CVII.[1] $\Delta^{5(6)}$-19-Nor Steroids, a New Class of Potent Anabolic Agents[2]

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Several Δ^5-3β-alcohols and Δ^5-3-ketones of the 19-norandrostene series have been synthesized and several of these substances have shown high biological activity.

The synthesis of 19-nortestosterone by Birch[3] opened a new field of biologically interesting compounds and paved the way for the preparation of the 19-nor analogs of most of the common steroid hormones,[4–7] compounds containing the Δ^4-3-keto system. Later work in this series led to various 3-keto-$\Delta^{5(10)}$-derivatives[8,9] and several recent publications have been devoted to ring A saturated 19-nor steroids.[10–12] With the exception of 19-nor-$\Delta^{5(6)}$-androstene-3β,17β-diol,[13] $\Delta^{5(6)}$-unsaturated analogs are unknown in this group and we should now like to report the synthesis of the 17α-methyl, ethyl, vinyl and ethynyl 19-nor-$\Delta^{5(6)}$-androstene-3β,17β-diols as well as the corresponding 3-ketones.

Since removal of the C-10 angular methyl group in 17α-methyl-[6] and -ethyltestosterone[8] has led to more favorable anabolic properties,[14] and since 17α-methyl-Δ^5-androstene-3β,17β-diol has enjoyed some use as a relatively non-virilizing anabolic agent,[15] it was of particular interest to prepare 17α-methyl- and 17α-ethyl-19-nor-$\Delta^{5(6)}$-androstene-3β,17β-diol.

The starting material for the ethynyl, vinyl and ethyl compounds was 17α-ethynyl-19-nortestosterone (Ia).[6] Treatment of Ia with acetic anhydride and *p*-toluenesulfonic acid led to the $\Delta^{3,5}$-enol acetate 17-acetate IIa, a compound reported so far only in the patent literature[16]; the position of the double bonds was established by the ultraviolet maximum at 235 mμ. Mild alkaline hydrolysis of IIa led to 17α-ethynyl-19-nortestosterone 17-acetate (Ib), a potent oral progestational agent.[16] Dauben and Eastham[17] had first shown that treatment of a steroidal $\Delta^{3,5}$-enol acetate with lithium aluminum hydride led to the Δ^5-3β-alcohol in low yield. Subsequently, however, three groups[18–20] reported that high yields were obtained when lithium aluminum hydride was replaced by sodium borohydride. Application of this reaction to IIa, reduction being carried out in a mixture of methanol–tetrahydrofuran, furnished 17α-ethynyl-19-nor-$\Delta^{5(6)}$-androstene-3β,17β-diol 17-acetate (IIIa). Removal of the 17-acetate was smoothly effected by reduction with lithium aluminum hydride, thus yielding the free diol IIIb. Hydrogenation of IIIb in pyridine solution over a palladium–calcium carbonate catalyst stopped with the uptake of one equivalent of hydrogen and gave the 19-nor-17α-vinyl 3,17-diol IIIc in good yield. When the reduction was conducted in dioxane solution over a palladium–carbon catalyst and interrupted after the uptake of two equivalents of hydrogen, the 17α-ethyl-19-nor-$\Delta^{5(6)}$-diol IIId could be obtained without difficulty.

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