185° (after drying at 130°), $[\alpha]_D$ +77° (dioxane), λ_{max} 234 mμ, log ε 4.20; infrared λ_{max}^{KBr} 5.77 (broad), 6.00, 6.12 and 6.21 μ.

Anal. Calcd. for $C_{25}H_{32}F_2O_8$: C, 60.23; H, 6.47; F, 7.62. Found: C, 60.71; H, 6.78; F, 7.24.

6α,9α-Difluoro-16α-hydroxyhydrocortisone (XIVb).—The incubation of 300 mg. of 6α,9α-difluorohydrocortisone with *Streptomyces roseochromogenus*, Rutgers Collection No. 3689, was carried out exactly as described for the preparation of Xa, part (b). The methylene dichloride extract was adsorbed onto a column containing a mixture of silica gel (10 g.) and Celite (2.5 g.) whence elution with methylene dichloride–acetone (70:30; 300 ml.) afforded a crystalline product which after one recrystallization from aqueous methanol gave 56 mg. of 6α,9α-difluoro-16α-hydroxyhydrocortisone (XIVb), m.p. 247–255°. The analytical specimen from acetone–hexane exhibited m.p. 242–248°, $[\alpha]_D$ +58° (dioxane), λ_{max} 234 mμ, log ε 4.18.

Anal. Calcd. for $C_{21}H_{28}F_2O_6 \cdot 1/2\ H_2O$: C, 61.90; H, 7.17. Found: C, 61.61; H, 6.92.

Acetylation as described for the preparation of Xb gave a diacetate identical with XIVa in all respects.

6α,9α-Difluoro-16α-hydroxyprednisolone 16,21-Diacetate (XVa).—The diacetate XIVa (290 mg.), *t*-butyl alcohol (30 ml.), pyridine (0.05 ml.) and selenium dioxide (150 mg.) were heated under reflux in a nitrogen atmosphere for 53 hours. Ethyl acetate was added, the mixture filtered through Celite and the filtrate evaporated to dryness. The residue was stirred well with water, filtered and the product chromatographed on 10 g. of silica. Elution with acetone–methylene chloride (1:19) and crystallization from methylene chloride gave 68 mg. of the dienone XVa, m.p. 212–215°. The analytical sample had m.p. 222–224°, $[\alpha]_D$ +51° (dioxane), λ_{max} 238 mμ, log ε 4.23; infrared λ_{max}^{KBr} 5.75 (broad), 6.00, 6.14 and 6.21(sh) μ. The compound was tenaciously solvated.

Anal. Calcd. for $C_{25}H_{30}F_2O_8$: C, 60.48; H, 6.09; F, 7.65. Found (dried at 130°): C, 60.35; H, 6.29. Calcd. for $C_{25}H_{30}F_2O_8 \cdot H_2O$: C, 58.36; H, 6.27; F, 7.34. Found (dried at 93°): C, 58.83; H, 6.06; F, 7.91.

6α,9α-Difluoro-16α-hydroxyprednisolone (XVb).—The foregoing diacetate XVa (430 mg.) was stirred in methanol (15 ml.) at 0° under nitrogen, and methanolic potassium hydroxide (4%, 2.2 ml.) was added. The material rapidly dissolved and reprecipitated after *ca.* 30 minutes at 0°. After 1 hour excess alkali was neutralized with acetic acid and the methanol removed *in vacuo*. Water was added and the product filtered. Crystallization from ethyl acetate–methanol afforded 285 mg. of XVb, m.p. 258–260°. Recrystallization gave an analytical sample, m.p. 266–268°, $[\alpha]_D$ +43° (dioxane), λ_{max} 238 mμ, log ε 4.23; infrared λ_{max}^{KBr} 5.83, 6.00, 6.15 and 6.20 μ.

Anal. Calcd. for $C_{21}H_{26}F_2O_6 \cdot CH_3OH$: C, 59.45; H, 6.80. Found: C, 59.64; H, 6.40.

6α,9α-Difluoro-16α-hydroxyprednisolone 16,17-Acetonide (XVc).—6α,9α-Difluoro-16α-hydroxyprednisolone (XVb) (250 mg.) was stirred in acetone (15 ml.) containing perchloric acid (70%, 5 drops). After 20 minutes all the material had dissolved and after a further 10 minutes water (50 ml.) containing a little sodium bicarbonate was added and the acetone removed *in vacuo*. The resulting needles (257 mg.) were isolated by filtration; m.p. 261–263°. Recrystallization from acetone–hexane gave the analytical sample, m.p. 265–266°, $[\alpha]_D$ +95°, λ_{max} 238 mμ, log ε 4.21.

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.70; H, 6.68; F, 8.40. Found (dried at 130°): C, 63.42; H, 6.78; F, 8.07.

Acknowledgment.—We are indebted to Dr. C. Casas Campillo of these laboratories and his staff for the microbiological transformations described above.

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

Steroids. CXL.[1] 11-Methyl Steroids

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The addition of methyllithium to 11-ketones of certain androstane and androstene derivatives is shown to provide the corresponding 11α-methyl-11β-ol's. Further transformations of these products to hormone analogs possessing either the 11α-methyl-11β-ol functions or the 11-methyl-$\Delta^{9(11)}$-system are described.

Advances in knowledge concerning the chemistry of steroidal 11-ketones have dispelled older beliefs concerning their inertness toward transformations other than those involving catalytic or chemical reduction. Thus it has been shown that under forcing conditions 11-ketones may be removed by Wolff–Kishner reduction[2] or converted to their 11-ethylene ketal[3] or oxime[4] derivatives.

In connection with a broad program directed toward the preparation of new anabolic agents, the action of methylmagnesium bromide on 5α-androstan-3β-ol-11,17-dione (I) in benzene–ether solution was investigated. In addition to the expected 17α-methyl-5α-androstan-3β,17β-diol-11-one (II) there was observed a second more polar product whose infrared spectrum exhibited no carbonyl absorption. On the basis of this spectroscopic evidence as well as the analytical data, it was obvious that the 11-ketone had undergone attack by the Grignard reagent and the substance was therefore assigned the structure of 11α,17α-dimethyl-5α-androstan-3β,11β,17β-triol (IIIa). Further characterization of this compound was accomplished by pyridine–chromium trioxide oxidation[5] to the 3-keto derivative IIIb. The assignment of configuration as the 11α-methyl-11β-ol in this series of compounds rests on the assumption that the reaction involves attack of the 11-ketone by a methyl carbanion and that the stereochemical course would be the same as for hydride reductions.[6]

Upon observing that replacement of the methyl Grignard reagent by methyllithium led to very high yields of IIIa, the action of this latter reagent was investigated on both 5β-pregnan-11-one (IVa)[7]

(1) Paper CXXXIX, A. Bowers, I. C. Ibáñez, E. Denot and R. Becerra, THIS JOURNAL, **82**, in press (1960).

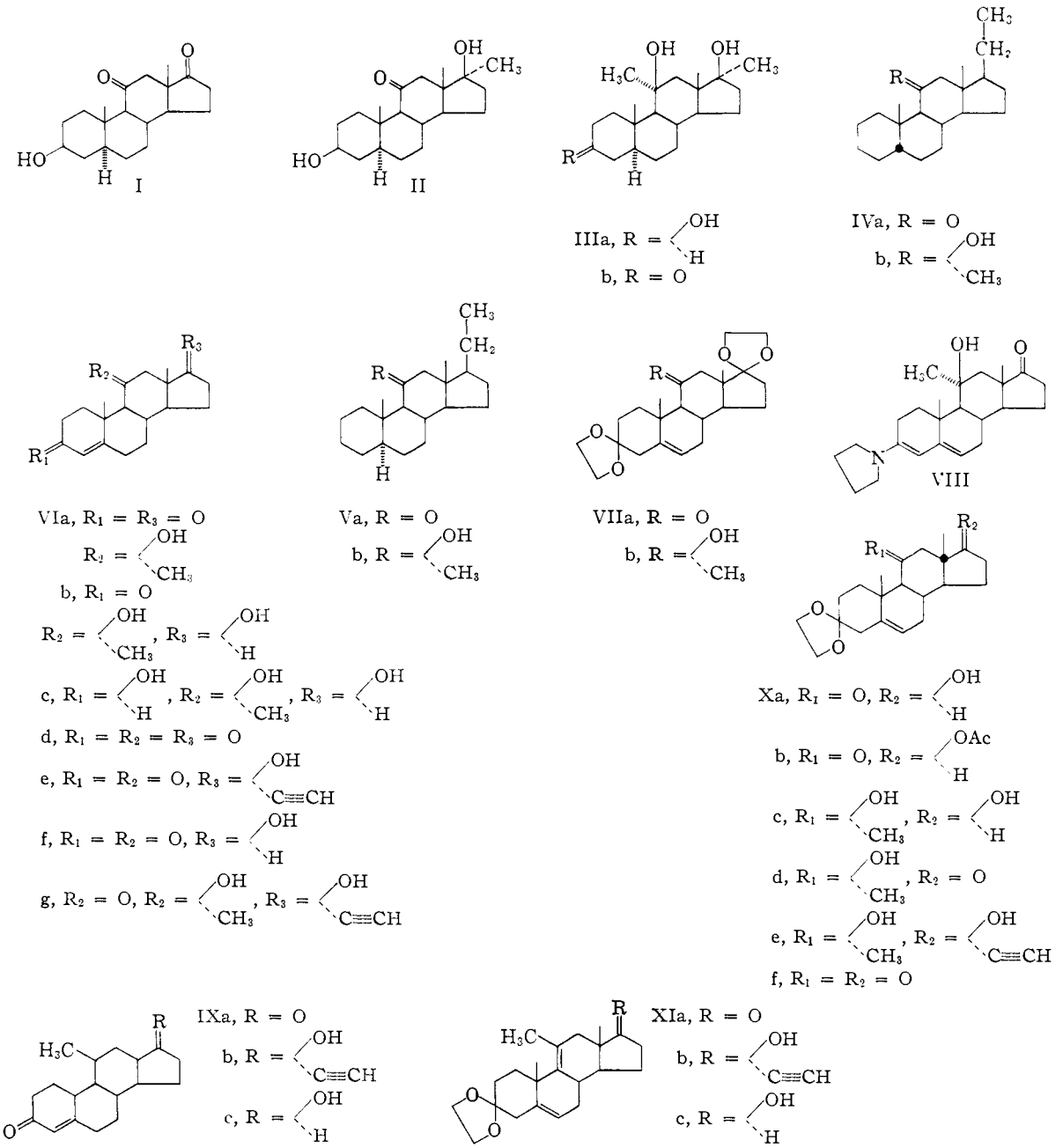
(2) R. B. Moffett and J. H. Hunter, *ibid.*, **73**, 1973 (1951).

(3) (a) B. J. Magerlein and R. H. Levin, *ibid.*, **77**, 1904 (1955); (b) C. Engel, *Can. J. Chem.*, **35**, 31 (1957).

(4) E. B. Hershberg, E. P. Oliveto and R. Rausser, *Chemistry & Industry*, 1477 (1958).

(5) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(6) For discussion see L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, pp. 268–269.



and 5α-pregnan-11-one (Va).[7] In each case facile addition to the 11-ketone occurred, thereby providing 11α-methyl-5β-pregnan-11β-ol (IVb) and 11α-methyl-5α-pregnan-11β-ol (Vb), respectively. While the former compound could not be obtained crystalline, its structure is probably as indicated since it no longer possessed a carbonyl band in the infrared and in a similar fashion to Vb it proved resistant to chromic acid oxidation.[8,9]

When the addition of methyllithium to adrenosterone bis-ethylene ketal (VIIa)[10] was investigated, the reaction was found to proceed in very high yield to 11α-methyl-Δ⁵-androsten-11β-ol-3,17-dione 3,17-bis-ethylene ketal (VIIb). Following hydrolysis of the ketal functions, 11α-methyl-Δ⁴-androsten-11β-ol-3,17-dione (VIa) was obtained and this material could then be converted to the corresponding testosterone hormone analog by several different methods.

Thus sodium borohydride reduction under Norymberski's selective conditions[11] led directly to 11α-methyl-11β-hydroxytestosterone (VIb). Alternatively VIa could be reduced with lithium aluminum

(7) F. Sondheimer, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 1090 (1957).

(8) A preliminary communication describing part of the material presented in this paper has appeared; H. J. Ringold, E. Batres and J. A. Zderic, *Tetrahedron*, **2**, 164 (1958).

(9) The addition of methylmagnesium bromide to a steroidal 11-carbonyl function was reported in the case of a ring A unsubstituted androstan-11,17-dione by J. C. Babcock at the Dallas, Tex., Meeting of the American Chemical Society, April, 1956.

(10) S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 1481 (1953).

(11) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

hydride to the triol VIc which was subjected then to manganese dioxide[12] oxidation thereby providing VIb. An additional synthesis was effected by the conversion[13] of VIa to the enamine VIII which, following reduction and hydrolysis, likewise provided authentic 11α-methyl-11β-hydroxytestosterone (VIb).

For purposes of bioassays it appeared to be of some interest to effect dehydration of the 11 β-hydroxyl group in VIb with the goal of preparing certain hormone analogs possessing the 11-methyl-$\Delta^{9(11)}$-system. Thus it was found that VIa upon treatment with thionyl chloride–pyridine at 0° was smoothly dehydrated to 11-methyl-$\Delta^{4,9(11)}$-androstadien-3,17-dione (IXa).

Attempts to effect direct 17α-ethynylation of IXa with acetylene and potassium *t*-butoxide[14] were not encouraging, although minute amounts of the expected 17α-ethynyl derivative IXb could be isolated. An even more complete resistance to this mode of ethynylation was observed with the 11α-methyl-11β-hydroxy-dione VIa. Since the method is applicable in reasonable yields to the conversion of adrenosterone[15] into its 17α-ethynyl derivative VIe,[16] the previously mentioned sluggishness of the reaction in the present series is most likely a reflection of new steric factors created by the presence of the 11-methyl substituent. Further support for such a view is the fact that ethynylation by acetylenedimagnesium bromide of both Xd and XIa (*vide infra*) required prolonged reaction periods (no less than 6 hours) as compared, for example, to dehydroepiandrosterone where ethynylation was essentially complete in 15 minutes.[17]

An alternate synthesis of IXb was eventually achieved in the following manner. Conversion of 11-keto testosterone[18] (VIf) to the corresponding 3-ethyleneketal Xa was effected under the usual conditions. This compound on treatment with methyllithium provided 11α-methyl-Δ^5-androsten-11β,-17β-diol-3-one 3-ethylene ketal (Xc), oxidized by pyridine–chromium trioxide to the 17-ketone Xd which was then heated at reflux temperature in tetrahydrofuran solution containing a large molar excess of acetylenedimagnesium bromide.[19] In this manner there was obtained in fair yield the 17α-ethynyl derivative Xe which, following perchloric acid hydrolysis of the 3-ethylene ketal, provided 11α-methyl-17α-ethynyl-Δ^4-androsten-11β,-17β-diol-3-one (VIg).

As a route to the previously mentioned 11-methyl-$\Delta^{9(11)}$ derivatives, attention was again turned to 11α-methyl-Δ^5-androsten-11β-ol-3,17-dione 3-ethylene ketal (Xd). While the attempted dehydration of Xd was not successful with phosphorus oxychloride in pyridine, 11-methyl-$\Delta^{5,9(11)}$-androsten-3,17-dione 3-ethylene ketal (XIa) could be prepared in good yield by the use of thionyl chloride in the same solvent. Upon treatment with acetylenedimagnesium bromide, addition to the 17-ketone occurred thereby providing the 11-methyl-17α-ethynyl-$\Delta^{5,9(11)}$-derivative XIb. After hydrolysis of the ketal function, XIb yielded 11-methyl-17α-ethynyl-$\Delta^{4,9(11)}$-androstadien-17β-ol-3-one (IXb) which was identical in all respects with the product obtained by direct ethynylation of the corresponding 3,17-dione; *vide supra*.

Similarly when XIa was first reduced with lithium aluminum hydride to XIc, the resulting compound on hydrolysis provided the 11-methyl-$\Delta^{9(11)}$-testosterone analog IXc.

Biological Data.—In the parabiotic rat assay (castrate male, intact female) 11-methyl-$\Delta^{9(11)}$-testosterone (IXc) proved to be inactive by the subcutaneous route as either an androgenic or myotrophic agent.[20] Similar results were observed for 11α-methyl-11β-hydroxytestosterone (VIb), 11α,-17α-dimethyl-5α-androstan-3β,11β,17β-triol (IIIa) and 11α,17α-dimethyl-5α-androstan-11β,17β-diol-3-one (IIIb) when administered by both the oral and subcutaneous routes.

As a progestational agent, 11α-methyl-17α-ethynyl-Δ^4-androsten-11β,17β-diol-3-one (VIg) was inactive at a 5-mg. oral dose in the Clauberg assay.

Experimental[21]

5α-Androstan-3β-ol-11,17-dione (I).—To 1050 ml. of 50% aqueous acetic acid containing 14 g. of 5α-pregnan-3β,17α,21-triol-11,20-dione was added with good stirring 186 g. of sodium bismuthate. After 30 minutes at room temperature the mixture was cooled to 0° and treated with 2110 ml. of 3 *N* aqueous potassium hydroxide. Following extraction with ethyl acetate (4 × 500 ml.) the combined extracts were washed neutral with water, dried over sodium sulfate and evaporated to dryness. The residue was then crystallized several times from ethyl acetate–hexane to yield 4.92 g. of I, m.p. 162–164°, $[\alpha]D$ + 127°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.56; H, 8.98.

By chromatography over 150 g. of neutral alumina an additional 2.3 g. of material (eluted with benzene–ether (9:1)) was isolated from the combined mother liquors.[22]

Action of Methylmagnesium Bromide on 5α-Androstan-3β-ol-11,17-dione (I).—Sixty ml. of anhydrous thiophene-free benzene containing 1.5 g. of I was treated with 8 ml. of 4 *N* ethereal methylmagnesium bromide and allowed to remain at room temperature overnight. Decomposition by aqueous ammonium chloride followed by benzene extraction and water washing provided a residue which was then chromatographed over 75 g. of unwashed alumina. Elution with benzene–ether (4:1) yielded 0.30 g. of starting material and 0.60 g. of semi-crystalline material which upon recrystallization from acetone–hexane led to pure 17α-methyl-5α-androstan-3β,17β-diol-11-one, m.p. 218–221°, $[\alpha]D \pm 0°$.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.95; H, 10.07. Found: C, 75.12; H, 9.93.

Further elution of the column with benzene–ether (60:40) yielded 0.30 g. of IIIa, m.p. 162–164°, which was obtained

(12) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

(13) J. Johnson, M. Herr, J. Babcock, A. Fonken, J. Stafford and F. Heyl, *ibid.*, **78**, 430 (1956).

(14) G. Zühlsdorf, German Patent 1,013,649.

(15) T. Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

(16) After the completion of this phase of the problem a different synthesis of VIe was reported; C. W. Marshall, J. W. Ralls, F. J. Saunders and B. Riegel, *J. Biol. Chem.*, **228**, 339 (1957).

(17) F. Sondheimer, O. Mancera, H. Flores and G. Rosenkranz, THIS JOURNAL, **78**, 1742 (1956).

(18) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, *ibid.*, **75**, 266 (1953).

(19) It has already been demonstrated that acetylene dimagnesium bromide will add only once with steroidal 17-ketones, see ref. 17.

(20) All bioassays were conducted by Endocrine Laboratories, Madison, Wisc.

(21) All melting points are uncorrected and the rotations have been determined in chloroform except where noted to the contrary. We are indebted to Dr. J. Matthews and his staff for the determination of all spectra and rotations reported.

(22) This compound was originally obtained in low yield by chromium trioxide oxidation of 5α-androstan-3β,11β-diol-17-one, m.p. 156–158°; T. Reichstein, *Helv. Chim. Acta*, **19**, 402 (1936).

pure by recrystallization from acetone–hexane; m.p. 164–166°, $[\alpha]D$ −5°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.32; H, 10.91.

Action of Methyllithium on 5α-androstan-3β-ol-11,17-dione (I).—Anhydrous ether (150 ml.), 3 g. of I and 60 ml. of methyllithium reagent[23] were stirred at room temperature for 40 hours. After dilution with 100 ml. of water the ether was removed by distillation and the aqueous phase was chilled in ice. Filtration yielded 2.6 g. of IIIa, m.p. 149–154°, which was obtained pure by recrystallization from acetone–hexane. The material thus obtained was identical in all respects with the dimethyl derivative IIIa described in the preceding experiment.

11α,17α-Dimethyl-5α-androstan-11β,17β-diol-3-one (IIIb).—A mixture of pyridine (150 ml.), chromium trioxide (2.0 g.) and 2.0 g. of IIIa was maintained at room temperature overnight. After dilution with 200 ml. of ethyl acetate the mixture was passed through a pad of Celite and then washed consecutively with dilute hydrochloric acid, aqueous sodium bicarbonate and finally water. Drying, evaporation and crystallization from acetone–hexane then yielded 1.3 g. of IIIb, m.p. 198–203°, raised to m.p. 202–205°, $[\alpha]D$ + 6°, on further recrystallization.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.24; O, 14.35. Found: C, 75.03; H, 10.08; O, 15.00.

11α-Methyl-5α-pregnan-11β-ol (Vb).—A solution of 160 ml. of anhydrous ether, 2.0 g. of 5α-pregnan-11-one[7] and 70 ml. of methyllithium reagent[22] was maintained at room temperature for 18 hours. After dilution with water and distillation of the ether the solution was filtered to provide 1.8 g. of low melting crystalline material. This material was then passed through a column of unwashed alumina in hexane solvent whence the early fractions were combined and crystallized from pentane to yield 1.44 g. of Vb, m.p. 108–110°. Repeated recrystallization from acetone then yielded pure Vb, m.p. 111–113°, $[\alpha]D$ + 24°, no absorption in the carbonyl region of the infrared spectrum.

Anal. Calcd. for $C_{22}H_{38}O$: C, 82.95; H, 12.02; O, 5.02. Found: C, 83.17; H, 11.77; O, 4.89.

11α-Methyl-5β-pregnan-11β-ol (IVb) was prepared by the same method described in the preceding experiment. Thus from 1.5 g. of 5β-pregnan-11-one (IVa)[7] there was obtained following chromatography 1.0 g. of clean colorless oil which could not be obtained crystalline. The infrared spectrum of this substance was devoid of any carbonyl absorption and was unchanged after the material was subjected to an 18-hour pyridine–chromium trioxide oxidation.

11α-Methyl-Δ⁵-androsten-11β-ol-3,17-dione 3,17-Bis-ethylene Ketal (VIIb).—To 155 ml. of anhydrous tetrahydrofuran was added 6.22 g. of adrenosterone bis-ethylene ketal[10] and 125 ml. of 0.25 *M* ethereal methyllithium.[22] After 1.5 hours at room temperature, 50 ml. of water was added and the organic solvents were removed by distillation. The resulting aqueous suspension of crystals was then filtered to provide 4.2 g. of material, m.p. 179–186°. Following several recrystallizations from benzene–hexane the analytical sample possessed m.p. 192–194°, $[\alpha]D$ −94.1° (pyridine).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 71.25; H, 8.97; O, 19.78. Found: C, 70.90; H, 9.01; O, 20.10.

11α-Methyl-Δ⁴-androsten-11β-ol-3,17-dione (VIa).—Fifty ml. of acetone containing 1.5 g. of VIIb was treated with 50 mg. of *p*-toluenesulfonic acid monohydrate for 18 hours at room temperature. After this time the solution was diluted with water and extracted three times with 50-ml. portions of ethyl acetate. After washing first with dilute aqueous sodium bicarbonate and then water, the solvent was evaporated to leave a gum which was chromatographed over 40 g. of unwashed alumina. Benzene–hexane (1:1) elution provided a substance which crystallized from methanol to yield 0.86 g., m.p. 147–150°. Further crystallization from acetone–hexane then yielded pure VIa, m.p. 151–152°, $[\alpha]D$ + 162°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.61; H, 8.89.

(23) During the early stages of this work it was found convenient to employ a stock solution of methyllithium. Thus, methyl iodide (17 ml.) and lithium metal (4.0 g.) were allowed to react in 200 ml. of ether thereby yielding an ethereal solution approximately 2.5 molar in methyllithium.

11α-Methyl-11β-hydroxytestosterone (VIb). A. By Sodium Borohydride Reduction of VIa.—One gram of VIa was dissolved in 200 ml. of methanol and the resulting solution cooled to 0°. Sodium borohydride (0.075 g.) was then added and the mixture was allowed to stand for 2 hours. Acetic acid (0.1 ml.) was added and the solution was concentrated to *ca.* 20 ml. Dilution with cold water provided 0.9 g. of crystals which were chromatographed on 20 g. of unwashed alumina. Benzene–ether (40:60) then provided 0.73 g. of VIb, m.p. 245–249°, which led to pure VIb on recrystallization from acetone; m.p. 255–256°, $[\alpha]D$ + 111°, λ_{max}^{EtOH} 244 mμ, log ε 4.19.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.20; H, 9.34.

By the Enamine VIII.—Methanol (4 ml.) containing 0.50 g. of VIa was treated at its boiling point with 0.3 ml. of pyrrolidine. After 3 minutes the mixture was chilled in ice and the resulting crystals were collected to provide 0.55 g. which gave the pure enamine VIII by recrystallization from methanol–pyridine; m.p. 249–250°, $[\alpha]D$ − 140° (pyridine), λ_{max}^{ether} 281 mμ, log ε 4.35.

Anal. Calcd. for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.55; N, 3.74. Found: C, 77.87; H, 9.43; N, 3.85.

Twenty ml. of tetrahydrofuran containing 0.5 g. of VIII was added rapidly to 120 ml. of anhydrous ether containing 0.3 g. of lithium aluminum hydride. After being heated for 10 minutes at reflux the excess hydride was destroyed with ethyl acetate and saturated aqueous sodium sulfate. Filtration and evaporation then provided 0.5 g. of colored gum which was heated on a steam-bath with 15 ml. of methanol, 1.1 g. of sodium acetate, 1.2 ml. of water and 0.6 ml. of acetic acid. After 4 hours the mixture was concentrated to 5 ml. and diluted with water. Following ethyl acetate extraction the extracts were washed with water, dried and evaporated to leave a residue which was chromatographed over unwashed alumina. Elution with benzene–ether (60:40) provided 0.23 g. of VIb, m.p. 243–246°. Recrystallization from acetone then gave material identical in all respects with that prepared above in A.

C. By Lithium Aluminum Hydride Reduction of VIa Followed by Manganese Dioxide Oxidation.—One gram of VIa dissolved in 30 ml. of tetrahydrofuran was added to 30 ml. of tetrahydrofuran containing 1.0 g. of lithium aluminum hydride. Following 2 hours at reflux temperature the excess hydride was destroyed by the cautious addition of 10 ml. of saturated aqueous sodium sulfate. The precipitated salts were then filtered and washed with ethyl acetate. The combined filtrates were evaporated to dryness leaving 0.67 g. of crystals, m.p. 205–210°, whose infrared spectrum exhibited no carbonyl absorption bands. When 0.58 g. of this material was stirred at room temperature for 15 hours in 60 ml. of chloroform containing 6 g. of manganese dioxide there was obtained, following filtration and evaporation, 0.48 g. of crystals, m.p. 233–235°. Several recrystallizations from acetone provided material identical in all respects with that obtained in part A above.

11-Methyl-Δ⁴,⁹⁽¹¹⁾-androstadien-3,17-dione (IXa).—A solution of pyridine (20 ml.) and 2.0 g. of 11α-methyl-Δ⁴-androsten-11β-ol-3,17-dione (VIa) was treated at 0° with 1.2 ml. of thionyl chloride. After 2 minutes at this same temperature the solution was diluted with 30 ml. of water and extracted with chloroform. The chloroform extract was then washed consecutively with dilute hydrochloric acid, 5% aqueous sodium bicarbonate and finally with water. After drying over sodium sulfate and evaporation there remained 1.4 g. of semi-solid material which was treated with decolorizing carbon in ether solution. Concentration provided 1.0 g. of crystals, m.p. 124–126° which were obtained pure after one further crystallization from this same solvent, m.p. 131–133°, $[\alpha]D$ + 225°, λ_{max}^{EtOH} 240 mμ, log ε 4.18.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 80.49; H, 8.78; O, 10.73. Found: C, 80.61; H, 8.75; O, 11.04.

11-Methyl-17α-ethynyl-Δ⁴,⁹⁽¹¹⁾-androstadien-17β-ol-3-one (IXb). A. By Direct Ethynylation of 11-Methyl-Δ⁴,⁹⁽¹¹⁾-androstadien-3,17-dione (IXa).—Potassium metal (0.5 g.) was dissolved in 15 ml. of *t*-butyl alcohol and to the resulting solution was added 0.5 g. of IXa and 40 ml. of benzene. The mixture was then stirred at room temperature for 15 minutes, whereafter a slow steady stream of acetylene was bubbled through the mixture for 15 hours. At the end of this time the solution was diluted with 50 ml. of benzene and washed

with 20 ml. of dilute hydrochloric acid. After being washed to neutrality with water, the organic phase was dried over sodium sulfate and evaporated to dryness. Infrared examination of the crude residue showed the presence of a short C–H stretching band indicative of the ethynyl grouping, but in addition there remained a fairly strong band at 5.77 μ (17-ketone) due to unreacted starting material. Upon chromatography over 10 g. of alumina there was obtained in the benzene–ether (8:2) fractions 50 mg. of oily crystals. Following rechromatography on 1 g. of alumina, benzene elution provided a small crystalline fraction which could be recrystallized from ether–hexane to give material with m.p. 168–170°, identical in all respects with the authentic ethynyl derivative obtained below in part B.

B. By Hydrolysis of 11-Methyl-17α-ethynyl-$\Delta^{5,9(11)}$-androstadien-17β-ol-3-one 3-Ethylene Ketal (XIb).—Two hundred mg. of XIb in 4 ml. of tetrahydrofuran was treated with 3.2 ml. of aqueous 3 *N* perchloric acid. After 3 hours at room temperature the solution was diluted with water and extracted with ethyl acetate. The extract was then washed with water, dried over sodium sulfate and evaporated to leave 0.12 g. of gum. Crystallization from acetone–hexane provided 40 mg. of crystals, m.p. 160–163°. One further recrystallization from the same solvent pair yielded the analytical sample, m.p. 168–170°, $[\alpha]_D$ + 24°, λ_{max}^{EtOH} 240 mμ, log ϵ 4.18; λ_{mix}^{KBr} 2.92, 3.08, 6.06 and 6.23 μ.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70; O, 9.86. Found: C, 81.12; H, 8.57; O, 10.14.

17α-Ethynyl-11-ketotestosterone (VIe).—One gram of adrenosterone was treated under the conditions reported above for the ethynylation of IXa. By these means there was obtained following recrystallization from benzene–acetone 0.40 g. of pure VIe, m.p. 297–299°, $[\alpha]_D$ + 185° (pyridine), λ_{max}^{EtOH} 238 mμ, log ϵ 4.21; lit.[16] m.p. 293–295°, $[\alpha]_D$ + 122° (dioxane), λ_{max}^{EtOH} 238 mμ, log ϵ 4.18.

11-Ketotestosterone 3-Monoethylene Ketal (Xa).—A solution consisting of 3.5 g. of 11-ketotestosterone (VIf),[18] 500 ml. of benzene, 40 ml. of ethylene glycol and 0.20 g. of *p*-toluenesulfonic acid monohydrate was heated at reflux temperature with a water separator for 15 hours. The solution was then washed with 100 ml. of 5% aqueous sodium bicarbonate followed by water. Drying and evaporation of the residue led to 3.2 g. of crystals, m.p. *ca.* 160°, which possessed no selective ultraviolet absorption in the 240 mμ region. Chromatography of a 0.20-g. aliquot of this material on 4.0 g. of alumina provided in the benzene–ether (8:2) eluates 120 mg. of crystals, m.p. 174–178°, which were obtained pure after several recrystallizations from acetone–hexane; m.p. 186–188°, $[\alpha]_D$ + 13°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.68; H, 8.87; O, 18.17.

Acetylation of this substance under the usual conditions employing pyridine–acetic anhydride provided **11-ketotestosterone 3-monoethylene ketal 17-acetate (Xb)** which was recrystallized from acetone–hexane; m.p. 183–185°, $[\alpha]_D$ − 34°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.60. Found: C, 70.95; H, 8.24; O, 20.36.

Further characterization of Xa was accomplished by pyridine–chromium trioxide oxidation which provided **adrenosterone 3-monoethylene ketal (Xf)**, recrystallized from acetone–hexane, m.p. 209–211°, $[\alpha]_D$ + 39°.

Anal. Calcd. for $C_{21}H_{28}O_4$ + 1/2 C_3H_6O: C, 72.35; H, 8.36; O, 19.28. Found: C, 72.36; H, 8.06; O, 19.40.

11α-Methyl-Δ^5-androsten-11β,17β-diol-3-one 3-Ethylene Ketal (Xc).—An ethereal solution (200 ml.) of methyllithium prepared as previously described[22] was added to 500 ml. of tetrahydrofuran containing 13 g. of Xa. After 3 hours at room temperature the reaction mixture was poured into water and the organic solvents were removed by distillation. The residual crystals were collected and chromatographed on 500 g. of neutral alumina. Benzene–ether (4:1) elution thus provided 5.1 g. of crystals, m.p. 195–200°, which were pure after two crystallizations from acetone, m.p. 208–210°, $[\alpha]_D$ − 44°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 72.89; H, 9.49; O, 17.66. Found: C, 73.27; H, 9.57; O, 17.34.

11α-Methyl-Δ^5-androsten-11β-ol-3,17-dione 3-Monoethylene Ketal (Xd).—Ten ml. of pyridine containing 0.6 g. of chromium trioxide was cooled to 0° and 0.40 g. of Xc dissolved in 7 ml. of pyridine was added. The solution was then allowed to warm up and after being kept at room temperature overnight it was diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was then percolated through a column containing 20 g. of alumina. Continued elution with ethyl acetate provided 0.42 g. of gum which was crystallized from acetone to give 0.25 g. of crystals, m.p. 231–235°. One further crystallization from the same solvent led to the analytical sample, m.p. 242–244°, $[\alpha]_D$ ± 0°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.06; H, 8.54; O, 18.25.

11-Methyl-$\Delta^{5,9(11)}$-androstadien-3,17-dione 3-Monoethylene Ketal (XIa).—A mixture of pyridine (8 ml.), 1.5 g. of Xd and 0.9 ml. of thionyl chloride was stirred at 0° for 5 minutes. At the end of this time the solution was diluted with water (5 ml.) and extracted 3 times with 15-ml. portions of ethyl acetate. After drying and evaporation at reduced pressure, the residue was crystallized from hexane to yield 1.0 g. of crystals, m.p. 129–131°. Recrystallization from the same solvent gave the pure compound, m.p. 135–136°, $[\alpha]_D$ + 103°, which decomposes slowly at room temperature.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83; O, 14.02. Found: C, 77.27; H, 8.69; O, 14.31.

11-Methyl-17α-ethynyl-$\Delta^{5,9(11)}$-androstadien-17β-ol-3-one 3-Ethylene Ketal (XIb).—To 100 ml. of tetrahydrofuran was added 25 ml. of methylmagnesium bromide. A slow steady stream of acetylene was then passed through the solution for 3 hours whereafter the acetylene stream was discontinued and 0.50 g. of XIa was added. The mixture was heated at reflux temperature for 6 hours and then kept at room temperature overnight. Decomposition of the salts and excess reagent was effected by the addition of 25 ml. of saturated aqueous ammonium chloride. Ethyl acetate extraction, followed by washing with water, drying and evaporation then gave 0.45 g. of semi-solid material which was chromatographed over 10 g. of neutral alumina. Elution with hexane–benzene (1:1) then gave 0.30 g. of crystals, m.p. 145–150°, raised by several recrystallizations from acetone–hexane to m.p. 161–162°, $[\alpha]_D$ − 46°.

Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75; O, 13.03. Found: C, 77.99; H, 8.87; O, 12.86.

11-Methyl-$\Delta^{5,9(11)}$-androstadien-17β-ol-3-one 3-Ethylene Ketal (XIc).—A solution of 0.25 g. of XIa in 10 ml. of tetrahydrofuran was added to 10 ml. of the same solvent containing 0.5 g. of lithium aluminum hydride. After 3 hours at reflux temperature the solution was cooled and the excess reagent was destroyed by the cautious addition of saturated aqueous sodium sulfate. Following filtration from the solid residue the filtrate was evaporated to leave 0.23 g. of clear gum which was difficult to crystallize the first time. Ether was used for the crystallizations and provided the analytical sample, m.p. 124–125°, $[\alpha]_D$ + 24°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.94. Found: C, 76.52; H, 9.81; O, 13.74.

11-Methyl-$\Delta^{4,9(11)}$-androstadien-17β-ol-3-one (IXc).—A 0.68-g. sample of XIa was treated exactly as was described in the preceding experiment thereby obtaining *ca.* 0.7 g. of clear gum. This material was then allowed to stand for 3 hours in a solution of 12 ml. of tetrahydrofuran and 11 ml. of 3 *N* aqueous perchloric acid. Following dilution with 20 ml. of water the opaque solution was maintained at 0° for 12 hours. Filtration then gave 0.45 g. of very fine crystals, m.p. 111–116°, which were readily obtained pure after 3 recrystallizations from ether; m.p. 131–133°, $[\alpha]_D$ + 112°, λ_{max}^{EtOH} 240–242 mμ, log ϵ 4.16.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.66. Found: C, 79.79; H, 9.40; O, 10.65.

11α-Methyl-17α-ethynyl-Δ^5-androsten-11β,17β-diol-3-one 3-Ethylene Ketal (Xe).—Acetylenedimagnesium bromide in 100 ml. of anhydrous tetrahydrofuran was prepared from 25 ml. of methylmagnesium bromide as previously described in the preparation of XIb. To the resulting reagent was then added 1.50 g. of Xd and the mixture was heated at reflux temperature for 6 hours. After remaining at room temperature overnight, the reaction was worked as previously described. Chromatography of the residue on 35 g. of neutral alumina provided in the benzene–ether (1:1) eluates 0.80 g. of crystals, m.p. 156–160°. Six recrystallizations from acetone–hexane was necessary to

obtain a 0.20-g. sample of constant melting point, 207–209°, $[\alpha]D - 74°$.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.55. Found: C, 74.70; H, 8.97; O, 16.41.

11α - **Methyl** - **17α** - **ethynyl** - Δ^4 - **androsten** - **11β,17β-diol** - **3** - **one** (**VIg**).—By the perchloric acid procedure previously described 0.34 g. of Xe was hydrolyzed to provide 0.34 g. of oily crystals. Two crystallizations from acetone and one from ethyl acetate yielded 0.14 g. of analytically pure material, m.p. 240–242°, $[\alpha]D + 20°$, λ_{max}^{EtOH} 242–244 mμ, log ε 4.15.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.70; H, 8.73.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Total Synthesis—Hydrochrysene Approach. Part XII.[1] An Alternative Route to Testosterone. The Synthesis of *l*-Testosterone and of *dl*-13-Isotestosterone

BY WILLIAM S. JOHNSON, WALTER A. VREDENBURGH AND J. E. PIKE

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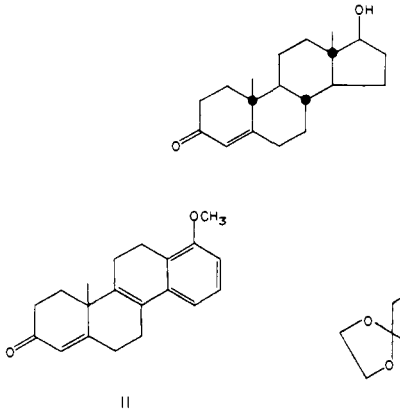
An alternative approach has been developed, which obviates some of the experimental difficulties attending the previous use of the ketal III in the first total synthesis of testosterone. The present synthesis involved the following steps. The hydroxy compound IV, available in three steps from the tetracyclic ketone II, was converted, by Birch reduction, into a mixture of α,β-unsaturated ketones V and VI, both of which could be hydrogenated to the same hydroxy ketone VII. The structure of this last substance was proved by conversion to the diketone and thence to the unsaturated diketone IX of established configuration. Condensation of the hydroxy ketone VII with furfural followed by methylation with potassium *t*-butoxide and methyl iodide gave a mixture of epimers X (R = αCH₃, R′ = H) and X(R = βCH₃, R′ = H), predominantly the former. The latter, as its acetate (R′ = Ac), was ozonized to give the diacid XI (R = H) which was converted, through a Dieckmann cyclization of the ester (R = CH₃), into *dl*-3α-hydroxyetiocholan-17-one (XII). This substance was oxidized to the diketone XIII, brominated and dehydrobrominated, to give *dl*-androstenedione (XIV). Phytochemical reduction afforded synthetic *d*-testosterone and *l*-androstenedione. The latter was converted by known methods into the hitherto unknown *l*-testosterone. *dl*-13-Isotestosterone was synthesized in connection with a continuation of the study of the previous approach to testosterone.

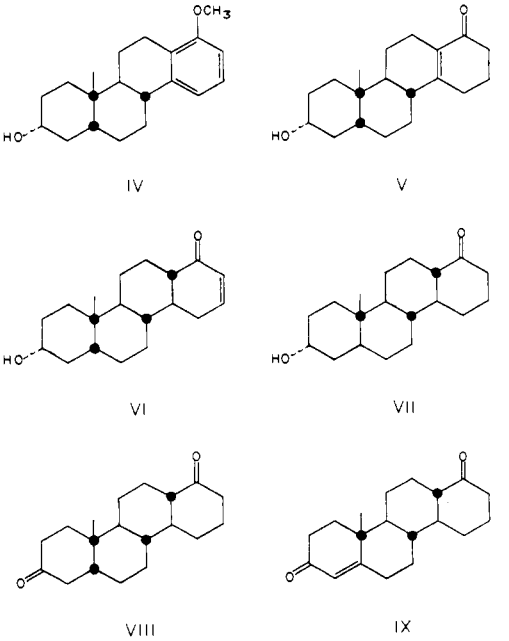
In a previous paper,[2] we described the total synthesis of testosterone (I) in ten steps from the readily accessible tetracyclic ketone II. The first step involved conversion to the ketal III in order to protect the sensitive ring A α,β-unsaturated ketone system which, in the last stage of the synthesis, was finally regenerated by hydrolysis. While this



II III

method of preserving the unsaturated ketone system provides a relatively short pathway to the desired objective, it suffers in that it limits the types of operations that can be performed on the intermediates. Thus mild acidic solvolytic conditions must be avoided, and all reactions that attack olefinic bonds, *e.g.*, hydrogenation and ozonization, must be performed selectively so as to minimize reaction with the double bond in ring B of the ketal III.

Another approach to the objective involves removal of the α,β-unsaturated ketone system of I by reduction of the A/B *cis*-saturated alcohol (*cf.* formula IV) then, at an appropriate later state, reintroduction of the unsaturated ketone residue by oxidation, bromination and dehydrobromination. Although less appealing intellectually, this more pedestrian approach has certain practical advan-



IV V VI VII VIII IX

tages over that involving the ketal. The present paper describes our studies on this second scheme which, although adding to the number of steps required, has led to a better over-all yield than the

(1) Paper XI, W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, THIS JOURNAL, **82**, 614 (1960).

(2) Paper X, W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).