235–245° dec. The analytical sample was recrystallized from acetone-ether, m.p. 242–247° dec., $[\alpha]_D$ +113°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,300), $\lambda\lambda_{max}^{nujol}$ 5.77, 5.82, 6.00, 6.12, 6.19, 7.02, 7.96, 8.04 μ.

Anal. Calcd. for $C_{23}H_{28}O_4Cl_2$: C, 62.87; H, 6.42; Cl, 16.14. Found: C, 63.03; H, 6.50; Cl, 16.23.

BLOOMFIELD, N. J.

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

Steroids. CLVI.[1] Ring D Unsaturated 16-Methylated Corticosteroids

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Two routes to 16α-methyl "S" (V) are described. While one route was straight-forward the second involved the novel hydrobromic acid–acetone cleavage of a 16β-methyl-16α,17α-oxido-20-keto steroid (IX) which led to a mixture of 16-methylene- and Δ[15]-16-methyl-17α-hydroxy-20-keto compounds (X). Catalytic reduction of X gave exclusively the 16α-methyl-17α-hydroxy-20-ketone (VI) readily convertible to V. Application of the hydrobromic acid opening to 16β-methyl-16α,17α-oxido-allopregnane-3β-ol-11,20-dione (XVI) gave predominantly the Δ[15]-16-methyl steroid (XVII) which was converted to Δ[15]-16-methylprednisone acetate (XXI).

Recently it has been demonstrated that introduction of a 16α-methyl substituent into the hydrocortisone or prednisolone molecule[3] as well as into 9-fluoro,[4] 6-fluoro[5a,e] and 6,9-difluorocorticoids[5b–d] increases anti-inflammatory activity while sodium retention is decreased. An ideal substrate for many of these cortical hormones would appear to be 16α-methyl-Δ[4]-pregnene-17α,21-diol-3,20-dione (Vb) (16α-methyl "S"), as fermentation with 11-hydroxylating organisms would lead to 16α-methylhydrocortisone or to 16α-methyl-11-epihydrocortisone. In this paper we describe the preparation of 16α-methyl "S" by two different routes as well as the preparation of the novel Δ[15]-16-methylprednisone acetate (XXI).

Our first route to 16α-methyl "S"[6] was straightforward[7] and unexceptional. 16α-Methyl-Δ[5]-pregnen-3β-ol-20-one acetate (I)[8] was chlorinated at low temperature in carbon tetrachloride yielding the 5α,6β-dichloride (II). Application of Gallagher's[9] 17-hydroxyl introduction followed. Prolonged treatment of II with boiling acetic anhydride in the presence of *p*-toluenesulfonic acid gave the Δ[17(20)]-enol acetate which was epoxidized with monoperphthalic acid. Alkaline hydrolysis then gave 5α,6β-dichloro-16α-methyl-allopregnane-3β,17α-diol-20-one (III), the over-all yield for this three-step sequence being somewhat low apparently due to the resistance of 16α-methyl-20-ketones to C_{-20} enol acetate formation. Bromination of III at C_{-21} in dioxane solution followed by successive displacement with sodium iodide and potassium acetate yielded the 21-acetate (IV), completing the build-up of the cortical side-chain. Oxidation of IV with 8*N* chromic acid in sulfuric acid–acetone[10] gave the 3-ketone-5,6-dichloride which, without isolation, was dechlorinated with zinc dust in hot acetic acid yielding 16α-methyl "S" 21-acetate (Va). The free 16α-methyl "S" (Vb) was readily obtained by low temperature saponification of Va with methanolic potassium hydroxide.

A second route to V proceeded from 16-methyl-Δ[5,16]-pregnadiene-3β-ol-20-one acetate[11] (VIII) which was converted to the 16α,17α-epoxide (IXa) by treatment with alkaline hydrogen peroxide. When the epoxide 3-acetate (IXb) in acetone solution was treated with concentrated aqueous hydrobromic acid for about twenty minutes at 5°, ep-

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(1) Paper CLV, in press.

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(3) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958); E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958).

(4) G. E. Arth, J. Fried, D. B. R. Johnson, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. J. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(5)(a) J. A. Edwards, A. Zaffaroni, H. J. Ringold, and C. Djerassi, *Proc. Chem. Soc.*, **87** (1959); (b) J. A. Edwards, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3156 (1959); (c) W. P. Schneider, J. H. Lincoln, G. B. Spero, H. C. Murray, and J. L. Thompson, *J. Am. Chem. Soc.*, **81**, 3167 (1959); (d) S. Karaday and M. Sletzinger, *Chem. and Ind.*, 1159 (1959); (e) J. A. Edwards, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 2318 (1960).

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(7) J. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1621 (1959); J. A. Cutler, Jr., J. F. Fisher, and J. D. Chemerda, *J. Org. Chem.*, **24**, 1629 (1959); J. A. Cutler, Jr., L. Mandell, J. F. Fisher, D. Shew, and J. D. Chemerda, *J. Org. Chem.*, **24**, 1629 (1959) have used a similar sequence for the preparation of compound "S" acetate.

(8) R. E. Marker and H. M. Crooks, *J. Am. Chem. Soc.*, **64**, 1280 (1942).

(9) T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951).

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(11) A. Wettstein, *Helv. Chim. Acta.*, **27**, 1803 (1944).

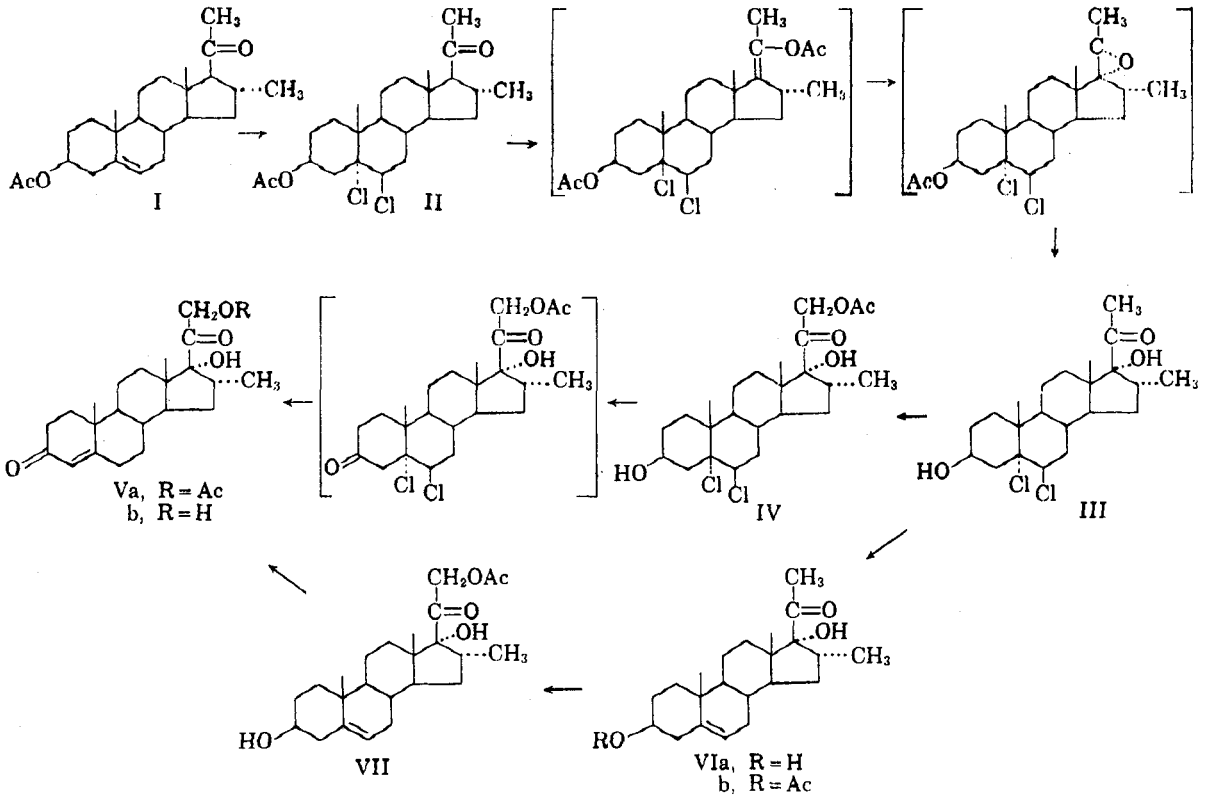
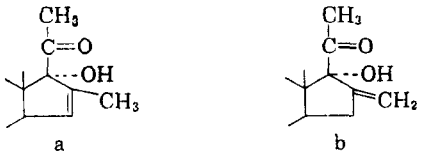


Figure 1

oxide opening occurred but the resultant product(s) (X) was bromine-free and not the anticipated bromohydrin.

The elemental analysis, infrared spectrum, and lack of high maximal absorption in the ultraviolet spectrum of X indicated that a hydroxyl group and an additional double bond had been introduced by epoxide cleavage. When it was found that X could be hydrogenated in methanol solution over a palladium-carbon catalyst to give in high yield 16α-methyl-Δ^5-pregnene-3β,17α-diol-20-one 3-acetate (VIb), a product which we had also obtained by zinc dechlorination and acetylation of the 5,6-dichloride (III), it was obvious that no skeletal or D-homo rearrangement had occurred. Thus only two structures were possible for X, the Δ^{15}-16-methyl formulation (a) or the exocyclic 16-methylene structure (b).



Determination of the NMR spectrum of X demonstrated that the product of melting point 190–195°, obtained in approximately 90% yield from IXb, was a mixture of about two parts of 16-methylene compound (b) and one part of Δ^{15}-16-methyl (a).[12] An analytical specimen of X, crystallized to constant melting point of 202–204° consisted of 40% 16-methylene and 60% of Δ^{15}-16-methyl isomer by NMR.[12,13] Additional confirmatory evidence for the presence of an allylic 17α-hydroxyl group in X was found in its facile dehydration by *p*-toluenesulfonic acid in benzene to 16-methyl-$\Delta^{5,14,16}$-pregnatrien-3β-ol-20-one acetate (XIII), λ_{max} 310 mμ, log ϵ 4.08. Plattner *et al.*[14] report for $\Delta^{5,14,16}$-pregnatriene-3β-ol-20-one, λ_{max} of 307 mμ.

Despite the preponderance of the 16-methylene isomer in X it was of interest that no exocyclic methylene group could be detected in the infrared spectrum.

For preparation of the important intermediate 16α-methyl-Δ^5-pregnene-3β,17α-diol-3-acetate (VIb) it was not necessary to purify X, and thus, the mixture of isomers of m.p. 190–195° was hydrogenated in high yield to VIb. Alkaline hydrolysis saponified the 3-acetate grouping and 16α-methyl-17α-hydroxypregnenolone (VIa) was iodinated[15] at C_{21} with iodine–calcium oxide in tetrahydrofuran-methanol. The resultant 21-iodo com-

(12) We are indebted to Dr. J. N. Shoolery of Varian Associates, Palo Alto, Calif., for the NMR spectra and their interpretation.

(13) It was found later that the exact isomer ratio varied with reaction conditions, prolongation of time and higher temperature favoring formation of the Δ^{15}-16-methyl isomer. Hydrochloric acid gave results essentially similar to hydrobromic acid.

(14) Pl. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, 31, 249 (1948).

(15) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, 80, 250 (1958).

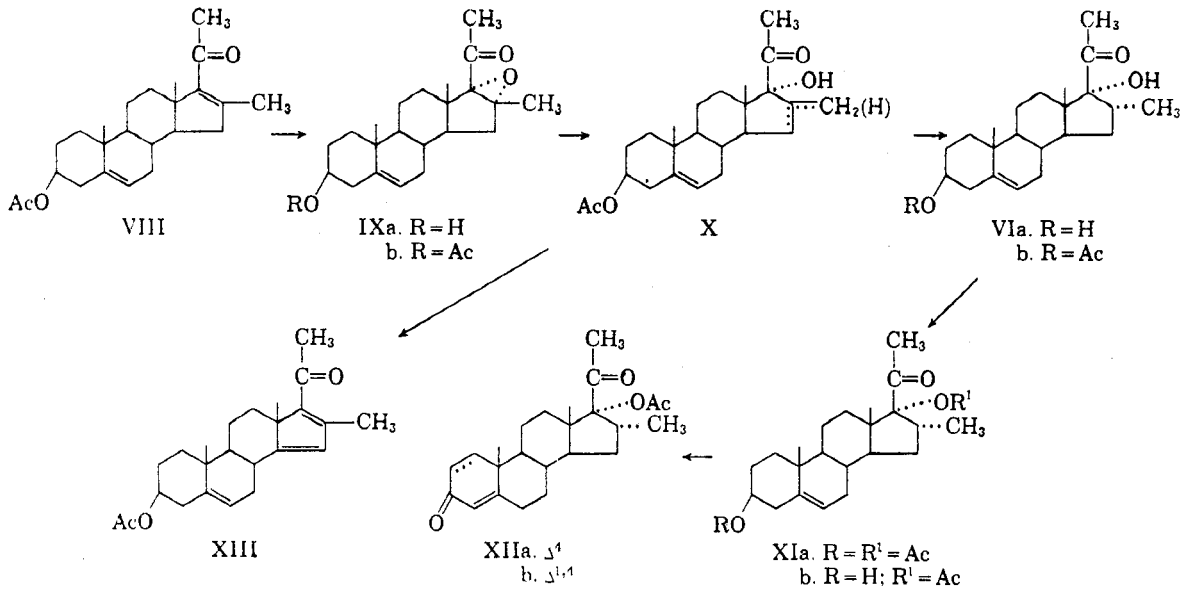


Figure 2

pound, without purification, was heated with potassium acetate in acetone yielding 16α-methyl-Δ^5-pregnene-3β,17α,21-triol-20-one 21-acetate (VII), the latter compound being converted to 16α-methyl "S" 21-acetate (Va) by oxidation with 8*N* chromic acid in acetone-sulfuric acid followed by acid isomerization of the intermediate $\Delta^{5(6)}$-3-ketone.

As 17α-acetoxyprogesterone is a moderately potent oral progestational agent[16] it was of interest to prepare 16α-methyl-17α-acetoxyprogesterone (XIIa) and the corresponding 1-dehydro compound (XIIb). For this purpose 16α-methyl-17α-hydroxypregnenolone 3-acetate (VIb) was converted to the 3,17-diacetate (XIa) by treatment with acetic anhydride–*p*-toluenesulfonic acid. Brief saponification with methanolic–potassium hydroxide gave the 17-monoacetate (XIb) which was converted by Oppenauer oxidation to 16α-methyl-17α-acetoxyprogesterone (XIIa).[17] Dehydrogenation of XIIa with selenium dioxide[18a–d] in *t*-butyl alcohol[18b,c] gave 1-dehydro-16α-methyl-17α-acetoxyprogesterone (XIIb).

We also investigated the hydrobromic acid-acetone cleavage of a 16-methyl-16α,17α-oxide in the 11-keto-allopregnanolone series.[19] Δ^{16}-Allopregnen-3β-ol-11,20-dione acetate[20] (XIV) was allowed to react with diazomethane[11] to yield the 16,17-pyrazoline which was thermally decomposed to 16-methyl-Δ^{16}-allopregnen-3β-ol-11,20-dione acetate (XV). Alkaline hydrogen peroxide yielded the 16β-methyl-16α,17α-oxide-3β-ol(XVI) which was allowed to react with hydrobromic acid in acetone yielding, as above, a mixture of 17α-hydroxy-Δ^{15}-16-methyl and 17α-hydroxy-16-methylene isomers (XVIIa). A sample of total reaction product (XVIIa), obtained in almost quantitative yield, was acetylated and the acetate (XVIIb) without crystallization submitted for NMR determination. In this case it was found that the product consisted of 70% of the Δ^{15}-16-methyl isomer and 30% of the 16-methylene isomer[12] and on the reasonable assumption that XVIIa consisted of the same isomer mixture it was decided to convert this mixture to the corresponding prednisone derivative. 21-Iodination as described above followed by potassium acetate displacement gave the corresponding 21-acetoxy compound (XVIIII). Oxidation with chromic acid in acetone–sulfuric acid gave the 3-ketone (XIX) which on dehydrogenation with selenium dioxide in 2-methyl-2-butanol in the presence of a small amount of pyridine gave a mixture, readily resolved by chromatography, of 16-methyl-$\Delta^{1,15}$-pregnadiene-17α-21-diol-3,11,20-trione acetate (XX) and of 16-methyl-$\Delta^{1,4,15}$-pregnatriene-17α-21-diol-3,11,20-trione acetate (XXI) (16-methyl-Δ^{15}-

(16) New Steroid Compounds with Progestational Activity, *Ann. N. Y. Acad. Sci.*, 71, 722 (1958).

(17) For applications of similar reaction sequences to the preparation of 17α-acetoxyprogesterone see R. B. Turner, *J. Am. Chem. Soc.*, 75, 3489 (1953); H. J. Ringold, B. Loken, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 78, 816 (1956).

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(19) After completion of our work G. Nomine, D. Bertin, and A. Pierdet [*Tetrahedron*, 8, 217 (1960)] reported the hydrochloric acid-acetone cleavage of 16β-methyl-16α,17α-oxido-pregnan-3α-ol-11,20-dione 3-acetate with results similar to ours.

(20) E. M. Chamberlin, W. U. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, *J. Am. Chem. Soc.*, 73, 2396 (1951); C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, 74, 3634 (1952).

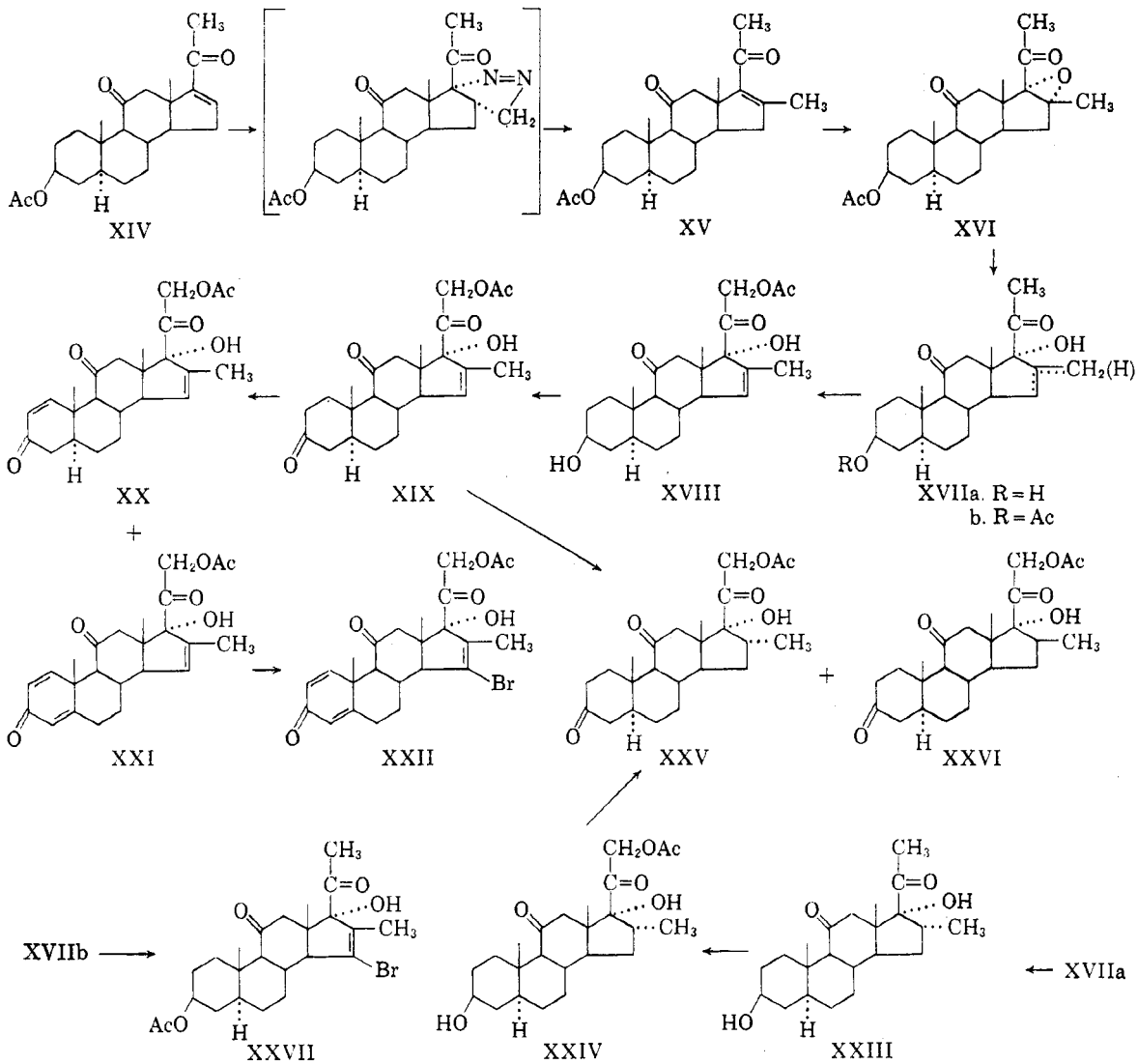

Figure 3

prednisone acetate). The NMR determination[12] of XX and XXI was not definitive but we prefer to formulate these compounds as primarily Δ^{15}-derivatives on the basis of the isomer ratio of the starting material XVIIa recognizing that they undoubtedly contain some of the 16-methylene isomer.

Treatment of the isomer mixture XVIIb with *N*-bromo-acetamide in dioxane–perchloric acid did not lead to the anticipated[21] bromohydrin but gave instead a vinyl bromo compound, 15-bromo-16-methyl-Δ^{15}-allopregnene-3β,17α-diol-11,20-dione 3-acetate (XXVII). The structure of XXVII was confirmed by elemental analysis, infrared spectrum, and NMR examination[12] which showed that there were no hydrogen atoms attached to a carbon-carbon double bond. Furthermore, separate peaks for five C-methyl groups could be observed. Application of this *N*-bromoacetamide reaction to 16-methyl-Δ^{15}-prednisone acetate (XXI) gave what appears to be a homogeneous bromo compound XXII to which, in analogy with XXVII, we assign the structure 15-bromo-16-methyl-$\Delta^{1,4,15}$-pregnatriene-17α,21-diol-3,11,20-trione acetate (15-bromo-16-methyl-Δ^{15}-prednisone acetate).

A number of structural inter-relations are worthy of mention. The isomer mixture XVIIa (primarily 16-methyl-Δ^{15}-allopregnene-3β,17α-diol-11,20-dione) was hydrogenated over palladium-carbon in methanol yielding a single product XXIII, 16α-methylallopregnane-3β,17α-diol-11,20-dione. This compound was converted to the 21-acetoxy derivative (XXIV) by the previously described 21-iodination sequence whence chromic acid oxidation yielded 16α-methyl-allopregnane-17α,21-diol-3,11,-20-trione acetate (XXV) identical with an authentic sample[22] prepared by an unambiguous route. When the 21-acetoxy compound XIX was hydrogenated

(21) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, 79, 1130 (1957).

(22) We are grateful to Dr. S. Szpilfogel (N. V. Organon, Oss, Holland) for providing us with this sample which was prepared from hecogenin.

under the same conditions approximately equal quantities of two dihydro isomers were obtained. One, the less polar on alumina, proved to be 16α-methyl-allopregnane-17α-21-diol-3,11,20-trione acetate (XXV) while the other, XXVI, can only be the corresponding 16β-methyl isomer. Apparently the presence of an acetoxy group at C_{21} is a steric bar to absorption of the catalyst and hydrogen on the steroid β-face, accounting for the lack of hydrogenation specificity in this case in contrast to the reduction of XVIIa and of X.

EXPERIMENTAL[23]

5α,6β-Dichloro-16α-methylallopregnan-3β-ol-20-one acetate (II). A solution of 16α-methyl-Δ⁵-pregnen-3β-ol-20-one acetate[8] (I) (10 g.) in 1 l. of carbon tetrachloride containing 2.5 ml. of pyridine was cooled to 0° and 37 ml. of a 0.8*N* solution of chlorine in carbon tetrachloride was added during 10 min. After standing for an additional 10 min. at 0° the reaction mixture was washed with dilute hydrochloric acid and water, dried over sodium sulfate, and the solvent removed *in vacuo*. Crystallization of the residue from ethyl acetate–hexane afforded 4.3 g. of II, m.p. 195–198°, and a second crop of 1.7 g., m.p. 194–197°. Several recrystallizations from the same solvent pair afforded the analytical specimen, m.p. 196–199°, $[\alpha]_D$ −5°.

Anal. Calcd. for $C_{24}H_{36}Cl_2O_3$: C, 64.98; H, 8.18. Found: C, 64.79; H, 8.06.

5α,6β-Dichloro-16α-methylallopregnane-3β,17α-diol-20-one (III). The 5,6-dichloride II (12 g.) and *p*-toluenesulfonic acid (5.2 g.) were dissolved in 1.2 l. of acetic anhydride and the reaction mixture subjected to slow distillation for 15 hr. whence about 800 ml. of distillate was collected. The cooled solution was diluted with 2 l. of benzene and then washed with cold 5% potassium hydroxide solution and finally with water to neutrality. The organic phase was dried over sodium sulfate, concentrated to *ca.* 500 ml. and adsorbed on a column of 500 g. of ethyl acetate–washed alumina. Elution with benzene yielded 10.6 g. of $\Delta^{17(20)}$-enol acetate as a yellow oil. The crude enol acetate was dissolved in 360 ml. of benzene and 60 ml. of solvent was distilled to remove moisture. The cooled solution was then treated with a solution of 4.4 g. of monoperphthalic acid in 42 ml. of ether and the epoxidation allowed to proceed for 16 hr. The phthalic acid which had precipitated was removed and the filtrate washed with 5% sodium carbonate solution and then water. After drying over sodium sulfate the solution was evaporated and the residual oil dissolved in 140 ml. of methanol. A solution of potassium hydroxide (12.8 g.) in methanol (115 ml.) and water (25 ml.) was added and the mixture allowed to stand for 1 hr. at room temperature before neutralization with acetic acid (13 ml.). Cooling of the solution in an ice bath for several hours gave 4.8 g. of III, m.p. 203–205°, and dilution of the mother liquors with water precipitated additional material which weighed 2.2 g., m.p. 200–205°, after crystallization from methanol. The two crops were combined and recrystallized from methanol yielding 4.3 g. of III, m.p. 210–212°. The analytical sample melted at 215–217°, $[\alpha]_D$ −61°.

Anal. Calcd. for $C_{22}H_{34}Cl_2O_3$: C, 63.29; H, 8.21; Cl, 17.00. Found: C, 62.96; H, 7.75; Cl, 16.46.

5α,6β-Dichloro-16α-methylallopregnane-3β,17α,21-triol-20-one 21-acetate (IV). A solution of 5 g. of III in 200 ml. of dioxane was treated dropwise over a 15-min. period with 2.1 g. of bromine in 10 ml. of dioxane and then poured into aqueous bicarbonate. The 21-bromo compound after filtration, drying and recrystallization from methanol melted at 194–196° dec. and weighed 4.3 g. Without further purification the compound was dissolved in acetone (250 ml.), sodium iodide (2.4 g.) was added and the mixture boiled for 3 hr. under reflux. Potassium acetate (20 g.) was added and heating continued for an additional 20 hr. Removal of solvent and water addition yielded 3.71 g. of IV, m.p. 125–132°. After crystallization from aqueous methanol the compound, a hemihydrate, exhibited a constant melting point of 127–134°, $[\alpha]_D$ −45°, λ_{max}^{KBr} 5.73, 5.82 μ.

Anal. Calcd. for $C_{24}H_{36}Cl_2O_5 \cdot {}^1/_2H_2O$: C, 59.49; H, 7.69; Cl, 14.63. Found: C, 59.33; H, 7.68; Cl, 14.93.

16α-Methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (Va) *from* IV. The oxidation of IV (1.6 g.) in acetone (50 ml.) with 1 ml. of 8*N* chromic acid–sulfuric acid reagent[10] was carried out at 0° for 3 min. Water was added precipitating 1.37 g. of 3-keto-5,6-dichloride, m.p. 183–196°. The product was dechlorinated by stirring for 2 hr. at 65–70° with 1.5 g. of zinc dust in 60 ml. of acetic acid. The filtered solution was concentrated *in vacuo*, water was added and the product isolated by methylene dichloride extraction. Crystallization from acetone-hexane yielded 0.47 g. of Va, double m.p. 98–103°, 160–167°, $[\alpha]_D$ +75°, λ_{max} 241 mμ, log ε 4.10, λ_{max}^{KBr} 5.73, 5.81, 6.00, 6.19 μ.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot {}^1/_2C_3H_6O$: C, 70.99; H, 8.64. Found: C, 71.02; H, 8.78.

16α-Methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione (Vb). To a suspension of 0.5 g. of Va in 10 ml. of methanol at 0° and under nitrogen was added 50 mg. of potassium hydroxide in 2 ml. of methanol containing 3 drops of water. The mixture was stirred for 1 hr. at that temperature and then neutralized with acetic acid and poured into water. The product was filtered and recrystallized from acetone-hexane yielding 0.27 g. of Vb, m.p. 187–191°, $[\alpha]_D$ +90°, λ_{max} 241 mμ, log ε 4.18, λ_{max}^{KBr} 5.87, 6.00, 6.19 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.94; O, 17.75. Found: C, 73.20; H, 8.88; O, 17.89.

16α-Methyl-Δ⁵-pregnene-3β,17α-diol-20-one (VIa) *from* III. 5α,6β-Dichloro-16α-methylallopregnane-3β,17α-diol-20-one (0.2 g.) was dissolved in 10 ml. of acetic acid and the resulting solution heated on a steam bath. Zinc dust (0.4 g.) was added in four portions to the stirred mixture at 90° and the reaction permitted to proceed for an additional 30 min. at this temperature. The cooled solution was filtered free of zinc, water was added, and the product which was isolated by methylene dichloride extraction weighed 0.11 g., m.p. 235–240°. Recrystallization from ethanol gave an analytical specimen, m.p. 253–255°, $[\alpha]_D$ −74° (pyridine).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89; O, 13.85. Found: C, 76.05; H, 9.83; O, 13.77.

16α-Methyl-Δ⁵-pregnene-3β,17α-diol-20-one 3-acetate (VIb). Acetylation of VIa with acetic anhydride–pyridine (30 min., 90°) and crystallization from methanol gave the 3-acetate (VIb), m.p. 203–205°, $[\alpha]_D$ −75°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.08; H, 9.37.

16α-Methyl-Δ⁵-pregnene-3β,17α,21-triol-20-one 21-acetate (VII). A suspension of VIa (10 g.) in aged[24] tetrahydrofuran (150 ml.) and methanol (90 ml.) was treated successively with single portions of iodine (18 g.) and finely powdered C.P. calcium oxide (18 g.). By means of a magnetic stirrer and without external cooling or heating the mixture was vigorously stirred for 3.5 hr. At the end of this period the pale yellow mixture was poured with stirring into 2.5 l. of ice water containing 5 g. of sodium thiosulfate. Acetic acid (35 ml.) was added, the mixture stirred for a few minutes, and the crude iodo compound filtered, washed, and dried *in vacuo*. The compound was then dissolved in acetone (500 ml.), anhydrous potassium acetate (26 g.) was added and

(23) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet spectra in 96% ethanol. We are grateful to Dr. J. Matthews for these determinations.

(24) Best results are obtained in this reaction with tetrahydrofuran containing a peroxide content equivalent to 0.01 g. of iodine per ml. of tetrahydrofuran.

the mixture boiled for 17 hr. The major portion of acetone was removed by distillation, water was added, and the crude VII filtered. Recrystallization from methanol yielded 4.67 g. of m.p. 185–187° (Fisher block) and a second crop of 0.35 g. of m.p. 187–190°. The analytical sample of VII from the same solvent exhibited m.p. 190–192° (Fisher), 181–183° (capillary), $[\alpha]_D$ −26°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.77. Found: C, 71.26; H, 8.78; O, 19.42.

16α-Methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (Va) *from* VII. A suspension of 0.2 g. of VII in 15 ml. of acetone was treated at 0° with 0.2 ml. of 8*N* chromic acid in sulfuric acid and the mixture stirred for 1 hr. at that temperature. Water was added and the resultant precipitate, m.p. 140–145°, filtered, washed, dried, and dissolved in 5 ml. of acetic acid. Concentrated hydrochloric acid (0.2 ml.) was added, the solution allowed to stand for 30 min. at room temperature to effect double bond rearrangement and then poured into water. Extraction with methylene dichloride and crystallization of the residue from aqueous methanol gave 0.13 g. of Va, m.p. 96–103°, λ_{max} 241 mμ, log ε 4.08. This product did not exhibit a double melting point as in the preparation above but infrared spectra and paper chromatographic analyses of the two specimens were identical.

16β-Methyl-16α,17α-oxido-Δ⁵-pregnen-3β-ol-20-one (IXa). A solution of 10 g. of 16-methyl-Δ⁵,¹⁶-pregnadien-3β-ol-20-one acetate[11] in a mixture of chloroform (60 ml.) and methanol (200 ml.) was treated at 15° with 5 g. of sodium hydroxide in 15 ml. of water and then with 22 ml. of 35% hydrogen peroxide. After standing for 72 hr. at room temperature water was added to the solution and the chloroform layer separated. The aqueous phase was extracted with chloroform and the combined extracts washed with water, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from acetone yielded 8.1 g. o IXa, m.p. 186–189°. Further crystallization from the sam solvent raised the m.p. to 188–190°, $[\alpha]_D$ −13°, no high selective absorption in the ultraviolet.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.94. Found: C, 76.38; H, 9.36; O, 14.38.

The 3-acetate (IXb), prepared by heating IXa with acetic anhydride–pyridine for 30 min. at 90° followed by crystallization from methanol, showed m.p. 177–179°, $[\alpha]_D$ −16°.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.55. Found: C, 74.70; H, 8.79; O, 16.65.

16-Methyl-Δ⁵,¹⁵(?)-pregnadiene-3β,17α-diol-20-one 3-acetate (X). 16β-Methyl-16α,17α-oxido-Δ⁵-pregnen-3β-ol-20-one acetate (IXb) (10 g.) was dissolved in 700 ml. of acetone and the solution at 0–5° treated with 40 ml. of 48% hydrobromic acid and allowed to stand for 20 min. at 5°. The solution was poured into water and the precipitate collected. Recrystallization from acetone-hexane yielded 9.50 g. of product, m.p. 189–192°, and after a second recrystallization from the same solvent pair, 8.71 g. of material, m.p. 190–195°, was obtained. This material by NMR was shown to consist of 33% of Δ¹⁵-16-methyl compound and 66% of 16-methylene isomer. Two additional crystallizations from acetone-hexane yielded a constant melting sample of m.p. 202–204°, $[\alpha]_D$ −146°, λ_{max}^{KBr} 5.80, 7.9, 8.0 μ, no methylene band visible at 11.22 μ. This specimen was shown by NMR to contain 60% of Δ¹⁵-16-methyl compound and 40% of 16-methylene derivative.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.55. Found: C, 74.80; H, 8.79; O, 16.65.

16α-Methyl-Δ⁵-pregnene-3β,17α-diol-20-one 3-acetate (VIb) *by hydrogenation of* X. A suspension of 8.6 g. of X, m.p. 190–195° (obtained above) in 300 ml. of methanol containing 1.5 g. of prereduced 5% palladium on carbon catalyst was hydrogenated at 580 mm. and 25°. After the absorption of 1.1 equivalents of hydrogen, in 30 min., the reduction was suspended, the catalyst removed, and the product crystallized from methanol yielding 7.8 g. of VIb, m.p. 197–200°. Recrystallization from methanol gave 5.4 g., m.p. 203–205°, $[\alpha]_D$ −74°. This product gave no melting point depression with VIb obtained from the 5,6-dichloride above and the infrared spectra were identical.

Saponification of 1 g. of VIb (m.p. 197–200°) by reaction with 45 ml. of 1% methanolic potassium hydroxide for 1.5 hr. at 25° gave after precipitation in water and crystallization from methanol 0.68 g. of VIa, m.p. 250–253°, identical with the product obtained above.

16α-Methyl-Δ⁵-pregnene-3β,17α-diol-20-one diacetate (XIa). A mixture of 1 g. of 3-monoacetate VIb, *p*-toluenesulfonic acid (100 mg.) and 25 ml. of acetic anhydride was heated for 1 hr. at 90°. The cooled solution was poured into ice water containing 3 ml. of pyridine, the mixture stirred for 30 min., and the precipitate collected and washed. Crystallization from acetone-hexane gave 0.8 g. of diacetate XIa, m.p. 165–170°. The melting point was raised to 169–172° by recrystallization from the same solvent pair, $[\alpha]_D$ −48°.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.76; H, 8.69; O, 18.97.

16α-Methyl-Δ⁵-pregnene-3β,17α-diol-20-one 17-acetate (XIb). A suspension of 3.0 g. of XIa in 50 ml. of 1% methanolic potassium hydroxide was stirred for 50 min. at room temperature with solution being complete after 20 min. Acetic acid (1 ml.) was added and the solution poured into water. The filtered, washed, and dried product was crystallized from acetone-hexane yielding 2.62 g. of 17-monoacetate XIb, m.p. 195–200°, raised to 203–205° by further crystallization from the same solvents, $[\alpha]_D$ −46°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 73.91; H, 9.16; O, 16.80.

16α-Methyl-17α-acetoxyprogesterone (XIIa). Twenty milliliters of solvent was distilled from a solution of 2 g. of 16α-methyl-Δ⁵-pregnene-3β,17α-diol-20-one 17-monoacetate (XIb) in 120 ml. of toluene and 40 ml. of cyclohexanone. Aluminum isopropoxide (2 g.) in 20 ml. of dry toluene was added and the mixture boiled for 1 hr. and then concentrated *in vacuo* to half its original volume. Water was added and the remaining solvent removed by steam-distillation. Concentrated hydrochloric acid (3 ml.) was added to the cooled suspension and the product collected and crystallized from acetone-hexane affording 1.49 g. of XII, m.p. 218–222°, λ_{max} 240 mμ, log ε 4.18. Further crystallization raised the m.p. to 239–240°, $[\alpha]_D$ +82°, λ_{max} 240 mμ, log ε 4.24, λ_{max}^{KBr} 5.78, 5.82, 6.01, 6.20 μ.

Anal. Calcd. for $C_{24}H_{34}O_4 \cdot {}^1/_2C_3H_6O$: C, 73.70; H, 8.97, O, 17.33. Found: C, 74.03; H, 8.72; O, 17.33.

16α-Methyl-Δ¹,⁴-pregnadien-17α-ol-3,20-dione acetate (XIIb). A solution of 1.8 g. of XIIa in 90 ml. of *t*-butyl alcohol containing 0.36 ml. of pyridine was treated with 1.26 g. of selenium dioxide and then boiled for 26 hr. under nitrogen. The cooled mixture was filtered and taken to dryness *in vacuo* at 30°. The residue was taken up in hot ethyl acetate, the solution washed to neutrality with 5% sodium carbonate solution and water, dried, and evaporated. The residue was then dissolved in benzene-hexane (2:1) and chromatographed on a column of 70 g. of neutral alumina. Elution with benzene-hexane (3:1) afforded a mixture of Δ⁴- and Δ¹,⁴-compound which after crystallization from acetone-hexane yielded 0.28 g. of XIIb, m.p. 242–243°, containing about 5% of XIIa by paper-chromatographic analysis. Continued elution with benzene-hexane (4:1 and 9:1) gave after crystallization from acetone-hexane (charcoal), 0.54 g. of XIIb, m.p. 243–244°, free of Δ⁴-compound. Further crystallization raised the melting point to 244–245°, $[\alpha]_D$ +31°, λ_{max} 244 mμ, log ε 4.22, λ_{max}^{KBr} 5.80, 5.85, 6.05, 6.20, 6.28 μ.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; O, 16.65. Found: C, 74.73; H, 8.51; O, 16.41.

16-Methyl-Δ⁵,¹⁴,¹⁶-pregnatrien-3β-ol-20-one acetate (XIII). A mixture of X (0.5 g., m.p. 190–195°), *p*-toluenesulfonic acid (100 mg.), and benzene (25 ml.) was boiled for 45 min. and then cooled. The solution was washed successively with sodium carbonate and water and then evaporated to dry-

ness. Chromatography of the residue on 30 g. of ethyl acetate-washed alumina and crystallization of the benzene-hexane (2:3) eluates from acetone-hexane yielded 0.29 g. of triene (XIII), m.p. 157–159°, $[\alpha]_D$ +275°, λ_{max} 310 mμ, log ε 4.08, λ_{max}^{KBr} 5.74, 6.11, and 6.53 μ.

Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75; O, 13.03. Found: C, 77.83; H, 8.60; O, 13.39.

16-Methyl-Δ¹⁵-allopregnen-3β-ol-11,20-dione acetate (XV). To 1 l. of ethereal diazomethane solution (prepared by the decomposition of 35 g. of *N,N'*-dinitroso-*N,N'*-dimethylterephthalamide) was added 25 g. of Δ¹⁵-allopregnen-3β-ol-11,20-dione acetate[20] (XIV) and the mixture stirred until solution was complete. The solution was allowed to stand for a further 18 hr. at room temperature and the excess diazomethane then destroyed by drop-wise addition of acetic acid. Removal of solvent left a solid residue of pyrazoline m.p. 178° dec., λ_{max} 289 mμ, log ε 2.14, which was pyrolyzed at 140–150° and 10 mm. When the evolution of nitrogen ceased, the bath temperature was slowly raised to 180° and kept at that temperature for 15 min. The product was then cooled and crystallized from acetone-ether yielding 19.28 g. of XV, m.p. 161–165°. The analytical specimen from the same solvents melted at 165–166°, $[\alpha]_D$ +26°, λ_{max} 249 mμ, log ε 3.98, λ_{max}^{KBr} 5.77, 5.85, 6.06, and 6.23 μ.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.89; H, 8.77.

16β-Methyl-16α,17α-oxido-allopregnan-3β-ol-11,20-dione (XVI). The Δ¹⁵-compound (XV) (15.0 g.) was dissolved in a mixture of 60 ml. of methylene dichloride and 450 ml. of methanol and the solution then cooled to 0°. A cold solution of 30 ml. of 10% sodium hydroxide was added and then 90 ml. of 35% hydrogen peroxide at such a rate that the temperature did not exceed 5°. After standing for 4 days at room temperature the solution was diluted with water and the product extracted with methylene dichloride. Crystallization from acetone-ether gave 13.09 g. of epoxide (XVI), m.p. 183–185°. An analytical specimen exhibited m.p. 185–186°, $[\alpha]_D$ +87°, no high selective absorption in the ultraviolet.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.22; H, 8.67.

16-Methyl-Δ¹⁵-allopregnene-3β,17α-diol-11,20-dione (XVIIa). A stirred solution of 5 g. of epoxide (XVI) in 100 ml. of acetone was cooled to 0° and 20 ml. of 48% hydrobromic acid added over a 5-min. period. Temperature rose to 20°. The mixture was then cooled in an ice bath for 15 min. and the resultant crystalline suspension diluted with 50 ml. of water. The precipitate of XVIIa, 4.9 g. m.p. 252–258° (Fisher), was filtered and dried. The analytical sample from acetone melted at 258–259°, $[\alpha]_D$ −60°, λ_{max}^{KBr} 5.90 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.37; H, 8.83.

The *3-acetate* (*XVIIb*), exhibited m.p. 191–192°, $[\alpha]_D$ −61°. NMR, demonstrated that the acetate of m.p. 189–191°, derived in quantitative yield from XVIIa of m.p. 252–258°, was a mixture containing 70% of the Δ¹⁵-16-methyl isomer and 30% of the exocyclic 16-methylene derivative.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51; O, 19.88. Found: C, 71 40; H, 8.53; O, 19.78.

16-Methyl-Δ¹⁵-allopregnene-3β,17α,21-triol-3,11,20-trione 21-acetate (XVIII). The 21-iodination and -acetoxylation of 2 g. of XVIIa (m.p. 252–258°) was carried out exactly as described for the preparation of VII. After the acetone–potassium acetate step an oil was obtained which was extracted with methylene dichloride. This residue was taken up in 25 ml. of methanol, sodium bisulfite (1 g.) in 15 ml. of water was added, and the mixture boiled for 1 hr. The solvent was removed *in vacuo*, water was added, and the product extracted with methylene dichloride yielding a solid residue which was chromatographed on 50 g. of neutral alumina. Elution with ether and methylene dichloride–ether (1:1) gave, after acetone–ether recrystallization, 1.05 g. of XVIII, m.p. 189–191°, $[\alpha]_D$ +14°. The analytical sample from the same solvent melted unchanged but occasionally a polymorphic form of m.p. 218–219.5° was obtained.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.13; H, 8.31.

16-Methyl-Δ¹⁵-allopregnene-17α,21-diol-3,11,20-trione 21-acetate (XIX). The oxidation of 2.5 g. of XVIII in 50 ml. of acetone with 2.25 ml. of 8*N* chromic acid in sulfuric acid was carried out for 5 min. at 10°. Ice water was added and the precipitate filtered, washed, and dried yielding 2.07 g. of 3-ketone (XIX), m.p. 235–236°. Crystallization from acetone-hexane raised the melting point to 235–238° $[\alpha]_D$ +36°.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.05; H, 7.55.

16-Methyl-Δ¹,¹⁵-allopregnadiene-17α,21-diol-3,11,20-trione 21-acetate (XX) *and 16-methyl-Δ¹,⁴,¹⁵-pregnatriene-17α,21-diol-3,11,20-trione 21-acetate* (*16-methyl-Δ¹⁵-prednisone acetate*) (XXI). A mixture of XIX (11.45 g.), selenium dioxide (6.87 g.), pyridine (2.3 ml.) and 2-methyl-2-butanol (460 ml.) was boiled with stirring for 24 hr. under nitrogen. The cooled suspension was filtered through Celite, the precipitate washed with ethyl acetate, and the combined solutions evaporated *in vacuo*. Water was added and methylene dichloride extraction gave a semisolid residue which was chromatographed on 400 g. of ethyl acetate–washed alumina. Elution with benzene-methylene dichloride (1:4) and methylene dichloride gave, after acetone crystallization, 2.17 g. of Δ¹-compound (XX), m.p. 228–229°, $[\alpha]_D$ +56°, λ_{max} 225 mμ, log ε 4.05, λ_{max}^{KBr} 5.70, 5.84, and 5.93 μ.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.41; H, 7.43.

Continued elution with methylene dichloride afforded 1.12 g. of Δ¹,⁴,¹⁵-trienone (XXI), m.p. 186–189°. An analytical sample from acetone-ether melted at 191–193°, $[\alpha]_D$ +127°, λ_{max} 237 mμ, log ε 4.21, λ_{max}^{KBr} 5.70, 5.81, 5.90, 6.04, and 6.20 μ.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.64; H, 7.10.

15-Bromo-16-methyl-Δ¹,⁴,¹⁵-pregnatriene-17α,21-diol-3,11,20-trione 21-acetate (XXII). A solution of 0.15 g. of 16-methyl-Δ¹⁵-prednisone acetate (XXI) in 1.5 ml. of pure dioxane was treated with 0.24 ml. of 0.4*N* perchloric acid and then, with stirring and in the dark, there was added 0.084 g. of *N*-bromoacetamide over a 20-min. period. After stirring the mixture for one additional hour at room temperature, 10% sodium sulfite solution was added until the starch iodide paper test was negative. The product was precipitated by the addition of ice water yielding 0.175 g. of 15-bromo-16-methyl-Δ¹⁵-prednisone acetate (XXII), m.p. 190° dec. Three recrystallizations from acetone-hexane yielded 0.14 g. of pure XXII, m.p. 195° dec., $[\alpha]_D$ +62°, λ_{max} 238 mμ, log ε 4.19, λ_{max}^{KBr} 5.70, 5.80, 5.98, and 6.13 μ.

Anal. Calcd. for $C_{24}H_{27}BrO_6$: C, 58.65; H, 5.53; O, 19.53. Found: C, 58.87; H, 5.60; O, 19.57.

16α-Methylallopregnane-3β,17α-diol-11,20-dione (XXIII). Δ¹⁵-16-Methylallopregnene-3β,17α-diol-11,20-dione (3 g.) in 300 ml. of methanol was hydrogenated over 0.3 g. of prereduced 10% palladium-carbon catalyst at 25° and 570 mm. After the uptake of 1 equivalent of hydrogen in 45 min., the mixture was filtered and the filtrate concentrated to a small volume and cooled, yielding 2.95 g. of 16α-methyl compound (XXIII), m.p. 258–261°. The melting point dropped to 254–255° after recrystallization from acetone, $[\alpha]_D$ +22° (pyridine), λ_{max}^{KBr} 5.90 μ (broad).

Anal. Calcd. for $C_{22}H_{34}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.07; H, 9.53. Found: C, 72.32; H, 9.38.

16α-Methylallopregnane-3β,17α,21-triol-11,20-dione 21-acetate (XXIV). The 21-acetoxylation of 2.0 g. of XXIII was effected exactly as described for the preparation of XVIII. Chromatography of the crude product on 44 g. of neutral alumina gave in the methylene dichloride eluates, 0.41 g. of XXIV, m.p. 201–204°. The analytical sample from acetone-ether melted at 203–204°, $[\alpha]_D$ +75°, λ_{max}^{KBr} 5.65, 5.74, and 5.85 μ.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.26; H, 8.53.

16α-Methylallopregnane-17α,21-diol-3,11,20-trione 21-acetate (XXV). (a) *By oxidation of* XXIV. The oxidation of 0.17 g. of XXIV in acetone solution with 8*N* chromic acid sulfuric acid as described above gave 0.15 g. of 3-ketone (XXV), m.p. 205–208°. Recrystallization from acetone raised the melting point to 209–210° $[\alpha]_D$ +84°, λ_{max}^{KBr} 5.70 and 5.83 μ. This sample was identical with an authentic one prepared by an unambiguous route.[22]

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, C, 68.88; H, 8.05.

(b) *By reduction of* XIX. The hydrogenation at 25° and 570 mm. of 0.5 g. of XIX in 50 ml. of methanol over 0.05 g. of 10% palladium-carbon was interrupted after 45 min. with the uptake of 1 equivalent of hydrogen. After removal of catalyst the methanol solution was taken to dryness and the crystalline residue chromatographed on 15 g. of neutral alumina. Benzene-ether (4:1) eluted 0.175 g. of *16α-methyl compound* (XXV), m.p. 207–209° $[\alpha]_D$ +84°, identical with the sample prepared according to procedure (a).

Continued elution with the same solvents gave a mixture of 16α- and 16β-methyl isomers and then 0.15 g. of pure *16β-methylallopregnane-17α,21-diol-3,11,20-trione 21-acetate* (XXVI), m.p. 211–212° $[\alpha]_D$ +122°, λ_{max}^{KBr} 5.75–5.85 μ (broad). The melting point was unchanged after recrystallization from acetone.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.62; H, 8.23.

15-Bromo-16-methyl-Δ^{15}-allopregnene-3β,17α-diol-11,20-dione 3-acetate (XXVII) (a). To a stirred solution of 1.0 g. of 16-methyl-Δ^{15}-allopregnene-3β,17α-diol-11,20-dione 3-acetate (XVIIb) in 10 ml. of dioxane was added 1.6 ml. of 0.4*N* perchloric acid followed over a period of 20 min. by 0.56 g. of *N*-bromoacetamide. After stirring for an additional hour sodium sulfite was added to the mixture and the product precipitated with water, yielding 1.17 g. of XXVII, m.p. 211° dec. Crystallization from methylene dichloride-methanol raised the melting point to 217° dec., $[\alpha]_D$ +11°, λ_{max}^{KBr} 5.70, 5.81 μ. The NMR spectrum demonstrated that this compound was the pure Δ^{15}-16-methyl derivative without contamination by the exocyclic methylene isomer.

Anal. Calcd. for $C_{24}H_{35}BrO_5$: C, 59.62; H, 7.29; O, 16.54; Br, 16.53. Found: C, 59.86; H, 6.64; O, 16.85; Br, 16.79.

(b) A stirred solution of 0.5 g. of XVIIb in 10 ml. of chloroform was treated at room temperature with a solution of 0.22 g. of bromine in 2.8 ml. of acetic acid. After standing for 10 min. the yellow solution was evaporated almost to dryness under reduced pressure and the residue crystallized from methylene dichloride–methanol yielding 0.15 g. of XXVII, m.p. 212–216° dec., whose infrared spectrum was identical with the product described under (a).

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

Steroids. CLVII.[1] 6-Aminoandrostanes

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Treatment of 5α,6α-oxido-3-cycloethylenedioxyandrostan-17β-ol (I) with dimethylamine or with piperidine yielded the corresponding 6β-amino-5α-ol (II). Hydrolysis of the ketal function, acetylation, and dehydration with thionyl chloride gave the 6β-aminotestosterone acetate (V) while treatment of II with hydrogen chloride in acetic acid led to the 6α-aminotestosterone (IV). The infrared and ultraviolet spectra of some of these derivatives are discussed.

While a number of nitrogen-substituted steroid derivatives have been prepared,[3] hormone analogs containing the Δ^4-3-ketone system and a 6-amino function have not been reported. Such compounds might be of possible interest as biologically acceptable "platforms" bearing substituents known to produce pharmacological responses of a non-hormonal nature. An ideal starting material for such compounds appeared to be a 3-cycloethylenedioxy-5α,6α-oxido steroid (I) since by analogy with methyl Grignard[4] and with cyanide[5] ion cleavage of 5α,6α-oxides as well as the known opening of simple epoxides with amines[6] or ammonia[6] it was anticipated that amines would react with I to yield the 6β-amino-5α-ols which in turn would be readily convertible to the 6β- and 6α-amino-Δ^4-3-ketones. This sequence of reactions was, in fact, found to be easily realized and in this paper we report the preparation of 6-piperidino- and 6-dimethylaminotestosterone derivatives while in a later paper we will report variation in the amino derivative as well as in the steroidal 3-cycloethylenedioxy-5α,6α-oxido substrate.

When 5α,6α-oxido-3-cycloethylenedioxyandrostan-17β-ol[7] (I) (testosterone ketal epoxide) was

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