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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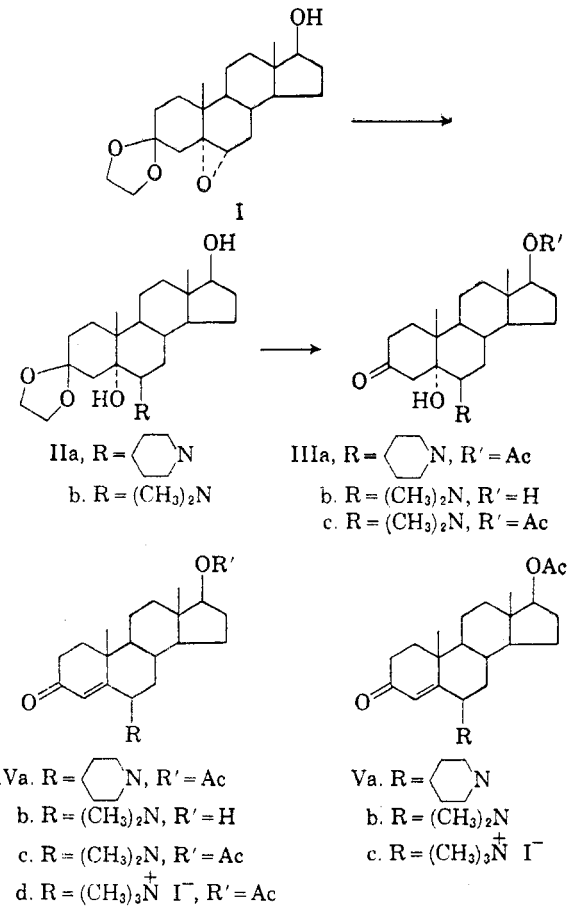
heated with piperidine in ethylene glycol for sixteen hours, oxide fission occurred yielding the 6β-piperidino-5α-ol (IIa). Although the reaction product resisted crystallization it was shown to be completely basic by its solubility in dilute hydrochloric acid. Reaction of IIa for several hours with hydrogen chloride in acetic acid resulted in concomitant ketal hydrolysis, dehydration of the tertiary 5α-alcohol (β-elimination) and inversion of the axial 6β-piperidino group to the 6α-equatorial derivative. The mixture of 6α-piperidinotestosterone and its 17-acetate (IVa) thus formed was converted completely to the 17-acetate by conventional acetylation and purified as such.

In order to prepare the 6β-amino-Δ^4-3-ketone, the ketal function of IIa was first hydrolyzed by treatment with *p*-toluenesulfonic acid in acetone and the 17-hydroxyl group then acetylated (IIIa). Treatment of IIIa with thionyl chloride in pyridine for a few minutes at 0° gave the thermodynamically unstable 6β-piperidinotestosterone acetate (Va) which could be converted in high yield to the 6α-derivative by hydrogen chloride treatment.

The 6-dimethylamino steroids were prepared by identical reaction sequences except that, due to the volatility of dimethylamine, the ketal epoxide cleavage in ethylene glycol was carried out in a sealed tube for fifteen hours at 150–155°. Thus 6α-dimethylaminotestosterone (IVb) and 6β-dimethylaminotestosterone acetate (Vb) were prepared. It was also of interest for biological evaluation to convert some of these derivatives into their quaternary ammonium salts. Reaction of 6α- and 6β-dimethylaminotestosterone acetate with methyl iodide for a number of days at room temperature gave the resultant methiodides IVd and Vc in crystalline form.

The ultraviolet absorption spectrum maxima of the 6-amino-Δ^4-3-ketones (IVa, IVb, Va, and Vb) were not significantly different from testosterone itself but the trimethylammonium iodides (IVd and Vc) exhibited a hypsochromic shift of about 20 mμ (λ_{max} 222 mμ). This effect is readily explained by the powerful electron-withdrawing properties of the positively charged nitrogen atom opposing the polarization of the α,β-unsaturated ketone function which is necessary to reach the excited state. A hypsochromic shift was noted in the case of 6-fluoro-[8] and 6-nitro-[9] Δ^4-3-ketones but the magnitude was not so great as that encountered with the formally charged trimethylammonium derivative.

The quaternary salts IVd and Vc exhibited, in the infrared, displacement of the α,β-unsaturated ketone function to about 5.9 μ which would appear



ADDED IN PROOF. An equimolecular mixture of testosterone and potassium iodide exhibits maxima of almost equal intensity at 225 and 239 mμ; therefore the bathochromic shift of the quaternary iodides IVd and Vc is partially attributable to iodide ion. We thank Prof. V. Georgian for calling this to our attention.

to be primarily a reflection of the inductive effect of the C_6 substituent. However, the uncharged 6β-piperidinotestosterone acetate (Va) and 6β-dimethylaminotestosterone acetate (Vb) also showed anomalous infrared carbonyl maxima, 5.94 and 5.91 μ respectively. Since the infrared maxima of the 6α-amino derivatives (IVa and IVb) were normal the displacement in the case of Va and Vb may be due to the severe 1,3-diaxial steric interaction of the 6β-substituted amino group with the C_{19} angular methyl group distorting the planarity of ring A and hence affecting polarization of the α,β-unsaturated ketone.

EXPERIMENTAL[10]

6β-Piperidino-3-cycloethylenedioxyandrostane-5α,17β-diol (IIa). A solution of 5α,6α-oxido-3-cycloethylenedioxyandrostan-17β-ol[7] (I) (5 g.) in 100 ml. of ethylene glycol and 25 ml. of piperidine was boiled for 16 hr., cooled, and poured into water. The amorphous precipitate, 5.5 g., m.p. 100–105° dec., of 6β-piperidino-3-cycloethylenedioxyandrostane-5α,-

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(8) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(9) A. Bowers, M. B. Sánchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959).

(10) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet spectra in 96% ethanol. We are grateful to Dr. J. Matthews for determination of constants.

17β-diol (IIa) which was collected exhibited complete solubility in 10% hydrochloric acid but resisted crystallization and thus was processed without further purification.

6α-Piperidinotestosterone acetate (IVa). Hydrogen chloride was bubbled under anhydrous conditions into a cold solution of 2.6 g. of IIa in 30 ml. of glacial acetic acid until saturation when the solution was allowed to stand at room temperature for 2 hr. The mixture was poured into 500 ml. of water and solid sodium carbonate added portion-wise until all of the acid had been neutralized. The precipitate which formed, 2.16 g., m.p. 203–207°, λ_{max} 241 mμ, log ε 4.14, was shown by infrared to be a mixture of 6α-piperidinotestosterone and the corresponding acetate (IVa). Acetylation of 2.0 g. of this mixture was carried out for 20 hr. at room temperature in 16 ml. of acetic anhydride and 16 ml. of pyridine. After pouring the acetylation solution into water and making it basic with potassium carbonate, 6α-piperidinotestosterone acetate, 2.07 g., m.p. 210–214° was filtered. Crystallization from acetone gave an analytical specimen, m.p. 219–220°, $[\alpha]_D$ + 95°, λ_{max} 241 mμ, log ε 4.16, λ_{max}^{KBr} 5.80, 6.04, and 6.23 μ.

Anal. Calcd. for $C_{26}H_{39}NO_3$: C, 75.50; H, 9.50; N, 3.38; Found: C, 75.41; H, 9.62; N, 3.60.

6β-Piperidinoandrostane-5α,17β-diol-3-one 17-acetate (IIIa). To 9.9 g. of 6β-piperidino-3-cycloethylenedioxyandrostane-5α,17β-diol in 150 ml. of acetone, 1.5 ml. of water and 5.5 g. of *p*-toluenesulfonic acid were added. The solution after standing for 2 hr., was poured into 2 l. of water and excess 10% sodium hydroxide solution was added. The resultant precipitate of 6β-piperidinoandrostane-5α,17β-diol-3-one, 8.49 g., m.p. 128° dec. was filtered, washed, dried, and acetylated with 40 ml. of pyridine and 40 ml. of acetic anhydride as described above. The product which was recovered by filtration, was crystallized from hexane yielding 8.54 g. of IIIa, m.p. 195–197°, $[\alpha]_D$ −43°. Recrystallization from acetone-hexane raised the melting point to 199–200°, $[\alpha]_D$ −45°, λ_{max}^{KBr} 5.80–5.85 μ (broad).

Anal. Calcd. for $C_{26}H_{41}NO_4$: C, 72.35; H, 9.57; N, 3.24. Found: C, 72.49; H, 9.33; N, 3.39.

6β-Piperidinotestosterone acetate (Va). A solution of 1 g. of 6β-piperidinoandrostane-5α,17β-diol-3-one 17-acetate (IIIa) in 15 ml. of pyridine was cooled to 0° and thionyl chloride (0.39 ml.) added dropwise with stirring over a 2-min. period. After standing for 1 min. more water was added and the product isolated by methylene dichloride extraction. Crystallization from hexane yielded 0.55 g. of 6β-piperidinotestosterone acetate (Va), m.p. 141–144°. Recrystallization from the same solvent gave material of m.p. 145–146.5°, $[\alpha]_D$ + 62°, λ_{max} 240 mμ, log ε 4.16, λ_{max}^{KBr} 5.75, 5.94, and 6.19 μ.

Anal. Calcd. for $C_{26}H_{39}NO_3$: C, 75.50; H, 9.50; N, 3.38. Found: C, 75.26; H, 9.25; N, 3.46.

Inversion of 6β-piperidinotestosterone acetate (Va) to IVa. A solution of 0.1 g. of Va in 2 ml. of glacial acetic acid was saturated with hydrogen chloride and allowed to stand for 2 hr. Water was added and then excess solid sodium carbonate. The precipitate of 6α-piperidinotestosterone acetate (0.08 g., m.p. 185–189°) was filtered, washed, dried, and recrystallized from acetone yielding 0.05 g. of IVa, m.p. 215–218°, λ_{max} 241 mμ, log ε 4.15. The infrared spectrum of this sample was identical with that of the product described above.

6β-Dimethylamino-3-cycloethylenedioxyandrostane-5α,-17β-diol (IIb). Dimethylamine gas, generated from the alkaline decomposition of 20 g. of dimethylamine hydrochloride, was bubbled into an ice cold solution of 5 g. of ketal epoxide (I) in 100 ml. of ethylene glycol contained in a strong-walled glass tube. The tube was sealed and heated in a steel bomb at 150–155° for 15 hr. The content of the tube was cooled and poured into water yielding, by filtration, 5.45 g. of IIb, m.p. 195–196°. The melting point of the analytical specimen from acetone was unchanged; $[\alpha]_D$ −87°.

Anal. Calcd. for $C_{23}H_{39}NO_4$: C, 70.20; H, 9.98; N, 3.55. Found: C, 70.49; H, 9.83; N, 3.70.

6α-Dimethylaminotestosterone (IVb). Anhydrous hydrogen chloride was bubbled for 2 hr. through a cold solution of 3.5 g. of IIb in 35 ml. of glacial acetic acid and the solution then poured into water and made basic with solid sodium carbonate. The 6α-dimethylaminotestosterone was extracted with and crystallized from ether yielding 1.06 g. of pure IVb, m.p. 179–180°, $[\alpha]_D$ +117°, λ_{max} 240 mμ, log ε 4.16, λ_{max}^{KBr} 5.99 and 6.20 μ.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.08; H, 10.03; N, 4.22. Found: C, 76.23; H, 9.66; N, 4.40.

6β-Dimethylaminoandrostane-5α,17β-diol-3-one (IIIb). To 3 g. of IIb dissolved in 42 ml. of acetone containing 0.36 ml. of water, *p*-toluenesulfonic acid (1.8 g.) was added and the solution allowed to stand for 2 hr. at room temperature before pouring into water. The mixture was made slightly alkaline with 10% sodium hydroxide and the product isolated by extraction with ether. The washed and dried ether extract was concentrated whereupon crystallization occurred yielding 2.32 g. of IIIb, m.p. 181–185°. An analytical sample, prepared by acetone-ether recrystallization, melted at 186–187°, $[\alpha]_D$ − 41°.

Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72.16; H, 10.09; N, 4.01. Found: C, 71.92; H, 9.83; N, 4.02.

6β-Dimethylaminoandrostane-5α,17β-diol-3-one 17-acetate (IIIc). Acetylation of 2.13 g. of 6β-dimethylaminoandrostane-5α,17β-diol-3-one was carried out with 6 ml. of pyridine and 6 ml. of acetic anhydride for 16 hr. at room temperature. The addition of water and sodium carbonate gave 2.29 g. of 17-acetate (IIIc), m.p. 204–207°, raised by acetone crystallization to 213–214°, $[\alpha]_D$ −44°.

Anal. Calcd. for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.57. Found: C, 70.86; H, 9.63; N, 3.68.

6β-Dimethylaminotestosterone acetate (Vb). 6β-Dimethylaminoandrostane-5α,17β-diol-3-one 17-acetate (IIIc) (1 g.) was dissolved in 15 ml. of dry pyridine. The solution was cooled to 0° and treated dropwise with 0.39 ml. of thionyl chloride over a period of 2 min. and then allowed to react for an additional minute at 0°. Water was added and the product extracted with methylene dichloride. Crystallization from hexane gave 0.77 g. of 6β-dimethylaminotestosterone acetate, m.p. 146–148°, $[\alpha]_D$ + 78°, λ_{max} 239 mμ, log ε 4.16, λ_{max}^{KBr} 5.71, 5.91, and 6.11 μ.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.72; H, 9.16; N, 3.82.

6α-Dimethylaminotestosterone acetate methiodide (IVd) 6α-Dimethylaminotestosterone (0.8 g.) was acetylated overnight at room temperature with acetic anhydride–pyridine (8 ml.; 1:1). The 6α-dimethylaminotestosterone acetate (IVd), isolated by ether extraction as an oil which resisted crystallization, was dissolved in 8 ml. of benzene. A few drops of benzene were distilled to remove moisture, 8 ml. of methyl iodide was added, and the stoppered mixture allowed to stand for 1 week at room temperature. The copious precipitate was filtered (crystallization began after 18 hr.), washed with benzene, dried, and extracted with water. Evaporation of this water extract gave a solid residue which was crystallized from acetone yielding 0.56 g. of quaternary salt (IVd), m.p. 208° dec., $[\alpha]_D$ +4°, λ_{max} 222 mμ, log ε 4.37, λ_{max}^{KBr} 5.74 and 5.90 μ (no c=c stretch band between 6.1 to 6.2 μ).

Anal. Calcd. for $C_{24}H_{38}INO_3$: C, 55.93; H, 7.43; I, 24.62; N, 2.71. Found: C, 55.75; H, 7.13; I, 24.61; N, 2.79.

6β-Dimethylaminotestosterone acetate methiodide (Vc). A solution of 0.5 g. of 6β-dimethylaminotestosterone acetate (Vb) in 5 ml. of benzene and 5 ml. of methyl iodide was allowed to stand for 19 days at room temperature The resultant precipitate was filtered, washed with benzene, dried, and extracted with water. The water extract was taken to dryness *in vacuo* and the residue crystallized from acetone-ether yielding 0.26 g. of quaternary salt (Vc), m.p. 177° dec. Crystallization from acetone gave the analytical sample m.p. 184° dec., $[\alpha]_D$ +11°, λ_{max} 222 mμ, log ε 4.37, λ_{max}^{KBr} 5.71, 5.91, and 6.11 μ.

Anal. Calcd. for $C_{24}H_{38}INO_3$: C, 55.93; H, 7.43; I, 24.62; N, 2.71. Found: C, 55.72; H, 7.57; I, 24.73; N, 3.08.

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