aqueous acetone afforded pure VIII as platelets: mp 64–65°; ν_{max} 8.92 (s), 12.95 (s), 14.78 (s) μ. The nmr spectrum showed absorption at τ 8.22 (4H, multiplet $-CH_2-$), 7.95 (4H, multiplet $-CH_2-$), 6.96 (4H, multiplet $-CH_2-N-$), 6.42 (4H, multiplet $-CH_2-O-$).

Anal. Calcd for $C_{10}H_{16}Cl_3Cl_3NO$: C, 44.06; H, 5.92; Cl, 39.02; N, 5.14. Found: C, 44.16; H, 5.94; Cl, 38.89; N, 5.11.

N-(1-Chlorocyclopentylcarbonyl)morpholine (IX).—A solution of VIII (6.8 g, 0.025 mole) in aqueous acetone was heated under reflux for 18 hr. Most of the acetone was removed by evaporation *in vacuo* and the residue taken up in chloroform. After washing the chloroform solution with water it was dried (Mg_2SO_4) and evaporated. The residual oil was distilled through a short-path distillation apparatus to give 2.5 g (46%): bp 107–110° (0.4 mm); $n^{25}D$ 1.5131; ν_{max} 6.12 (s), 8.96 (s) μ. The nmr spectrum showed absorption at τ 8.20 (4H, complex multiplet $-CH_2-$), 7.75 (4H, complex multiplet $-CH_2-$), 6.30 (8H, complex multiplet $-CH_2-$ of morpholine).

Anal. Calcd for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; Cl, 16.29; N, 6.44. Found: C, 54.98; H, 7.19; Cl, 16.38; N, 6.49.

1-Cyclopentene-1-carboxylic Acid (X). A. By Hydrolysis of VIII.—A solution of VIII (5.4 g, 0.02 mole) in aqueous ethanol (50 ml) was heated with excess aqueous 20% sodium hydroxide for 18 hr. The reaction mixture was cooled, diluted with water, and extracted with chloroform to remove neutral and basic materials. The aqueous layer was acidified with concentrated hydrochloric acid and again extracted with chloroform. Evaporation of the chloroform afforded an oily solid which on recrystallization from methylcyclohexane gave 1.5 g (68%) of X: mp 120–121°; $\nu_{max}^{CHCl_3}$ 5.95 (s), 6.15 (m) μ; lit.[10] mp 121°. The acid X gave *p*-nitrobenzyl ester:[14] mp 74–76° (from methylcyclohexane); $\nu_{max}^{CHCl_3}$ 5.86 (s), 6.15 (w) μ.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.20; H, 5.38; N, 5.56.

B. By Hydrolysis of IX.—The morpholide IX was hydrolyzed with aqueous ethanolic sodium hydroxide at the reflux temperature for 18 hr. A work-up similar to that under A afforded X, mp and mmp 120–121°.

N-[1-(Trichloroacetoxy)cyclopentylcarbonyl]morpholine (XV).—Sodium trichloroacetate (1.85 g, 0.01 mole) and VIII (2.75 g, 0.01 mole) in 20% aqueous acetone (50 ml) was heated at the reflux temperature for 16 hr. The acetone was then evaporated, water was added, and the mixture was extracted with chloroform. The chloroform extract was dried (Mg_2SO_4) and evaporated *in vacuo*. The residue was recrystallized from methylcyclohexane to give 1.2 g (35%) XV: mp 112–114°; $\nu_{max}^{CHCl_3}$ 5.68 (s), 6.10 (s), 9.0 (s) μ. The nmr spectrum showed absorption at τ 8.20 (4H, complex multiplet $-CH_2-$), 7.72 (4H, complex multiplet $-CH_2-$), 6.35 (8H, multiplet $-CH_2-$ of morpholine).

Anal. Calcd for $C_{12}H_{16}Cl_3NO_4$: C, 41.82; H, 4.68, Cl, 30.86; N, 4.07. Found: C, 42.01; H, 4.77; Cl, 30.91; N, 4.02.

Attempted Conversion of IX to XV.—Treatment of IX (0.01 mole) with sodium trichloroacetate (0.01 mole) in aqueous acetone for 16 hr followed by a work-up as above gave a quantitative recovery of unchanged IX.

Attempted Reaction of 5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one with Trichloroacetic Acid.—5,5-Dimethyl-3-N-morpholinylcyclohex-2-en-1-one[11] (5.25 g, 0.025 mole) in refluxing benzene (70 ml) was treated with a solution of trichloroacetic acid (4.1 g, 0.025 mole) in benzene (25 ml). Carbon dioxide was rapidly evolved during the addition and heating was continued for a further 2 hr. Evaporation of the benzene *in vacuo* afforded 5.2 g (99%) of enamino ketone, mp 127–129°, not depressed on admixture with authentic starting material.

11-Amino Steroids. II. 11-Amino- and 11-Acetamido-3,20-dioxypregnanes[1]

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5β-Pregnane-3α,20β-diol-11-one was converted to its 11-oxime, and then to the 11α-amine (Na–PrOH reduction) or the 11β-amine (Pt–H_2–HOAc reduction). By standard reactions, these were then converted to the corresponding 11-acetamidoprogesterones and their 1-dehydro analogs.

The intense interest in steroids possessing nitrogen atoms is best exemplified by the long list of references to scientific articles in three recent reviews on this subject.[3] In an earlier communication we reported[2] on the relatively facile preparation of 11α- and 11β-aminopregnanes from readily available 11-ketopregnanes; this paper describes such work in detail, as well as the conversion of these amines to certain steroid hormone analogs.

The 11-keto group in steroids containing both angular methyl groups is relatively unreactive toward the usual ketonic reagents, although vigorous conditions can sometimes effect transformations.[4] Similar unreactivity had been noted for 21-acetoxy-20-keto steroids (*e.g.*, they do not readily form ketals,[5] semicarbazones,[6] or 2,4-dinitrophenylhydrazones[7] at C-20 if the C-21 acetate is not hydrolyzed first). However, our observation[8] that 21-acetoxy-20-keto steroids reacted *normally* with hydroxylamine or hydrazine prompted us to explore the reactivity of 11-ketones with such smaller ketonic reagents, although it was generally believed that 11-ketones would not react.[9] Indeed, refluxing 3α,20β-dihydroxy-5β-pregnan-11-one with hydroxylamine hydrochloride in aqueous pyridine for 18 hr produced an excellent yield of the 11-oxime

(1) A portion of this work has been published previously.[2]

(2) E. B. Hershberg, E. P. Oliveto, and R. Rausser, *Chem. Ind.* (London), 1477 (1958).

(3) (a) M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, **14**, 325 (1962); (b) *ibid.*, **14**, 469 (1962); (c) M. Martin-Smith and M. Sugrue, *ibid.*, **16**, 569 (1964).

(4) Some examples of such reactions are given in these references: (a) ketal formation, B. Magerlein and R. Levin, *J. Am. Chem. Soc.*, **77**, 1904 (1955); C. Engel, *Can. J. Chem.*, **35**, 131 (1957); (b) Wolff–Kishner reduction, R. Moffet and J. Hunter, *J. Am. Chem. Soc.*, **73**, 1973 (1951); H. Heusser, K. Eichenberger, P. Kurath, H. Dallenbach, and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); L. F. Fieser, J. Herz, and W.-Y. Huang, *J. Am. Chem. Soc.*, **73**, 2397 (1951); L. F. Fieser, W.-Y. Huang, and J. Babcock, *ibid.*, **75**, 116 (1953); L. F. Fieser and W.-Y. Huang, *ibid.*, **75**, 5356 (1953); C. Djerassi and G. Thomas, *Chem. Ind.* (London), 1228 (1954); D. H. R. Barton, D. Ives, and B. Thomas, *J. Chem. Soc.*, 2056 (1955); C. Djerassi, A. Manson, and H. Bendas, *Tetrahedron*, **1**, 22 (1957); H. Osaka, *Chem. Pharm. Bull.* (Tokyo), **10**, 417 (1962); W. Nagata and H. Itazaki, *Chem. Ind.* (London), 1194 (1964); (c) alkyl- and aryllithium, H. Ringold, E. Batres, and J. Zderic, *Tetrahedron*, **2**, 164 (1958); G. Fonken and J. Hogg, *ibid.*, **2**, 365 (1958); G. Fonken, *J. Org. Chem.*, **23**, 1075 (1958); G. Fonken, J. Hogg, and A. McIntosh, *ibid.*, **24**, 1600 (1959); J. Elks, *J. Chem. Soc.*, 3333 (1960); G. Fonken, *J. Org. Chem.*, **30**, 2095 (1965).

(5) R. Antonucci, S. Bernstein, R. Lenhard, K. Sax, and J. Williams, *ibid.*, **17**, 1369 (1952); R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. Williams, *ibid.*, **18**, 70 (1953); J. von Euw, R. Neher, and T. Reichstein, *Helv. Chim. Acta*, **38**, 1423 (1955).

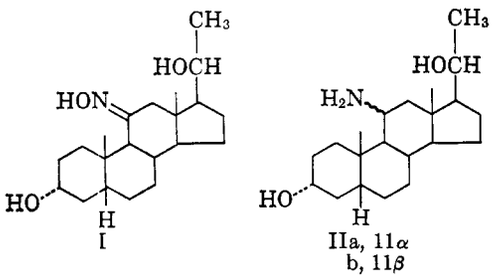
(6) N. L. Wendler, Huang-Minlon, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951); O. Mancera, *ibid.*, **72**, 5752 (1960).

(7) G. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951). See, however, H. Reich and B. Samuels, *ibid.*, **19**, 1041 (1954).

(8) E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 17 6 (1956).

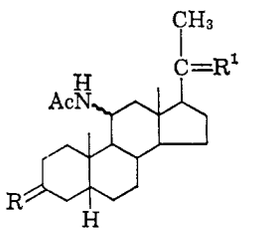
(9) L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed, Reinhold Publishing Co., New York, N. Y., 1949, pp 409, 655. Also see, *e.g.*, J. Elks and G. Phillipps, *J. Chem. Soc.*, 4326 (1956); O. Schindler, *Helv. Chim. Acta*, **39**, 1698 (1956).

CHART I

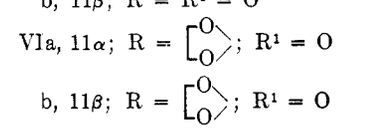


I

IIa, 11α
b, 11β

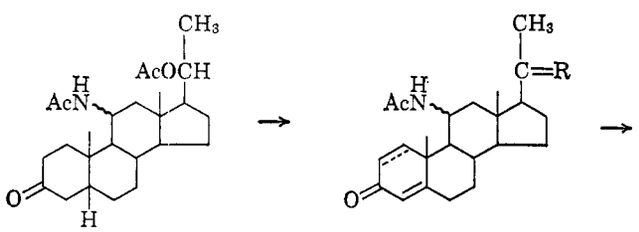


IIIa, 11α; R = R¹ = H, OAc
IVa, 11α; R = R¹ = H, OH
b, 11β; R = R¹ = H, OH
Va, 11α; R = R¹ = O
b, 11β; R = R¹ = O



VIa, 11α; R = ; R¹ = O
b, 11β; R = ; R¹ = O
VIIa, 11α; R = ; R¹ = H, OH
b, 11β; R = ; R¹ = H, OH

VIIIa, 11α; R = O; R¹ = H, OAc
b, 11β; R = O; R¹ = H, OAc



IXa, 11α; 4-Br
b, 11β; 4-Br
XIIIa, 11α; 2,4-Br₂
b, 11β; 2,4-Br₂

Xa, 11α; R = H, OAc
b, 11β; R = H, OAc
XIa, 11α; R = H, OH
b, 11β; R = H, OH
XIIa, 11α; R = O
b, 11β; R = O
XIVa, 11α; Δ¹; R = H, OAc
b, 11β; Δ¹; R = H, OAc
XVa, 11α; Δ¹; R = H, OH
b, 11β; Δ¹; R = H, OH
XVIa, 11α; Δ¹; R = O
b, 11β; Δ¹; R = O

I, and thus a path was now available for the preparation of 11-amino steroid hormone analogs.

Reduction of the oxime with sodium and *n*-propyl alcohol gave an amine formulated as 11α-amino-5β-pregnane-3α,20-diol (IIa, Chart I), based on the known preference for equatorial amine formation with this reducing system.[10] On the other hand, reduction of the oxime with hydrogen and platinum in acetic acid produced a different amine. Since this system is well known to reduce oximes to predominantly axial amines,[10] this compound is assigned the structure 11β-amino-5β-pregnane-3α,20β-diol (IIb). Further support for these assignments was obtained by comparison of the ultraviolet spectra of A-ring dienone derivatives (XVIa and b, *vide infra*) and by examination of nmr spectra.[11]

The chemical shifts of the C-18 and C-19 methyl signals of the 11α-amine IIa and 11β-amine IIb agree very closely with the shifts predicted if the 11-substituent had been a hydroxyl group (see Table I). In addition, the 11β-axial proton signal in IVa is much broader (as expected from the dihedral angles between the vicinal protons at C-11 and C-12) than the 11α-proton signal in IVb.

TABLE I

NMR DATA FOR EPIMERIC 11-HYDROXY AND 11-AMINO STEROIDS

	—C-18 methyl[a]—		—C-19 methyl[a]—	
	Calcd[b]	Obsd	Calcd[b]	Obsd
5β-Pregnane-3α,11α,20β-diol	46.0		62.5	
5β-Pregnane-3α,11β,20β-diol	59.0		71.0	
11α-Amino-5β-pregnane-3α,20β-diol (IIa)		44.0		62.0
11β-Amino-5β-pregnane-3α,20β-diol (IIb)		59.0		69.5

[a] The nmr spectra were obtained with a Varian A-60 spectrometer, using dimethylformamide-*d*, as solvent. Chemical shifts are reported in cycles per second from tetramethylsilane (TMS) which was used as the internal standard. [b] N. Bhacca and D. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

Treatment of the 11α-amine IIa with acetic anhydride and pyridine at room temperature gave the fully acetylated product IIIa. Refluxing this with aqueous methanolic sodium hydroxide produced a good yield of the 11α-acetamido-5β-pregnane-3α,20β-diol (IVa); more vigorous saponification conditions did not succeed in hydrolyzing the amide. Oxidation of the diol IVa to the dione Va could now be accomplished easily with N-bromoacetamide in aqueous acetone, without interference from an unprotected amino group. However, attempted monobromination of Va at C-4 followed by dehydrohalogenation failed to give appreciable 3-keto-Δ⁴-chromophore, and since a variety of products was formed, this approach was abandoned, and a more circuitous route was undertaken.

The 3-monoethylene ketal VIa was readily formed from Va by reaction with ethylene glycol and selenium dioxide.[12] Reduction with sodium borohydride gave an alcohol (VIIa) which was assigned the 20β configuration.[13] Hydrolysis of the ketal with aqueous acetic acid did not give a crystalline compound, but acetylation at C-20 gave crystalline VIIIa in high yield. Monobromination at C-4 was effected in methylene chloride–*t*-butyl alcohol, then dehydrobromination was accomplished with dimethylformamide and calcium carbonate to yield Xa. Hydrolysis of the C-20 acetate with aqueous methanolic sodium hydroxide,

(10) See, *inter alia*, D. H. R. Barton and R. Cookson, *Quart. Rev.* (London), **10**, 44 (1956); C. W. Shoppee, D. Evans, H. Richards, and G. Summers, *J. Chem. Soc.*, 1649 (1956); C. W. Shoppee, R. Cremlyn, D. Evans, and G. Summers, *ibid.*, 4364 (1957); J. Schmitt, J. Panouse, A. Hallot, P.-J. Cornu, H. Plucket, and P. Comoy, *Bull. Soc. Chim. France*, 1855 (1962); P. Crabbé, M. Durazo, R. Saloma, and P. Holton, *Bull. Soc. Chim. Belges*, **71**, 203 (1962). Note, however, C. W. Shoppee, S. Roy, and B. Goodrich, *J. Chem. Soc.*, 1583 (1961); M. Alauddin and M. Martin-Smith, *J. Org. Chem.*, **28**, 886 (1963).

(11) We are indebted to Dr. F. Vane for the nmr spectra and interpretation.

(12) E. P. Oliveto, H. Smith, C. Gerold, L. Weber, R. Rausser, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 2224 (1955).

(13) E. P. Oliveto and E. B. Hershberg, *ibid.*, **75**, 488 (1953).

followed by Jones oxidation, gave 11α-acetamidoprogesterone (XIIa).

Dibromination of VIIIa with bromine in acetic acid, followed by dehydrobromination with dimethylformamide, gave crystalline 11α-acetamido-20β-acetoxy-1,4-pregnadien-3-one (XIVa). Again, hydrolysis and Jones oxidation produced 11α-acetamido-1-dehydroprogesterone (XVIa).

The preparation of the 11β-acetamido analogs followed essentially the same scheme, except for minor variations. For example, acetylation of 11β-amino-5β-pregnane-3α,20β-diol (IIb) with acetic anhydride–pyridine gave an immediate crystalline precipitate which was clearly the 11β-amide diol IVb, thus eliminating the hydrolysis step. Oxidation of this diol to the dione Vb proceeded better with chromium trioxide–acetic acid than with the N-bromoacetamide used in the 11α series. Most of the subsequent intermediates in the 11β series could not be purified by crystallization, but the final compounds, 11β-acetamidoprogesterone (XIIb) and its 1-dehydro analog XVIa, were nicely crystalline, high-melting substances.

Comparison of the ultraviolet maxima of Xa and b with XIIa and b and XIVa and b with XVIa and b supports the original configurational assignments of the epimeric 11-amines. In the 3-keto-Δ^4 series (X–XII), the 11α-amides had ultraviolet maxima $\sim$4 mμ higher (at *ca.* 242 mμ) than the 11β-amides, while the 1-dehydro-11α-amides had ultraviolet maxima $\sim$10 mμ higher, at *ca.* 251 mμ. This compares well with the ultraviolet maxima of cortisol 21-acetate (240 mμ), 11-epicortisol 21-acetate (240 mμ), prednisone 21-acetate (238 mμ), prednisolone 21-acetate (242 mμ), and 11-epiprednisolone 21-acetate (248 mμ).

Experimental Section[14]

11-Oximino-5β-pregnane-3α,20β-diol (I).—A solution of 88 g of 3α,20β-dihydroxy-5β-pregnan-11-one and 88 g of hydroxylamine hydrochloride in 792 ml of pyridine and 88 ml of water was refluxed for 18 hr, then poured into ice and hydrochloric acid, and filtered. Two recrystallizations from aqueous ethanol gave 80 g (74%) of I: mp 227.0–228.5°; $[\alpha]_D$ +80.1° (dioxane); λ_{max}^{Nujol} 2.92, 3.14, and 6.06 μ.

Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.16; H, 10.09; N, 4.01. Found: C, 72.27; H, 10.01; N, 3.94.

11α-Amino-5β-pregnane-3α,20β-diol (IIa).—To a solution of 5.0 g of I in 1.25 l. of *n*-propyl alcohol was added 75 g of sodium during 10 min. The mixture was refluxed 5 hr, then 125 ml of water was added, and the organic solvent was removed by steam distillation. After cooling, the solids were removed by filtration, dried over magnesium sulfate, and crystallized from acetonitrile to give 3.40 g (71%) of II, mp 181–187°. The analytical sample, crystallized once more, melted at 187–191°, $[\alpha]_D$ −10.1° (dioxane), λ_{max}^{Nujol} 3.04 and 6.03 μ.

Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18. Found: C, 75.20; H, 10.90; N, 3.84.

11β-Amino-5β-pregnane-3α,20β-diol (IIb).—A solution of 1.0 g of 11-oximino-5β-pregnane-3α,20β-diol in 50 ml of acetic acid was hydrogenated at room temperature and atmospheric pressure overnight with the aid of 500 mg of platinum oxide. The catalyst was removed by filtration, and the acetic acid was neutralized with dilute sodium hydroxide to precipitate 800 mg of IIb. Crystallization from acetonitrile yielded 690 mg, mp 223–225°, $[\alpha]_D$ +30° (dioxane), λ_{max}^{Nujol} 3.1 and 6.2 μ.

Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18. Found: C, 74.88; H, 11.09; N, 4.33.

(14) All melting points are corrected. Rotations were measured at 25° at about 1% concentration. We thank the Physical Chemistry Department, Schering Corp., for the physical measurements and analytical data.

11α-Acetamido-5β-pregnane-3α,20β-diol Diacetate (IIIa).—A solution of 8.60 g of IIa in 86 ml of acetic anhydride and 172 ml of pyridine was allowed to stand at room temperature overnight. Water was added (*ca.* 500 ml) and the mixture was cooled and filtered to give 9.95 g of solid. Recrystallization from aqueous acetone gave 7.3 g (62%) of IIIa, mp 150° (resolidified and remelted at 239–241°). The analytical sample, crystallized from ether, melted at 155° (resolidified and remelted at 245–250°): $[\alpha]_D$ +34° (dioxane); λ_{max}^{Nujol} 2.86, 3.08, 3.25, 5.74, 5.85, 6.11, 6.44, and 8.08 μ.

Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.25; H, 9.39; N, 3.03. Found: C, 70.31; H, 9.22; N, 3.21.

11β-Acetamido-5β-pregnane-3α,20β-diol (IVb).—To a solution of 8.0 g of IIb in 80 ml of pyridine was added 2.48 ml of acetic anhydride (1.10 moles/mole of steroid). After standing in the refrigerator for 1 hr, the crystalline precipitate was removed by filtration: 8.03 g of IVb (89.5%); mp 339–340°; $[\alpha]_D$ +70° (HOAc); λ_{max}^{Nujol} 2.95, 3.04, 6.06, and 6.50 μ.

Anal. Calcd for $C_{23}H_{39}NO_3$: C, 73.16; H, 10.41; N, 4.06. Found: C, 72.95; H, 10.38; N, 3.86.

11α-Acetamido-5β-pregnane-3α,20β-diol (IVa).—A mixture of 6.90 g of III, 2.5 g of sodium hydroxide, 170 ml of methanol, and 25 ml of water was refluxed for 3 hr. Acetic acid was added to neutralize excess alkali, the organic solvent was removed by distillation, and water was added to precipitate 5.23 g (93%), mp 228–231°. Crystallization from ethyl acetate gave 4.22 g (75%) of IVa: mp 234–235°; $[\alpha]_D$ −6.7° (dioxane); λ_{max}^{Nujol} 2.99, 3.10, 3.22, 6.16, and 6.32 μ.

Anal. Calcd for $C_{23}H_{39}NO_3$: C, 73.16; H, 10.41; N, 3.71. Found: C, 73.27; H, 10.33; N, 4.06.

11α-Acetamido-5β-pregnane-3,20-dione (Va).—A solution of 3.85 g of IVa and 9.85 g of N-bromoacetamide in 192 ml of 80% acetone containing 1 drop of hydrochloric acid was allowed to react at 5° for 21 hr. Excess oxidizing agent was destroyed by the addition of dilute sodium sulfite solution, and the acetone was removed under reduced pressure. The residue was made alkaline with dilute sodium hydroxide and extracted with methylene chloride. The organic extracts were washed with water, dried over magnesium sulfate, and evaporated to give 3.56 g (94%), mp 213–220°. Two crystallizations from ethyl acetate gave 61% of Va: mp 229.8–230.4°; $[\alpha]_D$ +73.3° (dioxane); λ_{max}^{Nujol} 3.04, 3.26, 5.84, 6.09, and 6.44 μ.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.74; H, 9.28; N, 3.60.

11β-Acetamido-5β-pregnane-3,20-dione (Vb).—To a solution of 10.0 g (0.0265 mole) of IVb in 1000 ml of 80% aqueous acetic acid was added 7.10 g of chromic acid (0.071 mole). After allowing to react at 25° for 2 hr, the excess oxidizing agent was destroyed by the addition of ethanol; the reaction was concentrated to a low volume under reduced pressure and made alkaline with sodium hydroxide solution. It was extracted into methylene chloride, washed once with water, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to dryness to yield 6.15 g of solid. Crystallization from aqueous acetone gave 7.59 g (77%) of Vb: mp 130° dec; $[\alpha]_D$ +140° (dioxane); λ_{max}^{Nujol} 2.83, 3.02, 5.78, 6.08, and 6.50 μ.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.78; H, 9.29; N, 3.83.

11α-Acetamido-5β-pregnane-3,20-dione 3-Ethylene Ketal (VIa).—A two-phase system of 6.0 g of Va, 90 ml of ethylene glycol, 90 ml of alcohol-free chloroform, and 6.0 g of selenium dioxide was vigorously stirred at 25° for 23 hr, then poured into water containing 12 g of potassium carbonate, extracted into methylene chloride, and washed once with water. The methylene chloride was then dried over magnesium sulfate, filtered, and evaporated to a residue to yield 6.73 g. Two recrystallizations from acetonitrile yielded 5.20 g (78%) of VIa: mp 340–341°; $[\alpha]_D$ +80° (DMF); λ_{max}^{Nujol} 3.06, 3.26, 5.87, 6.09, 6.47, and 9.20 μ.

Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.89; H, 9.41; N, 3.36. Found: C, 72.13; H, 9.62; N, 3.32.

11β-Acetamido-5β-pregnane-3,20-dione 3-Ethylene Ketal (VIb).—In the same fashion as with Va, 7.0 g of Vb was treated with selenium dioxide and ethylene glycol to give 7.98 g (100%) of crude VIb, which could not be crystallized, but had $[\alpha]_D$ +128° (dioxane); λ_{max}^{Nujol} 3.01, 5.87, 6.10, 6.55, and 9.20 μ.

Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.89; H, 9.41; N, 3.36. Found: C, 71.76; H, 9.55; N, 3.47.

11α-Acetamido-5β-pregnan-20β-ol-3-one Ethylene Ketal (VIIe).—A solution of 6.2 g of VIa in 620 ml of methanol containing 1.2 ml of 20% sodium hydroxide was heated to reflux and to this

was rapidly added a solution of 6.2 g of sodium borohydride in 62 ml of water. After refluxing for 2 hr, 62 ml of acetone was added and the organic solvents were removed by steam distillation. Collection of the solids, after cooling, yielded 5.97 g. Crystallization from acetonitrile yielded 5.34 g (86%) of VIIa: mp 293–295°; $[\alpha]_D$ +13° (DMF); λ_{max}^{Nujol} 2.92, 3.03, 3.25, 6.06, 6.47, and 9.02 μ.

Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34. Found: C, 71.23; H, 9.69; N, 3.19.

11β-Acetamido-5β-pregnan-20β-ol-3-one Ethylene Ketal (VIIb).—In the same fashion, 6.2 g of VIb was reduced, and the product was crystallized from benzene–ether to give 5.01 g (67%) of VIIb: mp 100° dec; $[\alpha]_D$ +37° (dioxane); λ_{max}^{Nujol} 3.01, 6.10, 6.60, and 9.15 μ.

Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34. Found: C, 71.42; H, 9.77; N, 3.33.

11α-Acetamido-20β-acetoxy-5β-pregnan-3-one (VIIIa).—A solution of 13.0 g of VIIa in 130 ml of glacial acetic acid and 130 ml of water was maintained at 80° for 30 min, after which it was poured onto ice, made alkaline with sodium hydroxide, extracted into methylene chloride, washed once with water, dried over magnesium sulfate, filtered, and evaporated to a residue. This residue was dissolved in 240 ml of pyridine and 120 ml of acetic anhydride and allowed to react at room temperature for 1.25 hr, at which time it was precipitated into hydrochloric acid–ice–water. The mixture was extracted with methylene chloride, washed until neutral, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to dryness to yield 13.03 g. Crystallization from aqueous acetone yielded 11.83 g (92%): mp 251–255°; $[\alpha]_D$ −1° (dioxane); λ_{max}^{Nujol} 2.89, 3.11, 3.26, 5.77, 5.85, 6.11, 6.41, and 8.03 μ.

Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.89; H, 9.41; N, 3.36. Found: C, 71.45; H, 9.62; N, 3.28.

11β-Acetamido-20β-acetoxy-5β-pregnan-3-one (VIIIb).—In the same fashion, 4.96 g of VIIb was hydrolyzed, reduced, and acetylated. The crude solid could not be crystallized; it was dissolved in acetone and partially precipitated with water to give 4.46 g (90%), $[\alpha]_D$ +77° (dioxane), which gave the correct analysis for a monohydrate.

Anal. Calcd for $C_{25}H_{39}NO_4 \cdot H_2O$: C, 68.93; H, 9.49; N, 3.22. Found: C, 69.24; H, 9.36; N, 3.53.

11α-Acetamido-20β-acetoxy-4-bromo-5β-pregnan-3-one (IXa).—A solution of 6.75 g (0.0162 mole) of VIIIa in 68 ml of methylene chloride and 68 ml of *t*-butyl alcohol was warmed to 30°. To this was added a solution of 2.72 g of bromine (1 equiv plus 5% excess) in 5 ml of methylene chloride and 5 ml of *t*-butyl alcohol. The reaction was catalyzed by addition of 675 mg of *p*-toluenesulfonic acid monohydrate. After 3.5 hr at 25°, the reaction was negative to moistened KI–starch paper, so the methylene chloride was evaporated under reduced pressure, then water and sodium bicarbonate added. It was then extracted into methylene chloride, washed once with water, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to dryness to give 7.90 g. Recrystallization from aqueous acetone yielded 6.18 g (77%) of IXa, mp 172° dec, $[\alpha]_D$ +41° (acetone).

Anal. Calcd for $C_{25}H_{38}BrNO_4$: Br, 16.10. Found: Br, 16.18.

11β-Acetamido-20β-acetoxy-4-bromo-5β-pregnan-3-one (IXb).—The bromination of 4.40 g of VIIIb in the same manner required only 2.5 hr and gave 4.86 g of crude solid which would not crystallize. It was dissolved in acetone and partially precipitated with water to give 4.04 g (77%), mp 175° dec, $[\alpha]_D$ +78° (acetone).

Anal. Calcd for $C_{25}H_{38}BrNO_4$: Br, 16.10. Found: Br, 16.10.

11α-Acetamido-20β-acetoxy-4-pregnen-3-one (Xa).—A mixture of 6.10 g (0.0123 mole) of IXa, 122 ml of dimethylformamide, and 677 mg of calcium carbonate (1 equiv plus 10% excess) was refluxed for 3 hr and then poured into hydrochloric acid–ice. It was extracted into methylene chloride, washed neutral with water, then with dilute sodium hydroxide, again neutral with water, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to dryness to give 4.94 g. Recrystallization from aqueous acetone yielded 3.45 g (68%) of Xa as a monohydrate: mp 211–217°; $[\alpha]_D$ +106° (dioxane); λ_{max}^{MeOH} 241 mμ (ε 10,100); λ_{max}^{Nujol} 2.90, 3.11, 3.28, 5.78, 6.00, 6.10, 6.43, and 8.08 μ.

Anal. Calcd for $C_{25}H_{37}NO_4 \cdot H_2O$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.30; H, 9.08; N, 3.46.

11β-Acetamido-20β-acetoxy-4-pregnen-3-one (Xb).—In the same fashion, 4.04 g of IXb was dehydrobrominated to give 3.37 g (~100%) of crude Xb, $[\alpha]_D$ +145° (dioxane), λ_{max}^{MeOH} 238 mμ (ε 9600). This was not further purified, but put directly into the next step.

11α-Acetamido-20β-hydroxy-4-pregnen-3-one (XIa).—A solution of 3.72 g of Xa and 720 mg of sodium hydroxide in 74 ml of methanol and 14 ml of water was refluxed for 2.5 hr, then the methanol was removed by steam distillation. The product was extracted into methylene chloride, washed once with water, dried over magnesium sulfate, filtered, and evaporated to dryness to yield 3.24 g. This was chromatographed on 65 g of Florisil; the fractions eluted with methylene chloride containing 0.5–3% of methanol were combined and crystallized 2 times from ethyl acetate to yield 1.12 g (35%) of XIa: mp 244–248°; $[\alpha]_D$ +93° (dioxane); λ_{max}^{MeOH} 242 mμ (ε 13,000); λ_{max}^{Nujol} 3.05, 6.07, 6.20, and 6.48 μ.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.53; H, 9.53; N, 3.91.

11β-Acetamido-20β-hydroxy-4-pregnen-3-one (XIb).—In the same manner, 4.23 g of Xb was hydrolyzed to give 3.39 g of crude XIb. This was chromatographed on Florisil; the material eluted with 100% ether and with ether containing up to 3% methanol was combined: 1.03 g (27%); λ_{max}^{MeOH} 237 mμ (ε 11,100); λ_{max}^{Nujol} 2.95, 3.04, 5.82, 5.88, 6.02, 6.10, 6.18 (sh), 6.22 (sh), and 6.55 μ.

11α-Acetamidoprogesterone (XIIa).—A solution of 911 mg of XIa in 125 ml of acetone was oxidized with 1.25 ml of Jones reagent[15] at 25° for 0.5 hr. It was poured into water, made alkaline with sodium hydroxide, extracted into methylene chloride, and washed once with water. It was then dried over magnesium sulfate and filtered, and the filtrate was evaporated to dryness to give 820 mg. Two crystallizations from ethyl acetate yielded 543 mg (60%) of XIIa: mp 202–205°; $[\alpha]_D$ +185° (dioxane); λ_{max}^{MeOH} 242 mμ (ε 14,400); λ_{max}^{Nujol} 3.05, 3.15, 5.90, 6.05, 6.20, and 6.53 μ.

Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.56; H, 8.70; N, 4.06.

11β-Acetamidoprogesterone (XIIb).—In the same manner, 1.03 g of XIb was oxidized to 1.00 g of crude XIIb. This was chromatographed on Florisil, and the fractions eluted with ether and 1% MeOH–ether were combined and crystallized from ethyl acetate to yield 162 mg (16%) of XIIb: mp 212–213°; $[\alpha]_D$ +123° (dioxane); λ_{max}^{MeOH} 238 mμ (ε 14,900); λ_{max}^{Nujol} 3.02, 5.90, 6.00, 6.12, and 6.56 μ.

Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.01; H, 8.70; N, 3.85.

11α-Acetamido-20β-acetoxy-2,4-dibromo-5β-pregnan-3-one (XIIIa).—A solution of 1.19 g of bromine (0.00704 mole plus 5% excess) in 5 ml of glacial acetic acid was added to 1.47 g (0.00352 mole) of VIIIa in 14.7 ml of glacial acetic acid and 20 ml of dioxane, and then 6 drops of acetic acid saturated with hydrogen bromide was added. After 45 min, the reaction was negative to moistened KI–starch paper, and it was water precipitated. The solids were extracted into methylene chloride, the extract was washed with sodium bicarbonate solution and then water, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to dryness. Crystallization was not attempted, but reprecipitating the material with acetone–water, then filtering, yielded 1.77 g (87%) of XIIIa, mp 160° dec, $[\alpha]_D$ +34° (acetone).

Anal. Calcd for $C_{25}H_{37}BrNO_4$: Br, 27.78. Found: Br, 27.27.

11β-Acetamido-20β-acetoxy-2,4-dibromo-5β-pregnan-3-one (XIIIb).—In the same fashion, 2.58 g of VIIIb gave 2.50 g (70%) of XIIIb, mp 170° dec, $[\alpha]_D$ +53° (acetone).

Anal. Calcd for $C_{25}H_{37}Br_2NO_4$: Br, 27.78. Found: Br, 26.69.

11α-Acetamido-20β-acetoxy-1,4-pregnadien-3-one (XIVa).—A mixture of 5.23 g of XIIIa (0.0091 mole) and 1.00 g of calcium carbonate (0.0091 mole plus 10% excess) in 105 ml of dimethylformamide was refluxed for 3.5 hr, and then poured into hydrochloric acid–ice. It was extracted into methylene chloride, washed with water, dilute sodium hydroxide, and water, dried over magnesium sulfate, filtered, and evaporated to a residue. Crystallization from aqueous acetone yielded 2.53 g (67%) of

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

XIVa as a monohydrate: mp 211–215°; $[\alpha]_D$ +119° (dioxane); λ_{max}^{Nujol} 3.02, 5.79, 6.05, 6.19, 6.26, 6.60, and 8.09 μ; λ_{max}^{MeOH} 252 mμ (ε 16,500).

Anal. Calcd for $C_{25}H_{36}NO_4 \cdot H_2O$: C, 69.57; H, 8.64; N, 3.25. Found: C, 69.87; H, 8.60; N, 3.30.

11β-Acetamido-20β-acetoxy-1,4-pregnadien-3-one (XIVb).—In the same manner, dehydrobromination of 2.50 g of XIIIb gave 1.76 g (98%) of crude XIVb, λ_{max}^{Nujol} 242 mμ (ε 11,200). This was not further purified, but was carried directly into the next step.

11α-Acetamido-1,4-pregnadien-20β-ol-3-one (XVa).—A solution of 2.30 g of XIVa (0.0056 mole) and 448 mg of sodium hydroxide (0.0112 mole) in 46 ml of methanol and 10 ml of water was refluxed for 3 hr. Water (100 ml) was added, the methanol was distilled off, the mixture was cooled, and the product was collected by filtration to give 1.57 g. Crystallization from ethyl acetate yielded 1.46 g (71%): mp 296–297°; $[\alpha]_D$ +9° (DMF); λ_{max}^{MeOH} 252 mμ (ε 17,200); λ_{max}^{Nujol} 3.05, 3.27, 6.02, 6.10, 6.19, 6.26, and 6.45 μ.

Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.85; H, 9.18; N, 3.99.

11β-Acetamido-1,4-pregnadien-20β-ol-3-one (XVb).—In the same manner, 1.76 g of crude XIVb gave 1.68 g (89%) of crude XVb, and this was chromatographed on Florisil. The fractions eluted with methylene chloride and 2% methanol–methylene chloride were combined and crystallized from ethyl acetate–hexane to give 660 mg (35%) of XVb: mp 287–290°; $[\alpha]_D$ +96° (dioxane); λ_{max}^{MeOH} 241 mμ (ε 13,500); λ_{max}^{Nujol} 2.94, 3.00, 5.80, 6.03, 6.10, 6.16, 6.24, and 6.55 μ.

Anal. Calcd for $C_{23}H_{33}NO_3$: N, 3.77. Found: N, 3.99.

11α-Acetamido-1-dehydroprogesterone (XVIa).—A solution of 1.10 g (0.003 mole) of XVa in 330 ml of acetone was oxidized with 1.53 ml of Jones reagent[15] at 25° for 20 min. It was poured into water, extracted into methylene chloride, washed with dilute sodium hydroxide and water, dried over magnesium sulfate, filtered, and evaporated to a residue (960 mg). Two crystallizations from ethyl acetate yielded 652 mg (60%): mp 228–229°; $[\alpha]_D$ +187° (dioxane); λ_{max}^{MeOH} 250 mμ (ε 17,800); λ_{max}^{Nujol} 3.02, 5.87, 6.03, 6.16,6.24, and 6.53 μ.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.95; H, 8.48; N, 3.98.

11β-Acetamido-1-dehydroprogesterone (XVIb).—In the same manner, oxidation of 500 mg of XVb gave, after two crystallizations from ethyl acetate, 341 mg (61%) of XVIb: mp 275–276°; $[\alpha]_D$ +113° (dioxane); λ_{max}^{MeOH} 240 mμ (ε 14,600); λ_{max}^{Nujol} 2.99, 5.87, 6.00, 6.10, 6.20, and 6.52 μ.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.71; H, 8.54; N, 3.77.

11-Amino-Steroids. III. 11-Acetamido Derivatives of Cortexolone[1-3]

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5β-Pregnane-3α,17α,20β-triol-11-one converted to its 11-oxime, and then to the 11α-amine (Na–PrOH reduction) or the 11β-amine (Pt–H_2–HOAc reduction). These were then transformed, by known reactions, into the 11α- and 11β-acetamido-1-dehydrocortexolone 21-acetates.

The previous paper[3] described the preparation of 11α- and 11β-amino-5β-pregnane-3α,20β-diols and their conversion to 11-acetamidoprogesterones, including the 1-dehydro analogs. This paper describes the extension of such work to the preparation of 11-acetamidocortexolone analogs.

Reaction of 5β-pregnane-3α,17α,20β-triol-11-one (I) with hydroxylamine hydrochloride in refluxing aqueous pyridine gave a good yield of the 11-oxime II (see Scheme I). Reduction with sodium and *n*-propyl alcohol produced 11α-amino-5β-pregnane-3α,17α,20β-triol (IIIa), while the 11β-amino epimer IIIb was obtained from a platinum–acetic acid hydrogenation. The configurational assignment is based on analogy with the previous work[3] (method of reduction and ultraviolet and nmr data). Also, as in the 17-desoxy series,[3] the 11β-amines and -amides had consistently more positive rotations than their 11α epimers.[4]

Treatment of IIIa with acetic anhydride–pyridine at room temperature produced the fully acetylated compound IVa. Saponification with aqueous methanolic sodium hydroxide gave an excellent yield of 11α-acetamido-5β-pregnane-3α,17α,20β-triol (IVc), with no evidence for any hydrolysis of the amide function. Elaboration of the dihydroxyacetone side chain characteristic of cortexolone and the glucocorticoids required the presence of a 20-ketone, but no simple method was available for converting the 20β-ol to the necessary ketone without also affecting the 3α-ol. Accordingly, both hydroxyls were oxidized with N-bromoacetamide in aqueous acetone to yield 11α-acetamido-5β-pregnan-17α-ol-3,20-dione (Va), and the C-3 ketone was then selectively reduced with sodium borohydride in aqueous pyridine[5] to give *ca.* 50% of 11α-acetamido-5β-pregnane-3α,17α-diol-20-one (VIa).[6] Bromination in chloroform at C-21, followed by displacement with potassium acetate in aqueous acetone, completed the side-chain elaboration, producing VIc. The 3α-hydroxyl was oxidized with N-bromoacetamide in aqueous acetone to the saturated 3-ketone VII and the Δ^4 or $\Delta^{1,4}$ unsaturation was introduced by mono- or dibromination, followed by dehydrobromination. There was thus obtained 11α-acetamidocortexolone 21-acetate (VIII) and its 1-dehydro analog IXa.

The 11β series did not proceed in exactly this sequence. As in the 17-desoxy series,[3] reaction of 11β-amino-5β-pregnane-3α,17α,20β-triol (IIIb) with acetic anhydride in pyridine gave an immediate precipitate of the 11β-amide triol IVb. Satisfactory oxidation to 11β-acetamidopregnan-17α-ol-3,20-dione (V) required reaction with N-bromoacetamide in aqueous *t*-butyl alcohol–acetic acid for 4 days in the cold. The dione could not be reduced selectively at

(1) A portion of this work has been published previously.[2]

(2) E. B. Hershberg, E. P. Oliveto, and R. Rausser, *Chem. Ind.* (London), 1477 (1958).

(3) Paper II: R. Rausser, L. Weber, E. B. Hershberg, and E. P. Oliveto, *J. Org. Chem.*, **31**, 1342 (1966).

(4) This rotational effect is quite evident in 11-hydroxypregnanes: see E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953), for 11β-hydroxypregnanes, and compare with E. P. Oliveto, H. L. Herzog, and E. B. Hershberg, *ibid.*, **75**, 1505 (1953), for 11α-hydroxypregnanes.

(5) *Cf.* O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *ibid.*, **75**, 1286 (1953); A. Soloway, A. Deutsch, and T. F. Gallagher, *ibid.*, **75**, 2356 (1953).

(6) The configuration assigned at C-3 is by analogy with the work described in ref 5, and other references cited therein.