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).

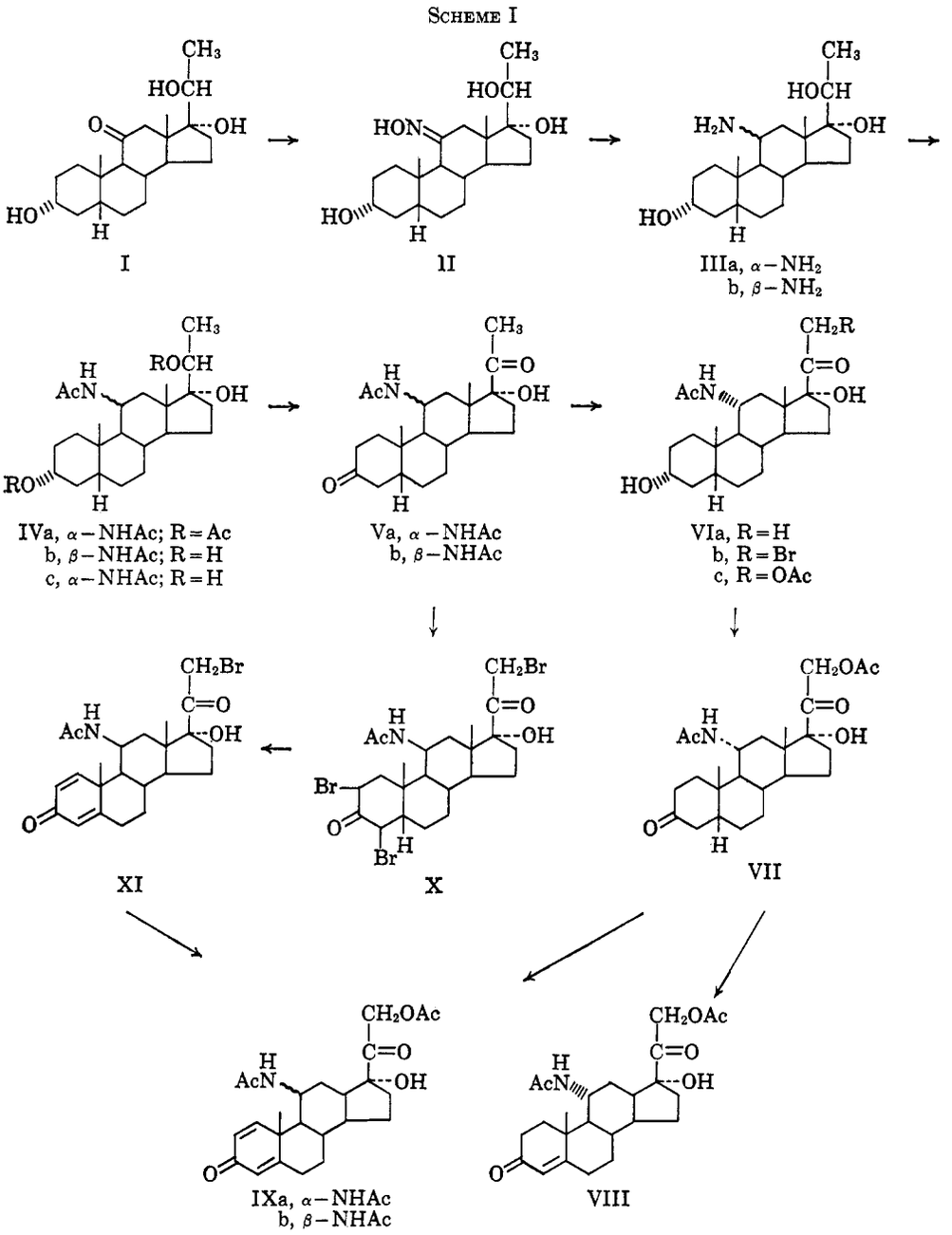
(3) Paper II: R. Rausser, L. Weber, E. B. Hershberg, and E. P. Oliveto, *J. Org. Chem.*, **31**, 1342 (1966).

(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.

SCHEME I



C-3 with sodium borohydride in a satisfactory fashion. Alternatively, it was brominated[7] in acetic acid to the 2,4,21-tribromide X, which, without substantial purification, was dehydrobrominated in the A ring with diethylacetamide and the remaining C-21 bromine was replaced with acetate in the usual manner. Chromatography then gave crystalline 11β-acetamido-1-dehydrocortexolone 21-acetate (IXb).

The ultraviolet data again[3] supported the original configurational assignment of the 11-amines: compound IXa, λ_{max} 252 mμ; compound IXb, λ_{max} 240 mμ; 11-epiprednisolone 21-acetate, λ_{max} 248 mμ; prednisolone 21-acetate, λ_{max} 242 mμ.

Experimental Section[8]

11-Oximinopregnane-3α,17α,20β-triol (II).—A solution of 10.0 g of pregnane-3α,17α-20β-triol-20-one (I) and 10 g of hydroxylamine hydrochloride in 100 ml of pyridine–water (90:10) was refluxed for 17 hr. The mixture was then concentrated to *ca.* one-half volume, water was added to incipient cloudiness, and the solution was heated to boiling. The addition of *ca.* 50 ml of methanol caused the precipitation of crystals. Upon cooling, the crystals were removed by filtration: 8.7 g (81%), mp 258–262° dec. The analytical sample, crystallized from ethanol, had mp 272.4–273.4° dec; $[\alpha]_D$ +55.4° (dioxane); λ_{max}^{Nujol} 2.90, 3.05, and 6.09 μ.

Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.94; H, 9.53; N, 3.99.

The triacetate was prepared by reaction of II with acetic anhydride and pyridine overnight at room temperature. The analytical sample, crystallized from methanol, had mp 217.2–218.0°, $[\alpha]_D$ +81.5° (dioxane).

Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.96; H, 8.41; N, 2.85. Found: C, 65.70; H, 8.08; N, 2.62.

11α-Amino-5β-pregnane-3α,17α,20β-triol (IIIa).—To a solution of 10.0 g of II in 2.5 l of *n*-propyl alcohol was added 150 g of sodium over a period of 15 min. The mixture was then re-

(7) *Cf.* G. Muller, R. Joly, G. Nomine, and D. Bertin, *Bull. Soc. Chim. France*, 1457 (1956); R. Joly, J. Warnant, G. Nomine, and D. Bertin, U. S. Patent 2,923,721 (Feb 2, 1960); R. Joly, G. Nomine, and D. Bertin, U. S. Patent 2,888,473 (May 26, 1959).

(8) All melting point 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.

fluxed until all the sodium had dissolved (*ca.* 2.75 hr) and then for 0.75 hr more. Water (*ca.* 500 ml) was added, and the solution was steam distilled to remove organic solvent, cooled, and filtered to give 10.68 g, mp 180–185° dec. One crystallization from acetonitrile gave 7.25 g (75%): mp 190.0–192.0° dec; $[\alpha]_D$ −50.9° (dioxane); λ_{max}^{Nujol} 2.83, 2.95, and 6.32 μ.

Anal. Calcd for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.99. Found: C, 71.66; H, 10.36; N, 4.08.

11α-Acetamido-5β-pregnane-3α,17α,20β-triol 3,20-Diacetate (IVa).—A solution of 1.54 g of IIIa in 62 ml of pyridine and 31 ml of acetic anhydride was allowed to stand at room temperature for 18 hr, then poured into ice–hydrochloric acid, and extracted into methylene chloride. The organic extracts were washed three times with water, dried, and evaporated to give 2.14 g, mp 229–234° dec. The analytical sample, crystallized twice from aqueous methanol, was obtained as the hydrate in 80% yield and had mp 246–250° dec; $[\alpha]_D$ +22.4° (dioxane); λ_{max}^{Nujol} 2.75, 2.87, 3.05, 3.25, 5.78, 5.86, 6.09, 6.40, 7.89, and 8.05 μ.

Anal. Calcd for $C_{27}H_{43}NO_6 \cdot H_2O$: C, 65.42; H, 9.15; N, 2.83. Found: C, 65.43; H, 9.52; N, 2.91.

11α-Acetamido-5β-pregnane-3α,17α,20β-triol (IVc).—A solution of 1.55 g of IVa in 30 ml of methanol and 4 ml of water containing 389 mg of sodium hydroxide was refluxed for 0.5 hr. Acetic acid was added to neutralize excess alkali, and the solution was concentrated to dryness under reduced pressure. Crystallization from acetonitrile gave 1.08 g (84%), mp 266–267°. One further crystallization gave 950 mg (74%): mp 266.8–268.0°; $[\alpha]_D$ −30.1° (MeOH); λ_{max}^{Nujol} 2.84, 2.95, 3.06, 3.22, 6.13, and 6.36 μ.

Anal. Calcd for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.26; H, 9.92; N, 3.50.

11α-Acetamido-5β-pregnan-17α-ol-3,20-dione (Va).—A solution of 10.78 g of IVc in 430 ml of acetone and 105 ml of water was cooled to 5°, and 1 ml of concentrated hydrochloric acid and 26.4 g of N-bromoacetamide were added. The reaction was allowed to proceed in the icebox for 23 hr, then 20 g of sodium sulfite in water was added. The acetone was removed by steaming, and the remaining mixture was made alkaline with sodium hydroxide, cooled, and filtered to give 10.28 g, mp 268–275° dec. Crystallization from acetonitrile gave 7.77 g (73%): mp 288–292° dec; $[\alpha]_D$ +19.1° (MeOH); λ_{max}^{Nujol} 2.98, 3.04, 5.84, 5.90, 6.08, and 6.51 μ.

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.14; H, 9.22; N, 3.67.

11α-Acetamido-5β-pregnane-3α,17α-diol-20-one (VIa).—A solution of 5.00 g of Va and 500 mg of sodum borohydride in 60 ml of pyridine and 2.5 ml of water was allowed to react at room temperature for 22 hr. Excess reducing agent was destroyed by the addition of concentrated hydrochloric acid, then the solution was poured onto ice and excess hydrochloric acid and filtered to give 3.32 g of VI, mp 272–275°. Two crystallizations from acetonitrile gave 2.55 g (51%): mp 279–283°; $[\alpha]_D$ +21.6° (MeOH); λ_{max}^{Nujol} 2.96, 5.88, 6.11, and 6.46 μ.

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.61; H, 9.57; N, 4.03.

11α-Acetamido-21-acetoxy-5β-pregnane-3α,17α-diol-20-one (VIc).—A mixture of 2.0 g of VIa in 200 ml of chloroform containing 0.75% of ethanol was saturated with hydrogen bromide and cooled to −15°. A solution of 860 mg of bromine in 50 ml of chloroform was added dropwise over 1.5 hr, maintaining the temperature between −14 and −16°. The solution was evaporated to a residue under reduced pressure, 600 ml of acetone, 15 ml of water, and 10 g of potassium acetate were added, and the resulting mixture was refluxed 16 hr. The organic solvent was removed under reduced pressure, water was added, and the mixture was extracted with methylene chloride. The organic extracts were dried and evaporated to a residue: 2.58 g, mp 209–219° dec. Two crystallizations from aqueous acetonitrile gave 1.87 g (81%): mp 236–239° dec; $[\alpha]_D$ +52.0° (dioxane); strong positive triphenyltetrazolium chloride (TPTZ) test; λ_{max}^{Nujol} 3.05, 5.72, 5.82, 6.40, and 8.12 μ.

Anal. Calcd for $C_{25}H_{39}NO_6 \cdot H_2O$: C, 64.21; H, 8.84; N, 3.00. Found: C, 64.94; H, 8.85; N, 3.04.

11α-Acetamido-21-acetoxy-5β-pregnan-17α-ol-3,20-dione (VII).—A solution of 1.87 g of VIc and 2.03 g of N-bromoacetamide in 94 ml of 80% aqueous acetone containing 1 drop of concentrated hydrochloric acid was allowed to react at *ca.* 5° for 17 hr. Excess oxidizing agent was destroyed by the addition of dilute sodium sulfite solution and the acetone was removed under reduced pressure. Extraction with methylene chloride, followed by drying and evaporation, gave 1.43 g (77%): mp 241–245° (crystallization from ethyl acetate raised the melting point to 247.8–249.6°); $[\alpha]_D$ +46.4° (dioxane); λ_{max}^{Nujol} 3.00, 3.10, 5.75, 5.83, 6.11, 6.44, and 8.12 μ.

Anal. Calcd for $C_{25}H_{37}NO_6$: N, 3.13. Found: N, 3.05.

11α-Acetamido-21-acetoxy-Δ⁴-pregnen-17α-ol-3,20-dione (VIII).—A solution of 448 mg of VII in 12 ml of *t*-butyl alcohol and 12 ml of methylene chloride was treated with 10 mg of *p*-toluenesulfonic acid and a solution of 165 mg of bromine in 4 ml of *t*-butyl alcohol, and the mixture was allowed to react 7 hr at 30°. The solvents were removed under reduced pressure, and the residual oil was crystallized by the addition of 10 ml of acetone and 20 ml of ether to give 500 mg of 11α-acetamido-21-acetoxy-4-bromopregnan-17α-ol-3,20-dione, mp *ca.* 225° dec. A solution of 430 mg of the bromide and 130 mg of semicarbazide in 20 ml of *t*-butyl alcohol and 6 ml of methylene chloride was shaken for 2 hr, and then it was evaporated to a residue under reduced pressure. Acetic acid (5 ml) and 2 ml of 92% pyruvic acid were added, and the resulting solution was allowed to stand at room temperature for 20 hr. Sodium acetate was added, and the volume was reduced to *ca.* one-third under reduced pressure. Extraction with methylene chloride gave 270 mg of a resin which was chromatographed on 9 g of Florisil. Elution with 3% methanol in methylene chloride gave 160 mg of crude VIII, and crystallization from ethyl acetate gave 120 mg: mp 267.5–270°; λ_{max}^{MeOH} 242 mμ (ε 15,000); λ_{max}^{Nujol} 2.97, 5.74, 5.84, and 5.98 μ.

Anal. Calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.91; N, 3.14. Found: C, 67.13; H, 7.91; N, 3.31.

11α-Acetamido-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (IXa).—A solution of 2.02 g of VII in 20 ml of dioxane and 2 ml of acetic acid was treated with a solution of 1.51 g of bromine in 7 ml of dioxane and 7 ml of acetic acid at room temperature. Rapid decolorization occurred. After 25 min, 1 ml of of 48% aqueous hydrogen bromide was added. Crystalline material formed during a further reaction time of 2 hr. The product was precipitated by pouring into 400 ml of water. This was saturated with sodium chloride, and extraction with methylene chloride, followed by removal of the solvent under reduced pressure, afforded 1.92 g of the 2,4-dibromide, mp 160° dec, $[\alpha]_D$ +34° (dioxane).

Anal. Calcd for $C_{25}H_{35}Br_2NO_6$: Br, 26.40. Found: Br, 27.21.

A portion of this crude dibromide (1.72 g) was refluxed with 284 mg of calcium carbonate in 34 ml of dimethylformamide for 2 hr, then poured over ice containing 34 ml of concentrated hydrochloric acid, and extracted with methylene chloride. The extracts were washed with water, dried with magnesium sulfate, and evaporated to a residue under reduced pressure (1.04 g). Chromatography on Florisil afforded, from the 1% methanol–methylene chloride eluates, 514 mg of crystalline solid. Two crystallizations from ethyl acetate gave 298 mg of IXa: mp 243–245°; $[\alpha]_D$ +148.3° (dioxane); λ_{max}^{MeOH} 252 mμ (ε 15,700); λ_{max}^{Nujol} 2.95, 3.08, 5.71, 5.78, 6.05, 6.18, 6.45, and 8.10 μ. The analytical sample, crystallized once more from ethyl acetate, had a melting point of 245–247°.

Anal. Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.21; H, 7.66; N, 3.02.

11β-Amino-5β-pregnane-3α,17α,20β-triol (IIIb).—A solution of 45 g of 11-oximinopregnane-3α,17α,20β-triol in 6.5 l. of glacial acetic acid was hydrogenated at 800 psi and at 60° for approximately 48 hr with 22.5 g of PtO_2 catalyst. When the reaction was complete, the catalyst was removed by filtration and the solution was evaporated to a residue under reduced pressure. This was dissolved in 2 l. of methanol, a solution of 45 g of sodium hydroxide in 300 ml of water was added, and the mixture was heated to reflux. Some material which was out of solution was removed by filtration and discarded. The organic solvent was then removed by steam distillation; the mixture was cooled to 10°, and filtered. The crude product was recrystallized from acetonitrile to yield in two crops 35.7 g (86.2%) of the 11β-amino compound: mp 247–249°; $[\alpha]_D$ +10.7° (MeOH); λ_{max}^{Nujol} 2.80, 2.92, and 6.10 μ.

Anal. Calcd for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.99. Found: C, 71.82; H, 10.49; N, 4.05.

11β-Acetamido-5β-pregnane-3α,17α,20β-triol (IVb).—A solution of 10.87 g of 11β-aminopregnane-3α,17α,20β-triol in 150 ml of pyridine was treated at room temperature with 3.22 ml of acetic anhydride (1 mole plus 10%). Crystallization took place

almost at once. The reaction was allowed to stand for 0.5 hr at room temperature, then 1 hr in the refrigerator, and the precipitated solid was removed by filtration, washed with pyridine and ether, and dried: 9.91 g; mp 318–324°; $[\alpha]_D$ +33.0° (MeOH); λ_{max}^{Nujol} 2.94, 6.11, and 6.47 μ.

Anal. Calcd for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.24; H, 9.91; N, 3.82.

11β-Acetamido-5β-pregnan-17α-ol-3,20-dione (V).—A mixture of 5.00 g of 11β-acetamidopregnane-3α,17α,20β-triol, 150 ml of acetic acid, 150 ml of *t*-butyl alcohol, 30 ml of water, and 17.6 g of N-bromoacetamide was allowed to react in the refrigerator for 4 days. A cold, aqueous solution of 20 g of sodium sulfite and 0.5 g of sodium bicarbonate was added and the solution was evaporated to dryness at room temperature. The residue was dissolved in methylene chloride and the organic extracts were washed with water, dried, and evaporated. Treatment of the resinous residue with ethyl acetate crystallized 3.79 g as a solvate: mp 156–164° with bubbling; $[\alpha]_D$ +67.1° (MeOH); λ_{max}^{Nujol} 2.89 (sh), 2.94, 5.86, 6.09, and 6.52 μ.

Anal. Calcd for $C_{23}H_{35}NO_4 \cdot 0.5C_4H_8O_2$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.17; H, 8.80; N, 3.58.

11β-Acetamido-2,4,21-tribromo-5β-pregnan-17α-ol-3,20-dione (X).—A solution of 2.59 g of bromine in 15 ml of acetic acid was added dropwise with stirring to a solution of 2.00 g of 11β-acetamidopregnan-17α-ol-3,20-dione in 40 ml of acetic acid containing 0.5 ml of 48% aqueous hydrogen bromide. Addition was complete in 15 min, at the end of 2 hr 0.5 g of sodium bicarbonate was added and the solution was evaporated to dryness at room temperature. The residue was triturated with water and filtered to give 3.13 g of crude tribromide.

Anal. Calcd for $C_{23}H_{32}Br_3NO_4$: Br, 38.28. Found: Br, 38.16.

11β-Acetamido-21-acetoxy-1,4-pregnadien-17α-ol-3,20-dione (IXb).—A mixture of 30 ml of diethylacetamide and 0.53 g of calcium carbonate was brought to reflux, and 3.10 g of crude tribromide was added with the aid of an additional 15 ml of diethylacetamide. Refluxing was continued for 10 min; then the mixture was poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sulfuric acid and water, dried, and evaporated at room temperature to an oil. This was dissolved in 100 ml of acetone containing 12 g of potassium acetate and the mixture was refluxed with stirring for 5 hr. The organic solvent was removed at room temperature and the residue was extracted with methylene chloride. The organic extracts were washed with water, dried, and evaporated. The residue was chromatographed on Florisil to give 1.20 g of crude product as an oil. Two crystallizations from ethyl acetate gave 0.5 g, mp 167–173°. The analytical sample, crystallized once more, had mp 163–167°; $[\alpha]_D$ +176.9° (dioxane); λ_{max}^{MeOH} 240 mμ (ε 12,900); λ_{max}^{Nujol} 3.02, 5.72 (sh), 5.80, 6.04, 6.15 (sh), 6.23 (sh), 6.56, 7.95, 8.13 μ. This material gave a postive TPTZ test.

Anal. Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.53; H, 7.52; N, 2.97.

3α,20-Dihydroxy-5β-pregn-9(11)-en-12-one. Side-Chain Conformations in the Light of Ultraviolet and Infrared Studies

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The unknown 3α,20α-dihydroxy-5β-pregn-9(11)-en-12-one (**4g**), the known 3α,20β-dihydroxy-5β-pregn-9(11)-en-12-one (**4c**), and some derivatives thereof have been prepared by conventional methods. Infrared and ultraviolet spectra demonstrate that the 20β-, but not the 20α-, hydroxyl group is intramolecularly hydrogen bonded to the 12-keto moiety. Conformations of the side chain of $\Delta^{9(11)}$-12-keto steroids possessing a C-20 hydroxyl group are shown.

Discussion

During recent studies in our laboratories, we prepared the two isomeric diolones **4c** and **4g**, of which only **4c** and its alleged diacetate have been reported recently.[1] Our interest in this type of compound was augmented by the observation that, because of the proximity of the C-20 hydroxyl and $\Delta^{9(11)}$-12-keto moieties, unique spectral evidence could be obtained regarding the conformations of the side chain of C-20 hydroxyl steroids. For this purpose, several derivatives of **4c** and **4g** were prepared, and their infrared and ultraviolet spectra were recorded.

The readily available bile acid derivative **1a** served as starting material, and was converted to the desired product as outlined in Scheme I. Reduction of **1a** with sodium borohydride followed by alkaline hydrolysis[2] afforded 3α,12α,20β-trihydroxy-5β-pregnane[1] (**2a**, 88%). Although protection of the 3α- and 20β-hydroxyl groups could be accomplished[1,2] by partial acylation of **2a** either with acetic or succinic anhydride, ethyl chlorocarbonate was employed in this work. Thus, treatment of **2a** with this reagent produced **2b**, which was oxidized with chromium trioxide in glacial acetic acid; the product, **3a**, could not be obtained in a crystalline form. Dehydrogenation of crude **3a** with selenium dioxide–glacial acetic acid[3] gave the unsaturated ketone **4b**, but crystallization could not be induced even in a chromatographically homogeneous sample. Nevertheless, basic hydrolysis of **4b** afforded the known[1] diolone **4c** in 71% over-all yield (**2b** → **3a** → **4b** → **4c**).

Alternatively, hydrolysis of the noncrystalline **3a** to **3b**, followed by acetylation to the known[4] diacetate **3c**, and dehydrogenation of the latter with selenium dioxide–glacial acetic acid gave 3α,20β-diacetoxy-5β-pregn-9(11)-en-12-one (**4a**, mp 149.5–150.5°, λ_{max}^{MeOH} 239.5 mμ). However, the same structure has been assigned recently[1] to a substance (mp 200.5–201.5°, λ_{max}^{EtOH} 244 mμ) obtained by acetylation of **4c** with a large excess of acetic anhydride–pyridine at room temperature. We have prepared the alleged diacetate (mp 206.5–207.5°, λ_{max}^{MeOH} 245 mμ) by usual acetylation of **4c**. This compound was found to be 3α-acetoxy-20β-hydroxy-5β-pregn-9(11)-en-12-one[5] (**4d**) by elemental analysis and by infrared spectroscopy, which revealed the presence of one acetoxy and one 20β-

(1) C. R. Engel and W. W. Huculak, *Can. J. Chem.*, **37**, 2031 (1959).
(2) P. L. Julian and A. Magnani, U. S. Patent 2,940,991 (1960).
(3) E. Schwenk and E. Stahl, *Arch. Biochem.*, **14**, 125 (1947); C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, p 233.
(4) G. Just and R. Nagarajan, *Can. J. Chem.*, **39**, 548 (1961).
(5) In a personal communication, Professor C. R. Engel informed us that he has also concluded that the product melting at 200.5–201.5° is in fact 3α-acetoxy-20β-hydroxy-5β-pregn-9(11)-en-12-one (**4e**). A mixture melting point of that product, kindly provided by Professor Engel, and **4e** showed no depression.