The Synthesis of 16β-Aminopregn-5-ene-3β,20β-diol and Related Compounds

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A synthesis of 16β-aminopregn-5-ene-3β,20β-diol (IIIb) has been developed. 3β-Acetoxy-16α-hydroxypregn-5-en-20-one (Ia) was converted into the 16α-mesylate Ib which was in turn reduced to 3β-acetoxy-16α-methanesulfonyloxypregn-5-en-20β-ol (IIa) with sodium borohydride. Treatment of IIa with sodium azide in N-methyl-2-pyrrolidone afforded 3β-acetoxy-16β-azidopregn-5-en-20β-ol (IIIa). Reduction with lithium aluminum hydride gave the desired 16β-aminopregn-5-ene-3β,20β-diol (IIIb). Acetylation gave the N-acetyl 3,20-diacetate IIIc, which on saponification provided the N-acetyl-3,20-diol IIId. 16β-Carbamidopregn-5-ene-3β,20β-diol (IIIe), 16β-benzyloxycarbonylaminopregn-5-ene-3β,20β-diol (IIIf), and 16β-(*o*-carboxybenzamido)pregn-5-ene-3β,20β-diol (IIIg) have also been prepared from IIIb. Oppenauer oxidation of the 16β-amino-3β,20β-diol IIIb gave an inseparable mixture, whereas the N-acetyldiol IIId gave 16β-acetamido-20β-hydroxypregn-4-en-3-one (Va) in low yield.

Interest in the properties of nitrogen-containing steroids[1] has led, *inter alia*, to a variety of investigations concerned with the synthesis of pregnenes with 16-substituents containing nitrogen. In particular, Gould and co-workers[2] have prepared a variety of biologically active[3] 16α-aminopregnanes and Hewett and associates,[4a,b] several 16β-amino-17α-hydroxypregnanes. Other 16-aminopregnanes have been described by Vargha and associates[5] (3,16-diamino-17α-hydroxypregnanes) and Husson and associates[6] (16α- and β-amino derivatives of paravallaridine). This report details synthetic work directed to the preparation of 16β-aminopregnenes which are not oxygenated at C-17 and, in particular, 16β-aminopregn-5-ene-3β,20β-diol (IIIb). The correspondence of this structural feature to that present in naturally occurring steroidal alkaloids containing a C-16 nitrogen[1,7] is apparent.

After an extensive exploratory investigation a pathway leading to the desired 16β-aminopregn-5-ene-3β,20β-diol (IIIb) was developed. The starting material, 3β-acetoxy-16α-hydroxypregn-5-en-20-one (Ia),[8] was converted into the 16α-mesylate Ib, which was, in turn, reduced with sodium borohydride to 3β-acetoxy-16α-methanesulfonyloxypregn-5-en-20β-ol (IIa).

Since it has been well demonstrated that a 20β-hydroxy configuration cannot always be assumed to result from metal hydride reduction of the carbonyl compound[9] and because of the needs of later work,[10] it was deemed necessary to determine conclusively the stereochemical configuration of the C-20 hydroxy function. When the molecular rotation of IIa was compared to that of the diacetate IIb, the shift in MD on acetylation was +86, a result strongly supporting a 20β-hydroxy configuration.[11] Moreover, treatment of IIa with lithium aluminum hydride afforded pregn-5-ene-3β,20β-diol (IVa). Acetylation gave the 3,20-diacetate IVb. Finally, the C-18 methyl signal in the nmr spectrum of IIa was at 0.82 ppm, while an upfield shift to 0.71 ppm was recorded for the diacetate IIb in accordance with a previous study[12] correlating the chemical shift of this signal with the configuration of 20β-hydroxy compounds.

Treatment of 3β-acetoxy-16α-methanesulfonyloxypregn-5-en-20β-ol (IIa) with sodium azide in N-methyl-2-pyrrolidone[13] afforded 3β-acetoxy-16β-azidopregn-5-en-20β-ol (IIIa). The assignment of the 16β configuration was based on the well-established observation that replacement of a mesylate group by azide ion proceeds with Walden inversion.[14,15] This assignment was confirmed, as described in the following paper,[10] by conversion of IIIa *via* the 16β amino analog IIIb to 16-β-piperidinopregn-5-ene-3β,20β-diol which was epimeric to the known 16α-piperidinopregn-5-ene-3β,20β-diol.[2a]

Reduction of the 16β-azide IIIa with lithium aluminum hydride gave the desired 16β-aminopregn-5-ene-3β,20β-diol (IIIb). Acetylation gave the N-acetyl 3,20-diacetate IIIc, and the N-acetyl 3,20-diol IIId was obtained on preferential saponification of the latter.

Treatment of the 16β-amino-3,20-diol IIIb with nitrourea in refluxing ethanol according to the procedure of Sah and Kao[16] gave 16β-carbamidopregn-5-ene-3β,20β-diol (IIIe). The N-carbobenzoxy derivative IIIf was also prepared in the conventional manner but the yield was low due to isolation difficulties. Attempts were made to prepare an N-phthaloyl derivative by direct fusion[17] or by the milder method of

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

(2) (a) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 3158 (1956); (b) E. B. Hershberg and D. H. Gould, U. S. Patent 2,965,640 (1960).

(3) C. R. Swain and D. R. Wand, *J. Pharmacol. Exptl. Therap.*, **128**, 259 (1960).

(4) (a) C. L. Hewett and D. S. Savage, British Patent 980,265 (1965); (b) C. L. Hewett, D. S. Savage, J. J. Lewis, and M. F. Sugrue, *J. Pharm. Pharmacol.*, **16**, 765 (1964).

(5) L. Vargha, M. Rados, E. Kasztreiner, and L. Szporny, U. S. Patent 3,125,570 (1964).

(6) (a) H.-P. Husson, P. Potier, and J. LeMen, *Bull. Soc. Chim. France*, 1721 (1965); (b) *ibid.*, 948 (1966).

(7) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 847.

(8) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(9) W. R. Benn, *ibid.*, **28**, 3557 (1963); G. Just and R. Nagarajan, *Can. J. Chem.*, **39**, 548 (1961); P. L. Julian, E. W. Meyer, W. J. Karpel, and W. Cole, *J. Am. Chem. Soc.*, **73**, 1777 (1951).

(10) M. Heller and S. Bernstein, *J. Org. Chem.*, **32**, 3981 (1976).

(11) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

(12) C. H. Robinson and P. Hofer, *Chem. Ind.* (London), 377 (1966).

(13) H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962).

(14) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. Rao, *Nature*, **166**, 178 (1950); C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.*, 2230 (1954).

(15) This part of the work was completed before the publication of H.-P. Husson, *et al.*[6]

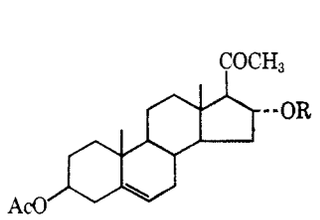
(16) P. P. T. Sah and I.-S. Kao, *Rec. Trav. Chim.* **58**, 460 (1939).

(17) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).

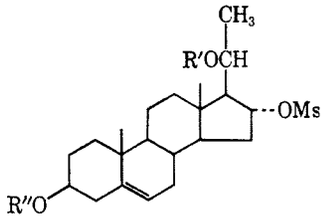
Nefkens,[18] but no desired product could be isolated. However, refluxing IIIb with phthalic anhydride in dioxane gave the phthalamic acid IIIg.[19] The latter could not be cyclized successfully to the phthalamido compound.

An investigation was then made of the oxidation at C-3 of a 16β-amino compound to provide the corresponding novel Δ^4-3-keto compound. Oppenauer oxidation of the 16β-amino-3β,20β-diol IIIb gave a multiplicity of products which eluded separation. However oxidation of the N-acetyldiol IIId gave 16β-acetamido-20β-hydroxypregn-4-en-3-one (Va). Unfortunately the yield was poor which was attributed to the insolubility of the starting material.

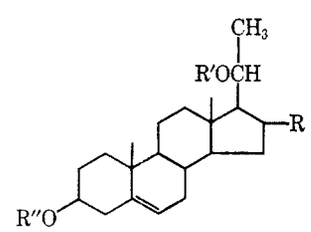
In view of these difficulties in obtaining a Δ^4-3-one, an alternate pathway was developed. Accordingly, 3β-acetoxy-16β-azidopregn-5-en-20β-ol (IIIa) was converted into the 20-tetrahydropyranyl derivative IIIh which in turn was saponified to give the 20-tetrahydropyranyl-3β-ol IIIi. Oppenauer oxidation of the latter followed by acid hydrolysis afforded 16β-azido-20β-hydroxypregn-4-en-3-one (Vb). The 3-ketal VIa prepared in the usual manner from Vb was reduced with lithium aluminum hydride in tetrahydrofuran to give the 16β-amino-3-ketal VIb. Acid hydrolysis of the latter compound presumably gave 16β-amino-20β-hydroxypregn-4-en-3-one (Vc) as an amorphous compound. Unfortunately, attempts to purify or crystallize this compound generated only increased impurity. It is possible, among other considerations, that Vc undergoes a "head-to-tail" reaction between two or more of the molecules leading to some of the contaminants. A small amount of Vc was acetylated to give 16β-acetamido-20β-acetoxypregn-4-en-3-one (Vd), apparently in an hydrated form. Definitive evidence for the desired structure was provided by its ultraviolet, infrared, and nmr spectra.



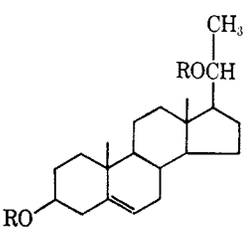
Ia, R = H
b, R = Ms



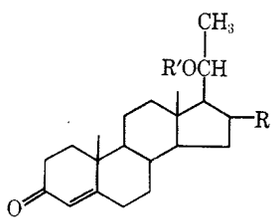
IIa, R′ = H, R″ = Ac
b, R′ = R″ = Ac



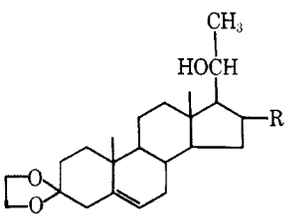
IIIa, R = N_3; R′ = H; R″ = Ac
b, R = NH_2; R′ = R″ = H
c, R = NHAc; R′ = R″ = Ac
d, R = NHAc; R′ = R″ = H
e, R = $NHCONH_2$; R′ = R″ = H
f, R = $NHCOOCH_2C_6H_5$; R′ = R″ = H
g, R = $NHCOC_6H_4COOH(o)$; R′ = R″ = H
h, R = N_3; R′ =  ; R″ = Ac
i, R = N_3; R′ =  ; R″ = H



IVa, R = H
b, R = Ac



Va, R = NHAc; R′ = H
b, R = N_3; R′ = H
c, R = NH_2; R′ = H
d, R = NHAc; R′ = Ac



VIa, R = N_3
b, R = NH_2

(18) G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. Chim.*, **79**, 688 (1960).

(19) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

Experimental Section[20]

3β-Acetoxy-16α-methanesulfonyloxypregn-5-en-20-one (Ib).—Treatment of a solution of 3β-acetoxy-16α-hydroxypregn-5-en-20-one (Ia)[8] (1 g) in pyridine (5 ml) with methanesulfonyl chloride (2 ml) at −5° in the usual fashion afforded after crystallization from acetone–water the mesylate Ib (1.01 g), mp 153–155°. The analytical sample had mp 159.5–160.5°; $[\alpha]^{25}D$ −29° (chloroform); ν_{max} 1740, 1710, 1361, 1248, and 1183 cm^{-1}.

Anal. Calcd for $C_{24}H_{36}O_6S$ (452.53): C, 63.70; H, 8.02; S, 7.07. Found: C, 63.46; H, 8.41; S, 7.19.

3β-Acetoxy-16α-methanesulfonyloxypregn-5-en-20β-ol (IIa).—A mixture of the mesylate 20-one Ib (5.2 g) and sodium borohydride (5.0 g) in absolute ethanol (780 ml) was stirred at room temperature 40 min whereupon complete solution occurred. The solution was added to ice water and the resultant precipitate (3.18 g) was collected, mp 158.5–159°. Crystallization from acetone–hexane gave the analytical sample: mp 161.5–162° dec; $[\alpha]^{25}D$ −110° (chloroform); ν_{max} 3450, 1728, 1332, 1245, and 1172 cm^{-1}; the nmr spectrum showed peaks at 0.82 (18 H, singlet), 1.02 (19 H, singlet), 1.34 (J = 9 cps) (21 H, doublet), 2.02 (OAc, singlet), 3.00 (SO_2CH_3, singlet), and 5.38 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{38}O_6S$ (454.54): C, 63.41; H, 8.43; S, 7.04. Found: C, 63.31; H, 8.42; S, 6.92.

16α-Methanesulfonyloxypregn-5-ene-3β,20β-diol Diacetate (IIb).—Acetylation of the methanesulfonyl acetate IIa (0.215 mg) in pyridine (5 ml) with acetic anhydride (1 ml) in the usual manner gave IIb (0.22 g), mp 165–167° dec. Crystallization from dilute acetone improved this to mp 172.5–173° dec; $[\alpha]^{25}D$ −83.5° (chloroform); ν_{max} 1732, 1362, 1242, and 1170 cm^{-1}; the nmr spectrum showed peaks at 0.71 (18 H, singlet), 1.03 (19 H, singlet), 1.32 (J = 6.5 cps) (21 H, doublet), 2.04 (two OAc, singlet), 3.01 (SO_2CH_3, singlet), and 5.38 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{26}H_{40}O_7S$ (496.58): C, 62.88; H, 8.12; S, 6.44. Found: C, 62.94; H, 8.25; S, 6.82.

3β-Acetoxy-16β-azidopregn-5-en-20β-ol (IIIa).—A mixture of the mesylate IIa (0.57 g) and sodium azide (0.45 g) in N-methyl-2-pyrrolidone (23.75 ml) and *t*-butyl alcohol (1.25 ml) was heated on the steam bath 28 hr. Water was added and the resultant amorphous brown solid (0.495 g) was collected. Crystallization from acetone-petroleum ether (60–70°) yielded IIIa (215 mg), mp 173.5–179°. The analytical sample was obtained from acetone–water: mp 186.5–187°; ν_{max} 2150 cm^{-1}; $[\alpha]^{25}D$ +19° (chloroform).

(20) All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The ultraviolet absorption spectra were done in methanol. All the analytical samples were shown to be homogeneous by tlc (silica gel G) analysis. The analyses were carried out by L. M. Brancone and associates. The infrared, ultraviolet absorption, nmr (Varian A-60 spectrometer, tetramethylsilane, internal reference), and optical rotational data were supplied by W. Fulmor, G. O. Morton, and associates. The partition chromatography was done by C. Pidacks and associates.

Anal. Calcd for $C_{23}H_{35}N_3O_3$ (401.53): C, 68.79; H, 8.79; N, 10.47. Found: C, 68.50, 68.51; H, 9.00, 8.92; N, 10.83.

Pregn-5-ene-3β,20β-diol (IVa).—A mixture of the 16α-methanesulfonyloxy-20β-ol (IIa) (0.47 g) and lithium aluminum hydride (0.5 g) in tetrahydrofuran (40 ml) was stirred and refluxed 22 hr. A saturated solution of potassium and sodium tartrate was added to the mixture and the latter was filtered. The residue was boiled in tetrahydrofuran and again filtered. The combined tetrahydrofuran solution was evaporated *in vacuo*. The residue was dissolved in methylene chloride and filtered and the filtrate was evaporated. Crystallization of the residue from methanol afforded IVa (81 mg): mp 204–207°; $[\alpha]^{25}D$ −74° (chloroform). The infrared spectrum was identical with that of an authentic sample.[21-24]

Pregn-5-ene-3β,20β-diol Diacetate (IVb).—Acetylation of the 3β,20β-diol IVa (188 mg) in pyridine (2 ml) with acetic anhydride (1.0 ml) in the usual manner afforded after crystallization from dilute methanol the diacetate IVb (32 mg): mp 130–131°; $[\alpha]^{25}D$ −35° (chloroform) (lit. mp 125–126°, $[\alpha]^{25}D$ −39°;[23] mp 138.5–140°, $[\alpha]D$ −36°;[24] mp 130–131°, $[\alpha]D$ −37°[22]).

Its infrared spectrum was identical with that of an authentic sample (Mann Research Laboratories).

16β-Aminopregn-5-ene-3β,20β-diol (IIIb).—A slurry of the 16β-azide IIIa (3.73 g) and lithium aluminum hydride (5.0 g) in ether (200 ml) was refluxed 16 hr. The excess hydride was cautiously decomposed with a saturated solution of potassium and sodium tartrate. The mixture was filtered and the residue was boiled in ethyl acetate. Upon addition of the ethyl acetate filtrate from the residue to the above ether filtrate, a precipitate of IIIb (1.48 g) was formed, which was separated, mp 238–242°. The analytical sample, crystallized from ethyl acetate, had mp 241–242°; $[\alpha]^{25}D$ −51° (methanol); ν_{max} 3310 and 1050 cm^{-1}. The nmr spectrum of IIIb could not be obtained due to its insolubility.

Anal. Calcd for $C_{21}H_{35}NO_2$ (333.50): C, 75.63; H, 10.58; N, 4.20. Found: C, 75.54; H, 10.66; N, 3.91.

16β-Acetamidopregn-5-ene-3β,20β-diol Diacetate (IIIc).—Acetylation of the 16β-amine IIIb in acetic anhydride–pyridine afforded IIIc, mp 185–186.5°, with an infrared spectrum identical with that of the sample described later.[10]

16β-Acetamidopregn-5-ene-3β,20β-diol (IIId).—To a solution of the N-acetyl 3,20-diacetate IIIc (2.3 g) in methanol (100 ml) was added 10% potassium carbonate solution (20 ml) and the resultant solution was refluxed for 2 hr, at which time complete reaction had taken place according to infrared spectral analysis. The resultant solution was poured into a large excess of water and the resulting solid was separated and crystallized from dilute methanol to give IIId (1.7 g), mp 281.5–282.5°. The analytical sample had mp 283–284°; $[\alpha]^{25}D$ −27° (methanol); the nmr spectrum gave peaks at 0.88 (18 H, singlet), 0.97 (19 H, singlet), 0.96 (J = 11 cps) (21 H, doublet), 1.80 (NAc, singlet), and 5.28 (6 H, multiplet) ppm (DMSO-d_6).

Anal. Calcd for $C_{23}H_{37}NO_3$ (375.53): C, 73.56; H, 9.93; N, 3.73. Found: C, 73.49; H, 10.19; N, 3.46.

16β-Carbamidopregn-5-ene-3β,20β-diol (IIIe).—A solution of the aminodiol IIIb (1.0 g) and nitrourea (364 mg) in 95% ethanol (20 ml) was refluxed for 15 min, whereupon a copious precipitate formed. This was collected to give IIIe (0.66 g), mp 251–252°, as an hydrate. Crystallization from methanol did not improve the melting point: $[\alpha]^{25}D$ −22° (methanol); ν_{max} 3320, 1655, 1600, and 1540 cm^{-1}; the nmr spectrum gave peaks at 0.83 (18 H, singlet), 0.95 (19 H, singlet), 1.02 (J = 7 cps) (21 H, doublet), 5.30 (6 H and $CONH_2$, multiplet), and 5.80 (NHCO, multiplet) ppm (DMSO-d_6).

Anal. Calcd for $C_{22}H_{36}N_2O_3 \cdot {}^1/_2 H_2O$ (383.55): C, 68.53; H, 9.67; N, 7.26. Found: C, 68.00; H, 9.54; N, 7.73.

16β-Benzyloxycarbonylaminopregn-5-ene-3β,20β-diol (IIIf).—To a solution of 16β-aminopregn-5-ene-3β,20β-diol (IIIb, 1.0 g) in pyridine (20 ml) was added carbobenzoxy chloride (1.0 ml) at 0°, and the mixture was allowed to stand at this temperature 0.5 hr, then at room temperature 1 hr. The mixture was then poured into ice water and the resultant precipitate (0.64 g) was collected. Crystallization gave 0.21 g of crude IIIf, mp 148–156°, which could not be purified further by recrystallization as shown by thin layer chromatography. A small portion (70 mg) of this crude sample was placed on a thin layer chromatography plate (silica gel, 20 cm × 20 cm × 0.5 mm) and developed 2 hr in the system benzene–acetone–water (2:1:2) (upper phase). The band containing the product (*ca.* 2.5–3.0 cm from the origin) was eluted with acetone and the product was crystallized from dilute acetone in a solvated form (46 mg), mp 164.5–165.5°; the nmr spectrum showed peaks at 0.85 (18 H, singlet), 1.08 (19 H, singlet), 1.19 (J = 9 cps) (21 H, doublet), 5.05 ($-CH_2O$, singlet), 5.30 (6 H, multiplet), and 7.30 (phenyl, singlet) ppm ($CDCl_3$).

Anal. Calcd for $C_{29}H_{41}NO_4 \cdot {}^1/_2H_2O$ (476.63): C, 73.07; H, 8.88; N, 2.93. Found: C, 73.02; H, 9.02; N, 3.22.

16β-(*o*-Carboxybenzamido)pregn-5-ene-3β,20β-diol (IIIg).—A solution of 16β-aminopregn-5-ene-3β,20β-diol (IIIa, 1.0 g) and phthalic anhydride (0.5 g) in dioxane (100 ml) was refluxed 26 hr. The solvent was removed *in vacuo* and the residue was crystallized from dilute methanol to give the hygroscopic IIIg (0.35 g), mp 188–190° (bubbles). An additional 0.44 g was collected as a post precipitate: $[\alpha]^{25}D$ −24.5° (methanol); ν_{max} 1709 and 1640 cm^{-1}.

Anal. Calcd for $C_{29}H_{39}NO_5 \cdot {}^1/_4H_2O$ (486.11): C, 71.65; H, 8.19; N, 2.88. Found: C, 71.84; H, 8.28; N, 3.10.

16β-Acetamido-20β-hydroxypregn-4-en-3-one (Va).—A mixture of the N-acetyl-3β,20β-diol IIId (0.6 g) in toluene (150 ml) and cyclohexanone (8 ml) was distilled until *ca.* 50 ml of solvent was removed. An aluminum isopropoxide solution (0.06 g/ml) in toluene (10 ml) was added, and the mixture was refluxed 18 hr. A saturated solution of potassium and sodium tartrate (50 ml) was added, and the resultant mixture was steam distilled until all the cyclohexanone was removed. The solid (0.22 g) was collected by filtration, heated in acetone, and filtered. The remaining insoluble residue (74 mg) was starting material. The material (145 mg) from the filtrate was adsorbed and chromatographed on a Florisil[25] column (40 g). Collection of the petroleum ether (30–60°)–acetone (1:1) eluates yielded 0.12 g of a glass. Crystallization from acetone–hexane afforded Va (48 mg): mp 262–263°; λ_{max} 241 mμ (ε 13,900); $[\alpha]^{25}D$ +49° (methanol); the nmr spectrum gave peaks at 0.91 (18 H, singlet), 0.95 (J = 7 cps) (21 H, doublet), 1.14 (19 H, singlet), 1.79 (NAc, singlet), and 5.60 (4 H, multiplet) ppm (DMSO-d_6).

Anal. Calcd for $C_{23}H_{35}NO_3$ (373.52): C, 73.95; H, 9.45; N 3.75. Found: C, 73.92; H, 9.62; N, 4.03.

16β-Azido-20β-tetrahydro-2′-pyranyloxypregn-5-en-3β-ol Acetate (IIIh).—To a solution of the 16β-azido acetate IIIa (1.0 g) in dihydropyran (10 ml) was added phosphorus oxychloride (two drops)[26] and the solution was allowed to stand 2 hr at room temperature. The solution was made basic with 5% potassium hydroxide–methanol solution and dilute methanol was added to the solution. As only an oil was formed, the entire mixture was concentrated almost to dryness *in vacuo*. The resultant amorphous solid was collected and crystallized from methanol to afford IIIh (572 mg), mp 108–110°. The analytical sample had mp 113.5–114.5°; $[\alpha]^{25}D$ +23° (chloroform); ν_{max} 2100, 1734, and 1030 cm^{-1}.

Anal. Calcd for $C_{28}H_{43}N_3O_4$ (485.65): C, 69.24; H, 8.92; N, 8.65. Found: C, 69.09; H, 9.07; N, 8.70.

16β-Azido-20β-tetrahydro-2′-pyranyloxypregn-5-en-3β-ol (IIIi).—A solution of the acetate IIIh (as a crude oil, *ca.* 5 g) in 5% potassium hydroxide–methanol (20 ml) and methanol (100 ml) was refluxed 1 hr. The solution was added to ice water, and the resultant precipitate collected. Crystallization from acetone–water gave the hydrated IIIi (4.32 g): mp 115–118°; $[\alpha]^{25}D$ +29° (chloroform); ν_{max} 3360 and 2110 cm^{-1}.

Anal. Calcd for $C_{26}H_{41}N_3O_3$ (448.11): C, 69.68; H, 9.34; N, 9.38. Found: C, 69.71; H, 9.43; N, 9.59.

16β-Azido-20β-hydroxypregn-4-en-3-one (Vb).—A mixture of the azido-3β-ol IIIi (1.32 g), aluminum isopropoxide in toluene (0.06 g/ml) (15 ml), cyclohexanone (10 ml), and toluene (150 ml) was reacted and worked up as in the preparation of Va to give an oil. This was chromatographed on Florisil[25] (80 g), which provided only an oil (1.0 g) from petroleum ether–acetone (47:3) eluates, and which consisted of one major and

(21) We experienced the same difficulties described by W. Klyne and E. Miller[22] in attempting to prepare an unsolvated molecule. The rotation of the authentic sample purchased from the Mann Research Laboratories, New York, N. Y. was $[\alpha]^{25}D$ −75° (chloroform). In the literature[22-24] the value $[\alpha]^{25}D$ −64° (chloroform) is given.

(22) W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950).

(23) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(24) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951)

(25) Florisil (Floridin Co.), a synthetic magnesium silicate.

(26) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2375 (1952).

two minor components by thin layer chromatographic analysis. This oil was heated on the steam bath for 5 min in a mixture of methanol (40 ml) and concentrated hydrochloric acid (0.5 ml) and then poured into ice water. The resultant precipitate was collected and crystallized from acetone-hexane to afford Vb (542 mg), mp 178–179°. The analytical sample had mp 178.5–179.5°; ν_{max} 240 mμ (ε 17,300); $[\alpha]^{25}D$ +143.5° (chloroform); the nmr spectra gave peaks at 0.97 (18 H, singlet), 1.20 (19 H, singlet), 1.30 (J = 6 cps) (21 H, doublet), and 5.75 (4 H, singlet) ppm ($CDCl_3$).

Anal. Calcd for $C_{21}H_{31}N_3O_2$ (357.48): C, 70.55; H, 8.74; N, 11.76. Found: C, 70.48; H, 8.78; N, 12.09.

16β-Azido-3-ethylenedioxypregn-5-en-20β-ol (VIa).—A mixture of the unsaturated ketone Vb (0.48 g), *p*-toluenesulfonic acid (30 mg), benzene (35 ml), and ethylene glycol (8 ml) was stirred and refluxed 4 hr under conditions of constant water removal. Sodium carbonate and water were then added, and the benzene layer was separated. The water layer was extracted with benzene, and the combined benzene extracts were dried and evaporated *in vacuo*. Crystallization of the residue from acetone–hexane afforded VIa (0.37 g), mp 207.5–208.5°. The analytical sample had mp 209–209.5°; $[\alpha]^{25}D$ +80° (chloroform); ν_{max} 3470, 2110, and 1090 cm^{-1}.

Anal. Calcd for $C_{23}H_{35}N_3O_3$ (401.53): C, 68.79; H, 8.79; N, 10.47. Found: C, 69.12; H, 9.24; N, 10.45.

16β-Amino 3-ethylenedioxypregn-5-en-20β-ol (VIb).—A mixture of the azido 3-ketal VIa (0.3 g), lithium aluminum hydride (0.3 g), and tetrahydrofuran (35 ml) was heated and worked up as in the preparation of IIIb. The collected residue was crystallized from ethyl acetate–hexane to give VIb (0.15 g): mp 221.5–223.5°; $[\alpha]^{25}D$ −28° (chloroform); ν_{max} 3420 and 1092 cm^{-1}.

Anal. Calcd for $C_{23}H_{37}NO_3$ (375.53): C, 73.56; H, 9.96; N, 3.73. Found: C, 73.35; H, 10.00; N, 3.78.

16β-Acetamido-20β-acetoxypregn-4-en-3-one (Vd).—A mixture of the 16β-amino-3-ketal VIb (*ca.* 1.75 g) in methanol (100 ml) and 8% sulfuric acid (5 ml) was refluxed 15 min and then poured into ice water. The solution was made basic with potassium carbonate, and the resultant precipitate was collected. The amorphous solid Vc (presumably 16β-amino-20β-hydroxypregn-4-en-3-one) could not be purified in any manner including partition chromatography so as to yield crystals. Attempts at crystallization only seemed to give further insoluble gums. The amorphous solid had λ_{max} 242 mμ (ε 16,200) and ν_{max} 1685 and 1623 cm^{-1}.

Treatment of the amine ketone Vc (0.2 g) with acetic anhydride (1 ml) and pyridine (2 ml) in the usual manner gave an amorphous solid (136 mg), mp 160–171° upon dilution with water. Partition chromatography on Celite[27] using the solvent system heptane–ethyl acetate–methanol–water (60:40:15:6) gave, upon evaporation of the third holdback volume and crystallization of the residue from acetone–hexane, Vd (70 mg): mp 222.5–223.5°; λ_{max} 239 mμ (ε 18,400); $[\alpha]^{25}D$ +77° (chloroform); ν_{max} 3310, 1732, 1670, 1620 (sh), 1533, and 1242 cm^{-1}; the nmr spectrum gave peaks at 0.79 (18 H, singlet), 1.17 (19 H, singlet), 1.17 (J = 6 cps) (21 H, doublet), 1.96 (OAc, singlet), 2.03 (NAc, singlet), and 5.72 (4 H, singlet) ppm ($CDCl_3$).

Anal. Calcd for $C_{25}H_{37}NO_4 \cdot {}^1/_4H_2O$ (420.05): C, 71.42; H, 9.00; N, 3.33. Found: C, 71.61; H, 9.17; N, 3.28.

Registry No.—Ib, 14570-93-5; IIa, 14570-94-6; IIb, 14734-09-9; IIIa, 14570-95-7; IIIb, 14570-69-5; IIId, 14570-97-9; IIIe, 14570-98-0; IIIf, 14570-99-1; IIIg, 14571-00-7; IIIh, 14571-01-8; IIIi, 14571-02-9; Va, 14571-03-0; Vb, 14571-04-1; Vc, 14571-05-2; Vd, 14571-06-3; VIa, 14571-07-4; VIb, 14735-85-4.

(27) Celite (Johns-Manville Co.), a diatomaceous silica product.

Some Reactions of 16β-Aminopregn-5-ene-3β,20β-diol

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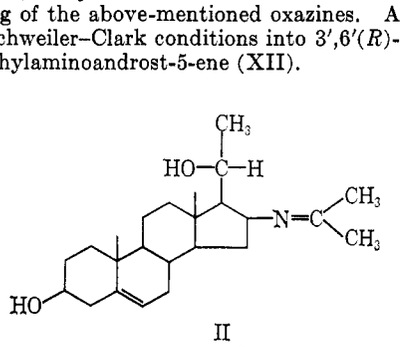
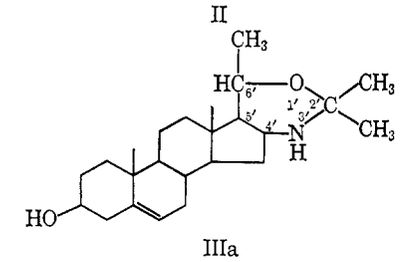
Treatment of 16β-aminopregn-5-ene-3β,20β-diol (Ia) with acetone afforded 2′,2′,6′(*R*)-trimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (IIIa). Analogous oxazines were prepared by reaction with formaldehyde and under Eschweiler–Clark conditions. 16β-Alkylamino derivatives were made by reduction of 16β-acylamino compounds or by reductive opening of the above-mentioned oxazines. A 3,16-diamino compound was also prepared and converted under Eschweiler–Clark conditions into 3′,6′(*R*)-dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino-[4′,5′:16β,17β]-3β-dimethylaminoandrost-5-ene (XII).

Subsequent to the development of a synthetic pathway leading to a 16β-amino-20β-hydroxypregnene,[1] it was decided to investigate some chemical features of such a compound and to extend our research to the preparation of 3,16-diamino steroids. In this paper we wish to detail our findings.

Crystallization of 16β-amino-20β-hydroxypregn-5-en-3β-ol (Ia)[1] from acetone led to a new structure which, according to elemental analysis, could be depicted either as the Schiff base II or the 1,3-oxazine IIIa. Acetylation did not resolve the ambiguity, since the product was the previously discussed 16β-acetamidopregn-5-ene-3β,20-diol diacetate (Ib).[1] The infrared spectrum, which did not possess a C=N absorption band,[2] pointed to the oxazine structure. Analysis of the nmr spectrum of this compound also



II



IIIa

provided evidence for the oxazine structure. The signals of the two methyl groups associated with the car-

(1) M. Heller and S. Bernstein, *J. Org. Chem.*, **32**, 3978 (1967).

(2) F.-X. Jarreau, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. France*, 1861 (1963).