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

MILTON HELLER AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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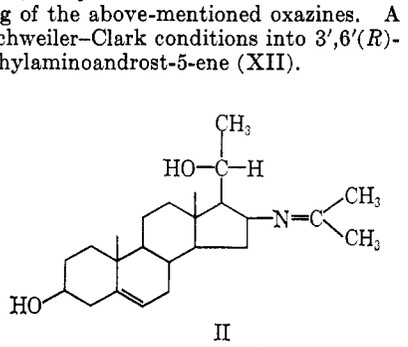
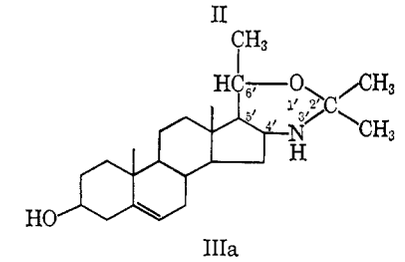
Treatment of 16β-aminopregn-5-ene-3β,20β-diol (Ia) with acetone afforded 2′,2′,6′(*R*)-trimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (IIIa). Analogous oxazines were prepared by reaction with formaldehyde and under Eschweiler–Clark conditions. 16β-Alkylamino derivatives 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).

bon atom presumably attached to the nitrogen and oxygen atoms were at 1.37 and 1.42 ppm, whereas the $N{=}C(CH_3)_2$ groupings were reported to have signals at 1.8 and 2.0 ppm.[3] Treatment of the compound with hydrogen chloride led, as expected,[4] to the amine hydrochloride IV.

Further confirmation of the oxazine structure was achieved by the following chemical transformations. Treatment of IIIa with methyl iodide and potassium carbonate gave 2′,2′,3′,6′(*R*)-tetramethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (IIIb) which was further characterized as the C-3 acetate IIIc. Acetylation of IIIa in a very large excess of pyridine (contrary to the experience described above with a smaller amount of pyridine) afforded 3′-acetyl-2′,2′,6′(*R*)-trimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol acetate (IIId) plus a small amount of the N-acetyl diacetate Ib.

It was further observed that methylation of the 16β-amino-3,20-diol Ia according to the method of Eschweiler and Clark verified the spatial proximity of the 16β-amino-20β-ol groupings by forming the methylated oxazine Va[5] plus its 3-formate Vb. The structure of the compound Va was supported by the nmr spectrum which contained an N-methyl signal at 2.00 and a pair of doublets at 3.48 and 4.35 ppm (J = 7 cps) which was due to the coupling of the 2′,2′-hydrogens on the oxazine ring. Further confirmation of this structure was obtained by preparing the 3β-carbethoxy derivative Vc of the oxazine Va.

A simple N-unsubstituted oxazine could also be prepared by reaction of the aminediol Ia with formaldehyde to give the very insoluble 6′(*R*)-methyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (Vd). The latter compound could be converted to the N-acetyl acetate Ve[6] and also could be transformed into the N-methyl homolog Va by treatment with methyl iodide.

Some interesting observations associated with these oxazines were noted. The first was the ease of formation, since it has been reported that acetonide formation did not occur at all on a 16β,20β-diol.[7] Second was the ease of opening (in particular compound IIIa) under acetic anhydride–pyridine conditions.[4] Finally, although a vast number of heterocyclic systems containing nitrogen fused on the steroid nucleus at the 16,17 position have been reported (see footnote 1 of ref 1), there are only a few incorporating the C-20 position of a pregnane. None have been previously reported,[8] which encompass a fused six-membered heterocyclic ring at C-20.

Efforts to N-alkylate 16β-aminopregn-5-en-20β-ol (Ia) directly by treatment with ethyl sulfate or ethyl iodide afforded intractable reaction mixtures.

However, reaction of 16β-acetamidopregn-5-ene-3β,20β-diol diacetate (Ib) with lithium aluminum hydride provided 16β-ethylaminopregn-5-ene-3β,20β-diol (Ic), which was further characterized as the triacetate Id.[9] Similarly, treatment of the 16β-amino-3,20-diol Ia with a limited amount of ethyl chloroformate afforded the N-carbethoxy derivative Ie which was reduced to 16β-methylaminopregn-5-ene-3β,20β-diol (If). The latter compound could also be heated with formaldehyde to prepare the aforementioned N-methyl-1,3-oxazine Va.

Treatment of the 16β-amino-3,20-diol Ia with 1,5-dibromopentane in *n*-butyl alcohol[10] gave 16β-piperidinopregn-5-ene-3β,20β-diol hydrobromide (VI), which in turn, was converted to the diol VIIa.[11–13] The latter compound was further characterized as the diacetate VIIb.

The various described oxazines were considered potentially excellent intermediates to prepare N-alkylated amines *via* a reductive opening of the heterocyclic ring.[14] Accordingly, treatment of the trimethyloxazine IIIa with lithium aluminum hydride gave 16β-isopropylaminopregn-5-ene-3β,20β-diol (Ig). In the same manner, the N-methyloxazine Va gave the 16β-dimethylamino analog Ih and the N-acetyl diacetate Ve yielded the 16β-ethylmethylaminopregn-5-ene-3β,20β-diol (Ii).

Consistent with the previous report[1] concerning Oppenauer oxidation of a nonacylated amino compound, Ih, IIIa, and Va gave similarly, in each case, a multiplicity of products according to thin layer chromatography. The oxidation procedure using chromium trioxide–acetone–sulfuric acid[15] on the 16β-piperidino compound IIIa similarly failed, but the reagent with the N-methyloxazine Va presumably gave the Δ^4-3-one VIII according to its nmr, infrared, and ultraviolet absorption spectra. However, the yield was so low it was not possible to purify the compound.

In view of investigations[16] dealing with steroidal natural products containing nitrogen atoms simultane-

(3) Private communication from Dr. Q. Khuong-Huu, Institute de Chimie des Substances Naturelles, Gif-sur-Yvette (S. & O.)

(4) The ease of opening a tetrahydro-1,3-oxazine under acidic conditions is discussed: Z. Eckstein and T. Urbanski, "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 333.

(5) (a) Reference 4, p 341, refers to reports in which tetrahydro-1,3-oxazine formation by reaction of an amino alcohol with an aldehyde is used to establish configuration in many alkaloids. (b) The use of the Eschweiler–Clark procedure to establish the stereochemistry of a 1,2-amino alcohol of a steroid by forming an oxazolidine is illustrated: M. Tomita, S. Uyeo, Jr., and T. Kikuchi, *Tetrahedron Letters*, No. 18, 1053 (1964). (c) An unusual tetrahydro-1,3-oxazine formation under Eschweiler–Clark conditions is detailed by H.-P. Husson, P. Potier, and J. LeMen, *Bull. Soc. Chim. France*, 1721 (1965); 948 (1966).

(6) The nmr spectrum of Ve was interesting in that one of the signals of the doublets for the 2′,2′-protons centering at 5.23 ppm was sharp while the other centering at 4.76 ppm was broad and diffuse. Heating the sample to approximately 88° gave a smooth symmetrical quartet of signals.

(7) S. Noguchi, K. Hiraga, T. Kishi, H. Nawa, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **11**, 144 (1963).

(8) (a) L. I. Klimova and N. N. Suvorov, *Zh. Obshch. Khim.*, **34**, 1357 (1964); N. N. Suvorov and L. I. Klimova, *ibid.*, **34**, 3518 (1964); S. Noguchi, M. Imanishi, and K. Morita, *Chem. Pharm. Bull.* (Tokyo), **12**, 1189 (1964); Y. Sato and H. Kaneko, *Steroids*, **5**, 279 (1965). (b) An unusual oxazolidine–oxazine system has been reported: K. Ponsold, B. Schönecker, and P. Grosse, *Chem. Ber.*, **99**, 3485 (1966).

(9) The nmr spectrum of the triacetate Id surprisingly revealed little of the ethyl grouping attached to the nitrogen. This grouping is very clearly seen in the nmr spectrum of the precursor Ic, which was also prepared by saponification of Id. The development of the nmr spectrum of Id at an elevated temperature did not change its signals.

(10) J. von Braun, *Ber.*, **44**, 1252 (1911); *ibid.*, **49**, 966, 2629 (1916); J. G. Erickson and J. S. Keps, *J. Am. Chem. Soc.*, **77**, 485 (1955).

(11) Compound VIIa is the epimer at C-16 of a compound previously described.[12,13]

(12) D. Gould, E. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1958).

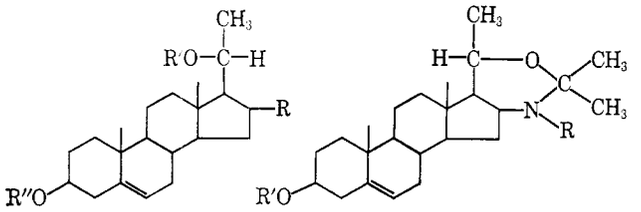
(13) C. R. Swaine and D. R. Waud, *J. Pharmacol. Exptl. Therap.*, **128**, 259 (1960).

(14) E. Testa, L. Fontanella, G. Cristiani, and G. Gallo, *J. Org. Chem.*, **24**, 1928 (1959), have recorded a reductive opening of a tetrahydro-1,3-oxazine with lithium aluminum hydride.

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

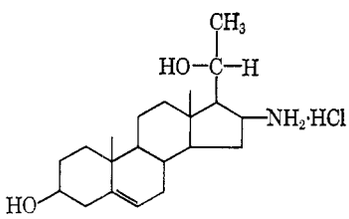
(16) R. Goutarel, "Les alcaloides steroidiques des Apocyanacees," Hermann, Paris, 1964.

ously at C-3 and other positions, we were stimulated to prepare a 3,16-diamino compound. Accordingly, 3β-acetoxy-16β-azidopregn-5-en-20β-ol (Ij)[1] was transformed into its C-20 benzoate Ik which was preferentially saponified[17] to the 3β-ol 20-benzoate Il. The latter was tosylated to give Im which in turn was reacted with potassium acetate in methanol to yield 16β-azido-6β-methoxy-3α,5α-cyclopregnan-20β-ol benzoate (IX) as an oil which could not be purified. Treatment of IX with hydrazoic acid and boron trifluoride etherate[18] afforded 3β,16β-diazidopregn-5-en-20β-ol benzoate (X), which was reduced with lithium aluminum hydride to give 3β,16β-diaminopregn-5-en-20β-ol (XI).

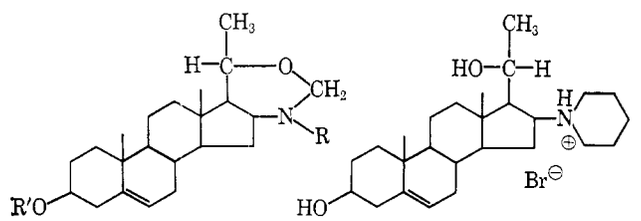


Ia, R = NH_2; R′ = R″ = H
b, R = NHAc; R′ = R″ = Ac
c, R = NHEt; R′ = R″ = H
d, R = NEtAc; R′ = R″ = Ac
e, R = NHCOOEt; R′ = R″ = H
f, R = NHMe; R′ = R″ = H
g, R = $NHCH(Me)_2$; R′ = R″ = H
h, R = $N(Me)_2$; R′ = R″ = H
i, R = N(Et)(Me); R′ = R″ = H
j, R = N_3; R′ = H; R″ = Ac
k, R = N_3; R′ = Bz; R″ = Ac
l, R = N_3; R′ = Bz; R″ = H
m, R = N_3; R′ = Bz; R″ = Ts

IIIa, R = R′ = H
b, R = Me; R′ = H
c, R = Me; R′ = Ac
d, R = R′ = Ac

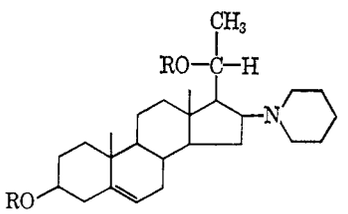


IV

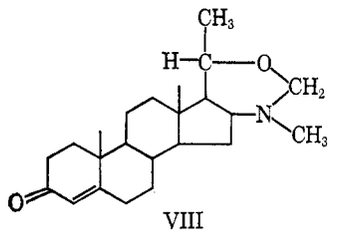


Va, R = Me; R′ = H
b, R = Me; R′ = OCH
c, R = Me; R′ = COOEt
d, R = R′ = H
e, R = R′ = Ac

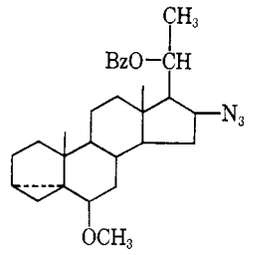
VI



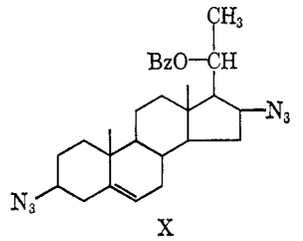
VIIa, R = H
b, R = Ac



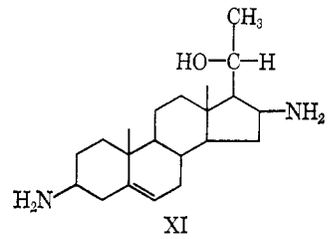
VIII



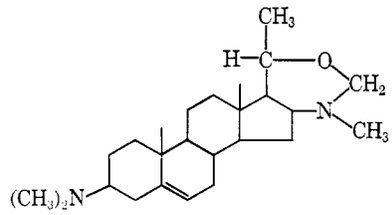
IX



X



XI



XII

The latter was transformed by the Eschweiler–Clark reaction to 3′,6′(*R*)-dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]-3β-dimethylaminoandrost-5-ene (XII).

Experimental Section[19]

2′,2′,6′(*R*)-Trimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (IIIa).—Reduction of the 16β-azide Ij (1.09 g) with lithium hydride (2.0 g) in ether (100 ml), as in the preparation of the 16β-amino-3,20-diol Ia,[1] and crystallization of the product from acetone–petroleum ether (30–70°) gave IIIa (285 mg), mp 169.5–171.5°. From the mother liquors there was accumulated an additional 410 mg, mp 165.5–167°. The analytical sample, obtained by crystallization from acetone, had mp 176.5–178.5°; $[\alpha]^{25}D$ −8° (methanol); nmr peaks appeared at 1.06 and 1.09 (18 H and 19 H, singlet), 1.35, (J = 7 cps) (21 H, doublet), 1.37 and 1.43 (isopropyl methyls, two singlets), and 5.42 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{39}NO_2$ (373.56): C, 77.16; H, 10.52; N, 3.75. Found: C, 77.36; H, 10.57; N, 3.56.

Compound IIIa was also obtained directly by crystallization of the 16β-amino-3,20-diol Ia from acetone.

16β-Acetamidopregn-5-ene-3β,20β-diol Diacetate (Ib).—A solution of the 1,3-oxazine IIIa (180 mg) in acetic anhydride (2 ml) and pyridine (5 ml) was allowed to stand 18 hr at room temperature. The solution was poured into water, and the resultant precipitate (220 mg) was collected. Crystallization from acetone–water gave Ib: mp 190–190.5°; $[\alpha]^{25}D$ −35° (methanol); ν_{max} 3310, 1730, 1650, 1532, and 1238 cm^{-1}.

Anal. Calcd for $C_{27}H_{41}NO_5$ (459.61): C, 70.55; H, 8.99; N, 3.05. Found: C, 70.35; H, 9.04; N, 3.00.

16β-Aminopregn-5-ene-3β,20β-diol Hydrochloride (IV).—Hydrogen chloride was bubbled for 30 sec into a solution of the 1,3-oxazine IIIa (0.22 g) in methylene chloride (10 ml) at room temperature. The solvent was evaporated *in vacuo* at room temperature, and crystallization of the residue from acetone gave a solid (135 mg), mp ~ 210°. Repeated recrystallization

(17) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).

(18) L. A. Freiberg and J. W. Cole, U. S. Patent 3,246,018 (1966).

(19) All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The ultraviolet absorption spectra were done in methanol except where otherwise noted. 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. Nmr spectral analyses were done on a Varian A-60 spectrometer with tetramethylsilane as the internal reference. The infrared, ultraviolet absorption, nmr, and optical rotational data were supplied by W. Fulmor, G. O. Morton, and associates. The partition chromatography was done by C. Pidacks and associates.

from methanol–ether gave IV: mp 331.5–332° dec; ν_{max} 3340, 1606, and 1050 cm^{-1}; $[\alpha]^{25}D$ −37° (methanol).

Anal. Calcd for $C_{21}H_{36}ClNO_2$ (369.963): C, 68.17; H, 9.81; N, 3.79; Cl, 9.61. Found: C, 67.55; H, 9.72; N, 3.59; Cl, 10.09.

2′,2′,3′,6′(*R*)-Tetramethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino-[4′,5′:16β,17β]androst-5-en-3β-ol (IIIb).—A mixture of the trimethyl-1,3-oxazine IIIa (0.51 g), potassium carbonate (0.5 g), and methyl iodide (4.0 ml) in acetone (50 ml) was refluxed 21 hr. The solvent was evaporated *in vacuo*, water was added, and the mixture was stirred and filtered. The residue was crystallized from dilute acetone to give IIIb (0.36 g), mp 192.5–195°. The analytical sample had mp 193–195°; $[\alpha]^{25}D$ −31° (chloroform); nmr peaks appeared at 1.01 (19 H, singlet), 1.19 (18 H, singlet), 1.30 (J = 7 cps) (21 H, doublet), 1.19 and 1.30 (isopropyl methyls, two singlets), 2.04 (N-methyl, singlet), and 5.32 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{25}H_{41}NO_2$ (387.59): C, 77.47; H, 10.67; N, 3.61. Found: C, 77.75; H, 10.69; N, 3.82.

2′,2′,3′,6′(*R*)-Tetramethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino-[4′,5′:16β,17β]androst-5-en-3β-ol Acetate (IIIc).—Acetylation of the tetramethyl-1,3-oxazino-3β-ol IIIb (155 mg) was carried out in the usual manner at room temperature with acetic anhydride (1.0 ml) in pyridine (5.0 ml) for 18 hr. The mixture was poured into water, and the resultant precipitate (0.13 g) was collected, mp 169–175°. The analytical sample of IIIc crystallized from dilute acetone had mp 179.5–180.5°; $[\alpha]^{25}D$ −39.5° (chloroform); ν_{max} 1720 and 1235 cm^{-1}; nmr peaks appeared at 1.01 (19 H, singlet), 1.18 (18 H, singlet), 1.28 (J = 8 cps) (21 H, doublet), 1.18 and 1.30 (isopropyl methyls, two singlets), 2.00 (Ac, singlet), 2.04 (N-methyl, singlet), and 5.37 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{27}H_{43}NO_3$ (429.62): C, 75.48; H, 10.09; N, 3.26. Found: C, 75.02; H, 10.31; N, 3.54.

3′-Acetyl-2′,2′,6′(*R*)-trimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol Acetate (IIId).—Acetylation of the trimethyl-1,3-oxazino-3β-ol IIIa (445 mg) in pyridine (10 ml) with acetic anhydride (1.0 ml) was carried out at room temperature for 18 hr. The mixture was poured into ice water, and the resultant oil was extracted with ethyl acetate. The dried extract was evaporated *in vacuo* to give an oil. This was dissolved in a small amount of methylene chloride and chromatographed on Florisil.[20] The eluates from acetone–petroleum ether (30–60°) (14:86), after removal of solvent, provided an oil which solidified upon being triturated with ether. Crystallization from acetone–hexane afforded IIId (56 mg), mp 201–204°. The analytical sample had mp 219–221°; nmr peaks appeared at 1.03 (19 H, singlet), 1.17 (18 H, singlet), 1.33 (J = 8 cps) (21 H, doublet), 1.67 (isopropyl methyls, singlet), 2.01 (OAc, singlet), 2.15 (NAc, singlet), and 5.38 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{28}H_{43}NO_4$ (457.63): C, 73.48; H, 9.47; N, 3.06. Found: C, 73.09; H, 9.68; N, 3.21.

Elution of the Florisil column with petroleum ether–acetone (83:17) and evaporation afforded 16β-acetamidopregn-5-ene-3β,20β-diol diacetate (Ib, 22 mg).

3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol Va and 3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol Formate (Vb).—A mixture of 16β-aminopregn-5-ene-3β,20β-diol (Ia, 2.125 g), formic acid (30 ml), and 40% formaldehyde (30 ml) was refluxed 4 hr and poured into ice water. The water solution was extracted with ether and was made basic with a concentrated potassium hydroxide solution. The precipitate was collected. Crystallization from acetone–water followed by acetone–hexane afforded Va (410 mg): mp 186–188°; $[\alpha]^{25}D$ −33° (chloroform); nmr peaks appeared at 1.01 (19 H, singlet), 1.19 (18 H, singlet), 1.38 (J = 7 cps) (21 H, doublet), 2.00 (NCH_3, singlet), 3.48 and 4.35 (J = 7 cps), (2′,2′ H, pair of doublets), and 5.32 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{23}H_{37}NO_2$ (359.53): C, 76.83; H, 10.37; N, 3.90. Found: C, 76.63; H, 10.48; N, 3.90.

Crystallization of the mother liquors from methanol–water gave the formate Vb (196 mg): mp 156–159°; $[\alpha]^{25}D$ −55.5° (chloroform); nmr peaks appeared at 1.04 (19 H, singlet), 1.19 (18 H, singlet), 1.37 (J = 7 cps) (21 H, doublet), 2.01 (NCH_3, singlet), 3.52 and 4.38 (J = 8 cps), (2′,2′ H, pair of doublets), 5.40 (6 H, multiplet), and 8.05 (J = 1.5 cps) (HCOO, doublet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{37}NO_3$ (387.54): C, 74.38; H, 9.62; N, 3.61. Found: C, 74.28; H, 9.62; N, 3.84.

3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]-3β-carbethoxyandrost-5-ene (Vc).—To a solution of the 1,3-oxazine Va (0.5 g) in pyridine (10 ml) at ice-bath temperature was added ethyl chloroformate (1.2 ml). The mixture was allowed to stand 24 hr at room temperature, then poured into water, and the resultant precipitate was collected. Crystallization from acetone–water gave Vc (405 mg), mp 124–125.5°. The analytical sample had mp 125–126°; $[\alpha]^{25}D$ −35° (chloroform); ν_{max} 1740, 1260, and 1250 cm^{-1}.

Anal. Calcd for $C_{26}H_{41}NO_4$ (433.61): C, 72.01; H, 10.00; N, 3.23. Found: C, 71.95; H, 9.69; N, 3.26.

6′(*R*)-Methyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]-androst-5-en-3β-ol (Vd).—A solution of 16β-aminopregn-5-ene-3β,20β-diol (Ia, 0.5 g) and 40% formaldehyde (25 ml) in methanol (25 ml) was refluxed 4.5 hr. Most of the methanol was distilled *in vacuo* and the solid was collected. Crystallization from methylene chloride–methanol–ether gave Vd (235 mg), mp 252–255°. The analytical sample had mp 264–266°; $[\alpha]^{25}D$ −34° (methylene chloride–methanol) (1:1); ν_{max} 3420 cm^{-1}.

Anal. Calcd for $C_{22}H_{35}NO_2$ (345.51): C, 76.47; H, 10.21; N, 4.05. Found: C, 76.15; H, 10.01; N, 3.73.

3′-Acetyl-6′(*R*)-methyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol Acetate (Ve).—A mixture of 6′(*R*)-methyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]-androst-5-en-3β-ol (Vd, 134 mg) in chloroform (4 ml), pyridine (4 ml), and acetic anhydride (2 ml) was heated on a steam bath until solution occurred (15 min) and then was allowed to stand at room temperature 20 hr. The solution was poured into water, and the resultant solid was collected and chromatographed on a Florisil column (25 g). Elution with petroleum ether–acetone (43:2) afforded, after evaporation, a solid which crystallized from acetone–hexane to give Ve (100 mg), mp 216–219°. The analytical sample had mp 224.5–226°; $[\alpha]^{25}D$ −53° (chloroform); nmr peaks appeared at 1.02 (19 H, singlet), 1.03 (18 H, singlet), 1.38 (J = 7 cps) (21 H, doublet), 2.01 (OAc, singlet), 2.07 (NAc, singlet), 4.75 and 5.21 (J = 8.5 cps) (2′,2′ H, pair of doublets), and 5.36 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{26}H_{39}NO_4$ (429.58): C, 72.69; H, 9.15; N, 3.26. Found: C, 72.85; H, 9.40; N, 3.47.

3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β-17β]androst-5-en-3β-ol (Va). A. From 6′(*R*)-Methyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-5-en-3β-ol (Vd).—A mixture of the 6′(*R*)-methyl compound Vd (866 mg), potassium carbonate (1.0 g), methyl iodide (5.0 ml), and methanol (50 ml) was refluxed for 22 hr. The solvent was removed *in vacuo*. The residue was washed with acetone and the resultant acetone filtrate was treated with a few drops of sodium sulfite solution to remove color. Further addition of water yielded Va (347 mg), mp 185–187°, with an infrared spectrum identical with that of the previously prepared sample.

B. From 16β-Methylaminopregn-5-ene-3β,20β-diol (If).—A solution of the 16β-methylamino compound If (0.3 g) in 40% formaldehyde (25 ml) and methanol (25 ml) was refluxed 6 hr. Most of the solvent was distilled *in vacuo*, water was added, and the resultant precipitate was collected. Crystallization from acetone–water afforded Va (176 mg), mp 186–189°, with an infrared spectrum identical with that of the previously prepared sample.

16β-Ethylaminopregn-5-ene-3β,20β-diol (Ic).—A mixture of the 16β-N-acetylaminopregn-5-ene-3,20β-diol diacetate (Ib, 1.6 g) and lithium aluminum hydride (2.27 g) in tetrahydrofuran (150 ml) was stirred and refluxed 16 hr. A saturated solution of potassium sodium tartrate was added to the cooled mixture and the mixture was filtered. The residue was stirred in methanol and filtered. The combined filtrates were evaporated under reduced pressure. Crystallization of the residue from dilute acetone, followed by acetone–hexane, yielded Ic (720 mg), mp 172.5–173°. The analytical sample had mp 181.5–182.5°; $[\alpha]^{25}D$ −17° (methanol); nmr peaks appeared at 0.98 and 1.00 (19 H and 18 H, singlets), 1.06 (J = 8 cps) (CH_3CH_2, triplet), 1.27 (J = 7 cps) (21 H, doublet), 2.62 (J = 4 cps) (CH_3CH_2, quartet), and 5.29 (6 H, multiplet) ppm ($CDCl_3$ and CD_3OD).

Anal. Calcd for $C_{23}H_{39}NO_2$ (361.55): C, 76.40; H, 10.87; N, 3.87. Found: C, 76.43; H, 11.07; N, 3.80.

(20) Florisil (Floridin Co.) is a synthetic magnesium silicate.

N-Acetyl-16β-ethylaminopregn-5-ene-3β,20β-diol Diacetate (Id).—Treatment of the 16β-ethylamino-3β,20β-diol Ic (347 mg) with acetic anhydride (2.0 ml) in pyridine (5.0 ml) for 18 hr at room temperature, afforded the N-acetyl diacetate Id (330 mg), mp 208.5–210.5°, upon pouring the solution into water and crystallization of the precipitate from acetone–water. The analytical sample had mp 211–212°; $[\alpha]^{25}D$ −70° (chloroform); ν_{max} 3410, 1735, 1642, and 1245 cm^{-1}.

Anal. Calcd for $C_{29}H_{45}NO_5$ (487.66): C, 71.42; H, 9.30; N, 2.87. Found: C, 71.18; H, 9.36; N, 2.84.

16β-Ethoxycarbonylaminopregn-5-ene-3β,20β-diol (Ie).—To an ice cold solution of 16β-aminopregn-5-ene-3β,20β-diol (Ia, 1.0 g) in pyridine (20 ml) was added ethyl chloroformate (0.268 ml). The mixture was allowed to stand at ice temperature for 0.5 hr, then at room temperature for 1 hr. The mixture was poured into ice water and the resultant precipitate was collected and crystallized from dilute methanol to give Ie (955 mg), mp 191–195°. Crystallization from acetone–hexane gave the analytical sample: mp 197–198.5°; $[\alpha]^{25}D$ −35° (chloroform); nmr peaks appeared at 0.90 (18 H, singlet), 0.99 (19 H, singlet), 1.17 (J = 7 cps) (21 H, doublet), 1.21 (J = 8 cps) (OCH_2CH_3, triplet), 4.05 (J = 7 cps) ($-OCH_2CH_3$, quartet), 5.28 (6 H, multiplet), and 5.50 (–NH, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{39}NO_4$ (405.56): C, 71.07; H, 9.69; N, 3.45. Found: C, 70.85; H, 9.68; N, 3.47.

16β-Methylaminopregn-5-ene-3β,20β-diol (If).—A mixture of the N-carbethoxydiol Ie (533 mg) and lithium aluminum hydride (0.5 g) in tetrahydrofuran (50 ml) was stirred and refluxed 4 hr. The resultant mixture was worked up as in the preparation of the 16-ethylamino compound Ic to give, after crystallization from methanol–water, If (430 mg), mp 194.5–198°. The analytical sample crystallized from acetone–hexane had mp 216–217°; $[\alpha]^{25}D$ −17° (methanol); nmr peaks appeared at 0.87 (18 H, singlet), 0.94 (19 H, singlet), 1.13 (J = 6 cps) (21 H, doublet), 2.18 ($-NCH_3$, singlet), and 5.32 (6 H, multiplet) ppm (DMSO-d_6).

Anal. Calcd for $C_{22}H_{37}NO_2$ (347.52): C, 76.03; H, 10.73; N, 4.03. Found: C, 76.04; H, 10.82; N, 3.85.

16β-Piperidinopregn-5-ene-3β,20β-diol Hydrobromide (VI).—A mixture of 16β-aminopregn-5-ene-3β,20β-diol (Ia, 300 mg), potassium carbonate (0.3 g), 1,5-dibromopentane (0.5 ml), and *n*-butyl alcohol (50 ml) was stirred and refluxed 24 hr. The solvent was removed *in vacuo* and water was added. The resultant precipitate was collected and crystallized from methanol-acetone to yield the hydrobromide VI (190 mg), mp 273.5–274°. The analytical sample had mp 277.5–278° dec; $[\alpha]^{25}D$ −55° (methanol); ν_{max} 3350 and 1460 cm^{-1}.

Anal. Calcd for $C_{26}H_{44}BrNO_2$ (482.54): C, 64.71; H, 9.19; N, 2.90; Br, 16.56. Found: C, 64.22; H, 8.99; N, 2.72; Br, 16.68.

16β-Piperidinopregn-5-ene-3β,20β-diol (VIIa).—To a solution of the hydrobromide VI (2.235 g) in methanol (50 ml) was added a 10% solution of potassium hydroxide in methanol (25 ml). After standing at room temperature for 2 min, the solution was poured into a saline solution, and the resultant precipitate was collected. Crystallization from dilute acetone afforded VIIa (1.24 g), mp 188–190°. The analytical sample had mp 193–196°; $[\alpha]^{25}D$ −12° (dioxane); nmr peaks appeared at 1.02 (18 H and 19 H, singlet), 1.33 (J = 7 cps) (21 H, doublet), 2.60 ($-CH_2NCH_2$, multiplet), and 5.35 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{26}H_{43}NO_2$ (401.61): C, 77.75; H, 10.79; N, 3.49. Found: C, 77.24; H, 10.87; N, 3.39.

16β-Piperidinopregn-5-ene-3β,20β-diol Diacetate (VIIb).—A mixture of the 16β-piperidinodiol VIIa (460 mg) and acetic anhydride (1.0 ml) in pyridine (4.0 ml) was allowed to stand at room temperature 20 hr and then poured into ice water, and the resultant precipitate was collected. Crystallization from acetone–water gave the diacetate VIIb (375 mg), mp 194–195.5°. The analytical sample had mp 195.5–196°; $[\alpha]^{25}D$ −1° (chloroform).

Anal. Calcd for $C_{30}H_{47}NO_4$ (485.88): C, 74.18; H, 9.75; N, 2.88. Found: C, 73.92; H, 9.62; N, 2.85.

16β-Isopropylaminopregn-5-ene-3β,20β-diol (Ig).—A mixture of the trimethyl-1,3-oxazine IIIa (215 mg) and lithium aluminum hydride (0.4 g) in dry ether (50 ml) and tetrahydrofuran (25 ml) was stirred and refluxed for 3 hr. The resultant mixture was worked up as in the preparation Ic. Crystallization of the crude product from dilute acetone afforded Ig (0.12 g), mp ~160°. The analytical sample had mp 169.5–170°; $[\alpha]^{25}D$ −24.5° (methanol); nmr peaks appeared at 1.03 (18 H and 19 H, singlet), 1.03 and 1.13 (isopropyl methyls, two singlets), 1.33 (J = 8 cps) (21 H, doublet), 4.32 (N–CH, multiplet), and 5.42 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{41}NO_2$ (375.58): C, 76.75; H, 11.00; N, 3.73. Found: C, 76.38; H, 11.19; N, 3.56.

16β-Dimethylaminopregn-5-ene-3β,20β-diol (Ih).—A mixture of the N-methyloxazine Va (971 mg) and lithium aluminum hydride (1.0 g) in tetrahydrofuran was stirred and refluxed for 24 hr. The mixture was worked up as in the preparation of the 16-ethylamino compound Ic to give, after crystallization from dilute methanol, Ih (583 mg), mp 168–173°. The analytical sample crystallized from acetone–hexane had mp 180.5–182°; $[\alpha]^{25}D$ −23° (chloroform); nmr peaks appeared at 1.00 and 1.01 (18 H and 19 H, singlet), 1.31 (J = 7 cps) (21 H, doublet), 2.39 ($-N(CH_3)_2$, singlet), and 5.28 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{23}H_{39}NO_2$ (361.55): C, 76.40; H, 10.87; N, 3.87. Found: C, 76.08; H, 11.20; N, 3.89.

16β-Ethylmethylaminopregn-5-ene-3β,20β-diol (Ii).—A mixture of N-acetyloxazine Ve (1.242 g) and lithium aluminum hydride (2.0 g) in tetrahydrofuran was stirred and refluxed 40 hr. The mixture was worked up as in the preparation of the 16-ethylamino compound Ic to give, after crystallization from dilute methanol, Ii (950 mg), mp 178–183°. The analytical sample crystallized from acetone–hexane had mp 178–180°; $[\alpha]^{25}D$ −39° (chloroform); nmr peaks appeared at 1.00 and 1.02 (18 H and 19 H, singlet), 1.03 (J = 6 cps) ($-NCH_2CH_3$, triplet), 1.31 (J = 7 cps) (21 H, doublet), 2.27 (NCH_3, singlet), 2.58 (J = 7 cps) ($-NCH_2CH_3$, quartet), and 5.30 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{24}H_{41}NO_2$ (375.58): C, 76.75; H, 11.00; N, 3.73. Found: C, 76.56; H, 11.04; N, 3.69.

3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]androst-4-en-3-one (VIII).—To a solution of the 1,3-oxazine Va (654 mg) in acetone (100 ml) in a nitrogen atmosphere at ice-bath temperature was added 1.0 ml of a solution of chromic acid (13.36 g) and sulfuric acid (11.5 ml of concentrated acid diluted to 50 ml with water). After being stirred in a nitrogen atmosphere 2.5 hr (the bath temperature was allowed to rise to room temperature), the mixture was filtered. The residue was dissolved in a small amount of water and concentrated sodium hydroxide was added. The mixture was extracted with methylene chloride, and the extract was dried and evaporated *in vacuo* to give an oil (0.3 g). This was adsorbed on a Florisil column (50 g) and chromatographed. Eluates from a petroleum ether–acetone (88–82:12–18) mixture on evaporation afforded a glass (0.17 g) which contained an α,β-unsaturated ketone according to its infrared spectrum. The glass was then chromatographed on Celite[21] with a heptane–methanol (1:1) system to give VIII (39 mg), mp 140–143° from dilute acetone. Further crystallization gave a poor recovery of material; hence, the compound was characterized at this stage: λ_{max} 241 mμ (ε 13,200); $[\alpha]^{25}D$ +91° (chloroform); nmr peaks appeared at 1.20 (18 H and 19 H, singlet), 1.37 (J = 7 cps) (21 H, doublet), 2.02 ($-NCH_3$, singlet), 3.52 and 4.33 (J = 7.5 cps) (2′,2′ H, pair of doublets), and 5.73 (4 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{23}H_{35}NO_2$ (357.55): C, 77.26; H, 9.87; N, 3.92. Found: C, 76.68; H, 9.36; N, 4.44.

16β-Azidopregn-5-ene-3β,20β-diol 3-Acetate 20-Benzoate (Ik).—To an ice-cold solution of 3β-acetoxy-16β-azidopregn-5-en-20β-ol (Ij, 3.4 g) in pyridine (15 ml) was added benzoyl chloride (2 ml). The mixture was allowed to stand 18 hr at room temperature and then was poured into ice–water. The resultant precipitate was collected and dissolved in methylene chloride. The solution was washed with dilute sodium hydroxide solution and evaporated *in vacuo*. Crystallization of the residue from acetone–hexane afforded Ik (3.6 g), mp 173.5–174.5°. The analytical sample had mp 174.5–175°; λ_{max} 229 mμ (ε 14,900), 273 (1120), and 280 (1010); $[\alpha]^{25}D$ −34° (chloroform).

Anal. Calcd for $C_{30}H_{39}N_3O_4$ (505.64): C, 71.26; H, 7.77; N, 8.31. Found: C, 70.95; H, 7.51; N, 8.21.

16β-Azido-20β-benzoyloxypregn-5-en-3β-ol (Il).—To an ice-cold solution of the acetoxy benzoate Ik (3.2 g) in methanol (15 ml) and methylene chloride (15 ml) was added a 5% solution of potassium hydroxide in methanol (8 ml). The solution was allowed to stand 17 hr at +5°, when acetic acid was added to neutralize the solution. The solution was poured into an

(21) Celite (Johns-Manville Co.) is a diatomaceous silica product.

excess of water and extracted with methylene chloride. Evaporation of the extract *in vacuo*, and crystallization of the residue from methanol gave II, mp 122–130°. The analytical sample (dried over benzene) had mp 122.5–126°; λ_{max} 229 mμ (ε 14,200) 273 (930), and 280 (810); $[\alpha]^{25}D$ −34° (chloroform).

Anal. Calcd for $C_{28}H_{37}N_3O_3$ (463.60): C, 72.54; H, 8.04; N, 9.06. Found: C, 72.53; H, 8.13; N, 9.11.

16β-Azidopregn-5-ene-3β,20β-diol 3-*p*-Toluenesulfonate 20-Benzoate (Im).—A solution of the benzoate II (6.4 g) and *p*-toluenesulfonyl chloride (6 g) in pyridine (46 ml) was allowed to stand at room temperature 20 hr and then poured into ice-water. The resultant precipitate was collected and crystallized from methylene chloride to give Im, mp 179.5–180.5°. The analytical sample, crystallized from methylene chloride–hexane, had the same melting point; $\lambda_{max}^{MeOH-CHCl_3}$ 227 mμ (ε 28,500); $[\alpha]^{25}D$ −26° (chloroform).

Anal. Calcd for $C_{35}H_{43}N_3O_5S$ (617.72): C, 68.05; H, 7.02; N, 6.80; S, 5.19. Found: C, 67.82; H, 6.76; N, 6.79; S, 5.27.

16β-Azido-6β-methoxy-3α,5α-cyclopregnan-20β-ol Benzoate (IX).—A mixture of the tosylate benzoate Im (6.29 g) and potassium acetate (12.5 g, oven dried at 105°) in methylene chloride (100 ml) and methanol (1 l.) was refluxed 22 hr, whereupon complete solution resulted. Most of the solvent was distilled *in vacuo*, and the remainder was added to ice water. An amorphous solid resulted which could not be crystallized. It contained three components (one major and two minor) as revealed by thin layer chromatography. Chromatography on Florisil (500 g) gave IX as a noncrystallizable oil (4.5 g) from the petroleum ether–acetone (9:1) eluates, ν_{max} 2100, 1710, 1250, and 1020 cm^{-1}. A minor contaminant was present as shown by thin layer chromatography.

3β,16β-Diazidopregn-5-en-20β-ol Benzoate (X).—A solution of the cyclopregnane benzoate IX (4.50 g) in benzene (100 ml) containing hydrazoic acid[22] and freshly distilled boron trifluoride etherate (3.1 ml) was allowed to stand 3.5 hr at room temperature. Ammonium hydroxide (6 *N*, 100 ml) and then ether (200 ml) were added to the reaction mixture. The organic layer was collected, washed with 6 *N* ammonium hydroxide and water, and dried. Evaporation gave an oil which solidified on standing. Crystallization from acetone–hexane afforded X (3.65 g), mp 146–148°. The analytical sample had mp 155.5–156.5°; $[\alpha]^{25}D$ −14° (chloroform); ν_{max} 2100, 1718, and 1270 cm^{-1}; nmr peaks appeared at 0.82 (18 H, singlet), 0.95 (19 H, singlet), 1.40 (J = 5.5 cps) (21 H, doublet), 3.19 (3 H, multiplet), 5.35 (6 H, multiplet), 4.18 (16 H, multiplet), 7.50 and 8.05 (phenyl, multiplets) ppm ($CDCl_3$).

Anal. Calcd for $C_{28}H_{36}N_6O_2$ (488.62): C, 68.82; H, 7.43; N, 17.20. Found: C, 69.04; H, 7.46; N, 17.24.

3β,16β-Diaminopregn-5-en-20β-ol (XI).—A mixture of the diazido benzoate X (2.77 g) and lithium aluminum hydride (4.0 g) in tetrahydrofuran (250 ml) was refluxed 17 hr and worked up as in the preparation of Ic. The residue obtained was dissolved in methanol and concentrated with heating to give a precipitate of an unknown material (0.25 g), mp 234–236°. Addition of ethyl acetate to the filtrate and concentration by heating gave XI (750 mg), mp 214–219°. Further crystallization gave an analytical sample: mp 224–225°; $[\alpha]^{25}D$ −36° (methanol); ν_{max} 3360 cm^{-1}; nmr peaks appeared at 0.90 and 0.94 (18 H and 19 H, singlet), 1.12 (J = 5 cps) (21 H, doublet), and 5.28 (6 H, multiplet) ppm (DMSO-d_6), (the nmr spectral signals were very weak due to poor solubility).

Anal. Calcd for $C_{21}H_{36}N_2O$ (332.51): C, 75.85; H, 10.91; N, 8.43. Found: C, 75.80; H, 11.15; N, 8.45.

3′,6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-1′,3′-oxazino[4′,5′:16β,17β]-3β-dimethylaminoandrost-5-ene (XII).—A solution of the 3β,16β-diamino-20β-ol XI (590 mg) in formaldehyde (10 ml) and formic acid (10 ml) was refluxed 7 hr. The reaction mixture was poured into ice water and made basic with dilute potassium hydroxide, and the resultant precipitate was collected. Crystallization from acetone–water gave XII (310 mg), mp 126.5–127°. The analytical sample had mp 127.5–128.5°; $[\alpha]^{25}D$ −29° (chloroform); nmr peaks appeared at 1.01 (19 H, singlet), 1.19 (18 H, singlet), 1.39 (J = 7 cps) (21 H, doublet), 2.03 (N-methyl, singlet), 2.30 (N-dimethyl, singlet), 3.51 and 4.38 (J = 8 cps), (2′2′ H, pair of doublets), 3.91 (20 H, multiplet), and 5.33 (6 H, multiplet) ppm ($CDCl_3$).

Anal. Calcd for $C_{25}H_{42}N_2O$ (388.60): C, 77.66; H, 10.95; N, 7.25. Found: C, 77.45; H, 11.01; N, 7.05.

Registry No.—Ia, 14570-69-5; Ib, 14570-70-8; Ic, 14570-71-9; Id, 14570-72-0; Ie, 14570-73-1; If, 14570-74-2; Ig, 14570-75-3; Ih, 14734-05-5; Ii, 14570-76-4; Ik, 14570-77-5; Il, 14570-78-6; Im, 14734-06-6; IIIa, 14754-81-5; IIIb, 14570-79-7; IIIc, 14735-83-2; IIId, 14570-80-0; IV, 14570-81-1; Va, 14570-82-2; Vb, 14734-07-7; Vc, 14734-08-8; Vd, 14570-83-3; Ve, 14570-84-4; VI, 14570-85-5; VIIa, 14570-86-6; VIIb, 14570-87-7; VIII, 14570-88-8; IX, 14570-89-9; X, 14570-90-2; XI, 14570-91-3; XII, 14570-92-4.

(22) P. A. S. Smith, *Org. Reactions*, **3**, 327 (1946).

Terpene–Formaldehyde Reactions. I. α-Terpinene[1]

A. T. BLOMQUIST AND J. D. MEADOR[2]

Department of Chemistry, Cornell University, Ithaca, New York 14850

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Reaction of α-terpinene with formaldehyde is best effected in solvent acetic acid at 110–115° in the absence of added catalyst. The reaction product (70% yield) comprises mainly (75%) a 2:1 mixture of *p*-mentha-2,4(8)-diene-1-methanol acetate and *p*-mentha-2,4-diene-1-methanol acetate. The stannic chloride catalyzed reaction, in solvent methylene chloride, gives a mixture of products (75% yield) whose principal component (80%) is the 1,3-dioxane, 6-methyl-9-isopropyl-2,4-dioxabicyclo[4.4.0]dec-9-ene. *p*-Menthane-1-methanol is obtained easily by hydrogenation of mixtures of the aforementioned acetates followed by hydrolysis.

Especial interest attaches to a study of the terpenes of gum turpentine as basic raw materials for the synthesis of primary alcohols and related compounds, in good yield and reasonable purity. To this end, a careful examination of terpene–formaldehyde reactions seems to merit specific consideration, giving attention to the more available terpenes. The conjugated diene α-terpinene, which is now conveniently available *via* isomerization of the pinenes,[3] is of particular interest. Up to the present time there is no report on its reactions with formaldehyde.

The most useful of the α-terpinene–formaldehyde reactions studied is the "noncatalyzed" thermal condensation in glacial acetic acid. Upon heating the

(1) For the preceding report from this laboratory on olefin–formaldehyde reactions, see A. T. Blomquist and J. Wolinsky, *J. Am. Chem. Soc.*, **79**, 6025 (1957).

(2) Abstracted from part of the Ph.D. dissertation presented by J. D. Meador to the Graduate School of Cornell University, June 1967.

(3) H. Kroeper, W. Rau, and F. Wirth, U. S. Patent 2,792,436; *Chem. Abstr.*, **51**, 16550 (1957).