Aza Steroids. V.[1] Introduction of 11-Hydroxy and 11-Amino Groups

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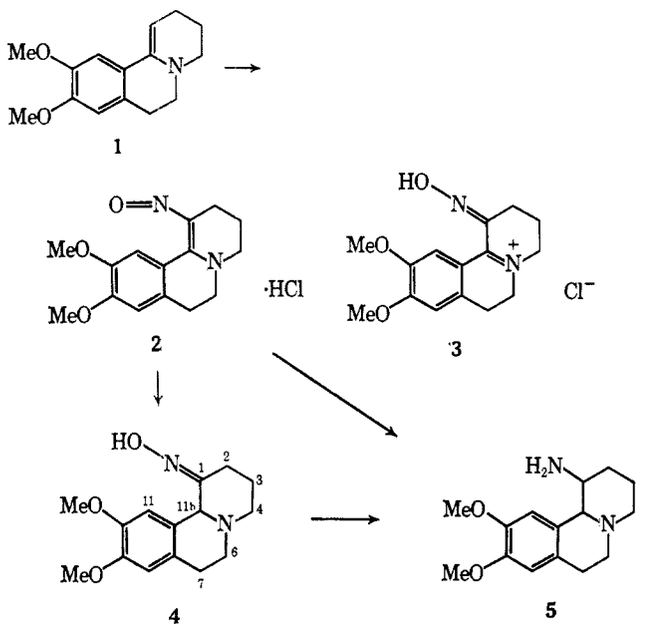
Received May 13, 1968

Introduction of hydroxyl and amino groups at position 11 of the 8-aza steroid nucleus has been accomplished. The configurations of the products were deduced by spectral methods.

As part of a continuing program[1] in this laboratory on the synthesis of 8-aza steroids, a convenient method for introduction of the 11β-hydroxyl group characteristic of corticosteroids was needed. The present report describes this work and a concurrently discovered route to 11-amino-8-aza steroids.

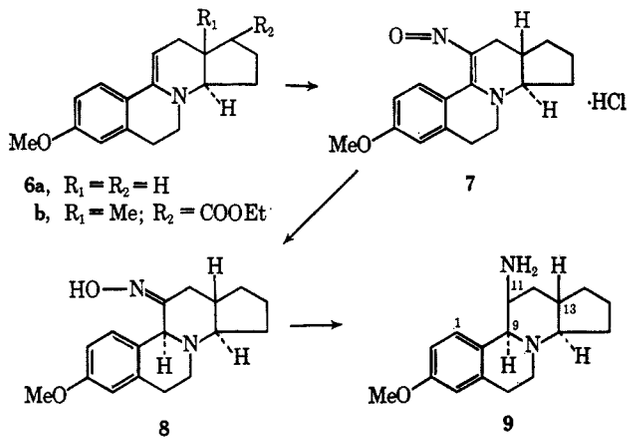
Initial studies were carried out in the related tricyclic benzo[*a*]quinolizine series in order to bypass possible stereochemical complications due to the C–D ring fusion of the aza steroid nucleus. The known[2] cyclic enamine **1** was treated with nitrosyl chloride[3] at low temperature to give a bright yellow 1:1 adduct **2** in high yield. This product was assigned the nitroso structure rather than that of the tautomeric quaternary oxime **3** on the basis of spectral data. Thus the infrared spectrum showed no oxime hydroxyl absorption nor any bands in the 1620–1640-cm^{-1} region characteristic of quaternary salts such as **3**. In addition, the presence of an N–H salt band at 2650 cm^{-1} gave further indication of the nitroso form **2**.



Reduction of **2**, either catalytically or with borohydride, gave a single oxime, **4**. In this product, the B–C ring junction appears to be in the *cis* conformation, as evidenced by the lack of Bohlmann bands[4] in the ir spectrum and the low-field position[5] (4.55 ppm) of the nmr singlet[6] of the angular proton at C-11b. Further, examination of Dreiding models shows that the B–C *trans* oxime is destabilized relative to both *cis* conformations by severe crowding between the oxime nitrogen and the aromatic C-11 proton.

Catalytic reduction of either **2** or **4** furnished a single aminoquinolizidine, **5**. For this product, a *trans*-quinolizidine conformation is indicated by the presence of Bohlmann bands[4] and an upfield[5] (3.23 ppm) signal for the angular hydrogen. This signal appeared as a broad singlet, $W_{1/2}$ = 5 cps, indicative of coupling between the axial C-11b proton (required for *trans* ring fusion) with an equatorial hydrogen at position 1. Thus the amine group in **5** must be axial;[7] this configuration minimizes interaction of the functional group with the nearby aromatic proton.[8]

In the tetracyclic series, an analogous series of reactions was carried out to furnish, starting with enamine **6a**, nitroso adduct **7**, oxime **8**, and amine **9**. As



observed in the tricyclic series, spectral data for these products showed a *cis*-quinolizidine conformation for **8** but a *trans*-quinolizidine conformation and axial amino group for **9**. The relationship of the hydrogens at C-9 and C-13 in **9** must be *anti*[9] [as shown in con-

(1) Part IV: R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Med. Chem.*, **10**, 451 (1967).

(2) (a) R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931); (b) Y. Ban and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **8**, 653 (1960).

(3) H. Metzger, *Tetrahedron Lett.*, 203 (1964).

(4) (a) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); (b) F. Bohlmann, *Ber.*, 91, 2157 (1958); (c) W. E. Rosen, *Tetrahedron Lett.*, 481 (1961).

(5) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).

(6) The fact that this signal is unsplit is clear evidence that the original nitrosation had indeed taken place at C-1.

(7) Drieding models of the two *cis* conformations of **4** reveal no reason to expect significant stability differences between the two, with the likelihood that both conformers are present in equilibrium. For either one, reduction from the side of the oxime farthest removed from the aromatic ring can be predicted from the models; for both conformers, this would introduce the hydrogen at C-1 *cis* to the angular hydrogen at C-11b. One conformer would give initially a *cis*-quinolizidine with an equatorial amine; the other, a *cis* quinolizidine and an axial amine. Both of these intermediates would undergo inversion at the ring nitrogen to give the more stable *trans*-quinolizidine with an axial amine.

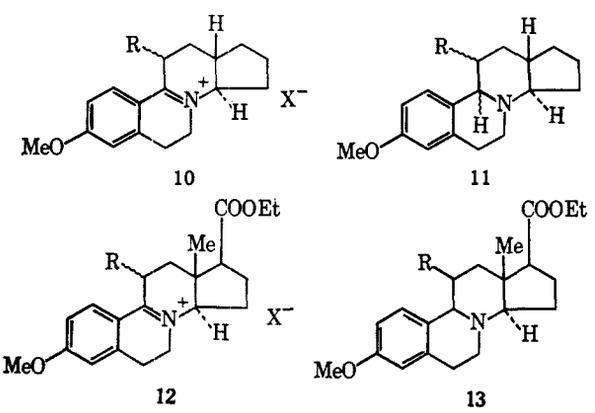
(8) The aromatic signals for products **4** and **5** and the N acetate of **5** appeared in the range of 6.5–6.7 ppm, as reported[5] for a number of *cis*-and *trans*-dimethoxybenzoquinolizines unsubstituted at position 1. Thus it appears that no significant interaction occurs between an axial C-1 substituent and the aromatic proton at C-11. This is in contrast to the observation made for products, **11c** isomers A and C, containing an equatorial C-1 substituent.

(9) In this series of papers, the terms *syn* and *anti* refer to the relationship of the hydrogen at C-9 and the substituent at C-13.

formational diagram **11c**, isomer B (NH_2 in place of OH)] since the axial C-9 hydrogen in **9** and the *trans* C–D ring junction allow only one configuration and conformation, that containing the normal steroid backbone.

Although the oximes described above afforded a good route to aminoaza steroids, they failed in their primary purpose of providing a route for hydroxylation of position 11. When products **2**, **4**, **7**, and **8** were treated with 10% H_2SO_4 and 6 *N* HCl, both with and without added formalin, with levulinic acid in HCl, or with sodium nitrite in both acetic acid and HCl, ketonic material was formed (as evidenced by ir analysis), but in no case could a pure ketone be obtained. Further work on hydrolysis was abandoned when the procedure described below was developed.

Low temperature bromination[10] of enamine **6a** gave an immediate crystalline yellow precipitate of the 11-bromo quaternary bromide, **10a** (X = Br), as an epimeric mixture (*ca.* 3:1 ratio by tlc). Borohydride reduction of this mixture gave a single bromo base, **11a**, which slowly lost HBr on standing. The same sequence on the more highly substituted enamine, **6b**, gave different results. The mixture of salts, **12a**, (X = Br; 1:1 ratio by tlc), gave on reduction no product corresponding to **13a**, but instead a single isomer of the product of reductive debromination, **13e**. A similar reduction may have been responsible for loss of the second isomer of **10a**.



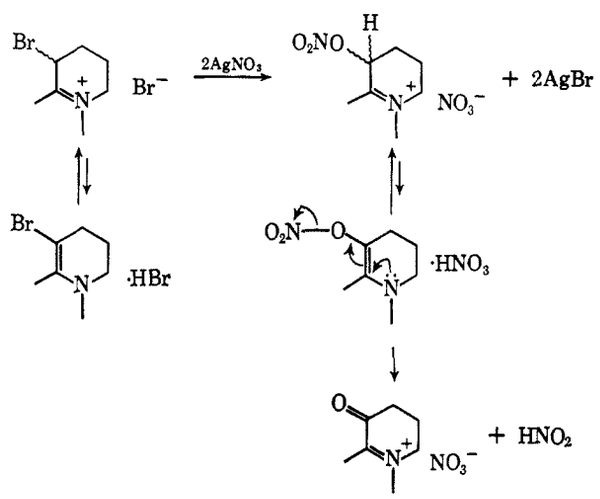
a, R = Br
b, R = OAc
c, R = OH
d, R = O
e, R = H

Product **11a** was found to resist displacement reactions with nucleophilic agents, all reactions leading to recovered **11a** or to enamine **6a** *via* elimination. However, treatment of the 11-bromo quaternary bromides **10a** and **12a** (X = Br) with potassium acetate in acetic acid gave, from **10a**, a 30% yield of a mixture of the corresponding acetoxy salts, **10b**, and from **12a**, a 10% yield of a single isomer of **12b**, both conveniently isolated as their perchlorates (X = ClO_4).

The mixture of acetoxy salts **10b** could not be separated and was therefore reduced and hydrolyzed to afford a mixture of three (isomers A, B, and C) of the four possible isomers of **11c** about the two new assymmetric centers. This mixture was easily separated by chromatography on alumina. In contrast, the single isomer of **12b** was reduced and hydrolyzed to give one isomer of **13c**.

A better yield in the displacement step was accomplished by modification of a procedure developed by Emmons.[11] Treatment of mixtures **10a** and **12a** (X = Br) with silver nitrate in acetonitrile afforded the corresponding ketones **10d** and **12d** (X = ClO_4), respectively, in up to 70% yields. This is in contrast to the reported[11] course of this reaction, in which a base such as piperidine was required to cleave the initially formed nitrate ester, the reaction being an example of a concerted α elimination initiated by base-catalyzed abstraction of an α-hydrogen atom. In the case at hand, the addition of base is not required owing to the enamine–immonium ion tautomeric equilibrium known[2b] to exist in such systems. Thus, the schematic representation shown in Scheme I can be written for the process.

SCHEME I



Reduction of the two keto salts **10d** and **12d** with potassium borohydride in ethanol proceeded in high yield to give, in the case of **10d**, two (isomers A and B) of the three isomers of **11c** described above and, in the case of **12d**, the same single base **13c**.

The configurations of alcohols **11c**, isomers A, B, and C, and alcohol **13c** were deduced by spectral methods, and the assigned structures are given in the conformational diagrams shown in Chart I.

For **13c**, the presence of Bohlmann bands[4] and an upfield[5] signal for the C-9 hydrogen established the *trans*-quinolizidine conformation and thus the *anti-trans* steroidal backbone. The hydroxyl group in **13c** is assigned the axial or β orientation on the basis of the data summarized in Table I.

TABLE I

	C-13 methyl δ (CHCl₃)	C-13 methyl δ (pyr)	C-13 methyl δ (D_2O) on ·HCl	Carbinol H δ	Carbinol H $W_{1/2}$, cps	C-1 H, δ
13c	1.00	1.33	1.20	4.4	8	7.32
13e[a]	0.82	0.93	0.95			7.32

[a] Reference 1.

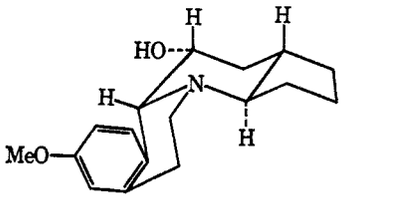
The downfield shift of a steroidal angular methyl signal due to the presence of a 1,3 diaxially disposed

(10) R. L. Pederson, J. L. Johnson, R. P. Holysz, and A. C. Ott, *J. Amer. Chem. Soc.*, **79**, 1115 (1957).

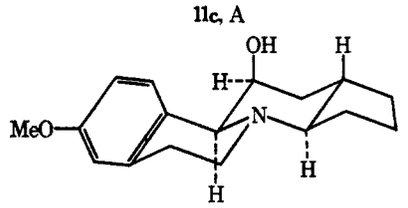
(11) W. D. Emmons and J. P. Freeman, *ibid.*, **77**, 4415 (1955).

hydroxyl group is well known.[12] It is seen that the methyl signal of the unsubstituted base **13e** is shifted downfield by the hydroxyl group of **13c** by 0.18 and 0.40 ppm, respectively, in $CDCl_3$ and pyridine, and by 0.25 ppm when comparisons are made of the hydrochloride salts in D_2O. Furthermore, the half band width of a carbinol proton signal (5–10 cps for equatorial and 15–30 cps for axial) has been used for direct configurational assignment of a hydroxyl group.[13] For **13c**, this value is 8 cps (after D_2O exchange to remove coupling with the hydroxyl proton), and this is in good agreement with the reported value for an equatorial carbinol proton.

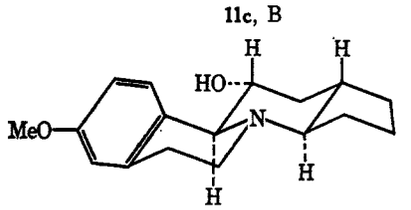
CHART I



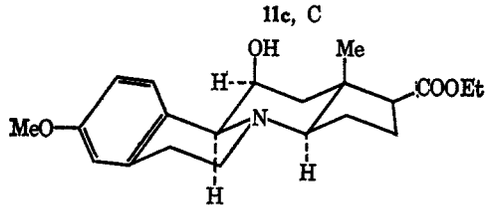
11c, A



11c, B



11c, C



13c

The aromatic region of the nmr spectrum of **13c** is identical with that of **13e** (unsubstituted position 11) and with that of ethynylestradiol (Varian Spectra Catalogue #343). Since molecular models reveal severe crowding between an 11α (equatorial) substituent and the aromatic proton at C-1, the unperturbed aromatic signal for **13c** provides further evidence for an axial substituent.[14]

The spectral data obtained for the three isomers of **11c** are given in Table II.

TABLE II

Isomer	1 H, δ	9 H, δ	11 H, δ	11 H, $W_{1/2}$ (cps)	Bohlmann bands
A	8.16 d	4.15–4.6	4.15–4.6	*ca.* 24	–
B	7.32 d	3.2 or less	4.4	6	+
C	7.88 d	3.2 or less	3.5–4.0	*ca.* 24	+

Isomers B and C both show strong Bohlmann bands[4] and no downfield signal[5] for the angular (C-9) proton. These two products thus have the same *anti–trans*[9] steroidal backbone as **13c**. Isomer B has the configuration corresponding to **13c** in that it has an axial hydroxyl group, as evidenced from the downfield chemical shift (4.4 ppm) and half band width (6 cps) of the equatorial carbinol proton. Also like **13c**, isomer B shows an unperturbed signal for the aromatic C-1 proton.

Isomer C is the 11 epimer of isomer B. The equatorial nature of the hydroxyl group is shown by the downfield displacement of the aromatic C-1 signal[14] and by the broad upfield[15] signal of the axial carbinol proton.

Isomer A is the C-9 epimer of isomer C. Its *cis*-quinolizidine conformation is indicated by lack of Bohlmann bands.[4] A broad three-proton signal centered at 4.35 ppm was shown by D_2O exchange to include the hydroxyl proton as well as the C-9 and C-11 protons. Thus the C-9 proton is found well downfield from its axial counterpart in isomers B and C, as expected, owing to its equatorial nature.[5] The hydroxyl group in isomer A is shown to be α or equatorial by the large downfield displacement of the aromatic C-1 proton and the broad half band width (24 cps after D_2O exchange) due to the axial carbinol proton.[16]

Products **13c** and isomers A, B, and C of **11c** show interesting differences in the hydroxyl regions of the ir spectrum. Aaron and coworkers[17] have shown that simple 1-, 2-, and 3-hydroxyquinolizidines exist in the *trans* conformation, and that those products in which the hydroxyl and electron pair are 1,3 diaxially disposed exhibit strong intramolecular hydrogen bonding. Of the three available isomers of **11c**, only B showed a hydrogen bond which dilution studies indicated to be intramolecular. This observation supports the configurational assignment. The conformationally analogous **13c** shows no intramolecular hydrogen bond, which is, however, not surprising when it is considered that, in the OH···N bonded conformation of this compound, the hydroxyl hydrogen would be subject to steric compression by the *syn* axial methyl group.

Product **13c** thus contains five assymetric centers, all of which are in the same configuration as found in carbocyclic steroids. Use of this product for further elaboration of 8-aza steroids will be described in subsequent publications.

(12) K. Tori and E. Kondo, *Steroids*, **4**, 713 (1964). These authors reported an average downfield displacement of the 18-methyl signal by an 11β-hydroxyl group of 0.24 ppm in $CDCl_3$ and 0.51 ppm in pyridine. In contrast an 11α (equatorial) hydroxyl group displaced the methyl signal upfield by 0.03 and 0.08 ppm, respectively.

(13) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

(14) The spectra of the dicentrine bases (Varian Spectra Catalogue #342 and #349) provide examples of the displacement of an aromatic proton by a similarly positioned substituent. Compare also isomers A and C of **11c**.

(15) Axial carbinol protons are generally found *ca.* 0.5 ppm upfield from their equatorial epimers: E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Strothers, *Tetrahedron Lett.*, 741 (1962).

(16) The large downfield shift of the axial carbinol proton in isomer A compared to that of isomer C, while surprising at first sight, finds an explanation when it is taken into account that A has an axial substituent (C-9) in the position adjacent to the carbinol whereas C has an equatorial substituent in this position. Analogous cases in simple alkyl-substituted cyclohexanols have been described in the literature.[15]

(17) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

Experimental Section[18]

Nitroso Hydrochloride 2.—Enamine **1** was liberated from 25.0 g (0.0767 mol) of its quaternary iodide by treatment of an aqueous solution of the salt with excess 10 *M* potassium hydroxide, and the base was extracted into toluene (*ca.* 500 ml). The toluene solution was dried (potassium carbonate) and filtered, then chilled in an acetone–Dry Ice bath to −80°. A solution of 5.5 g (0.084 mol) of nitrosyl chloride in 150 ml of toluene was then added, with stirring, during 90 min, maintaining the reaction mixture at −80°. After stirring for a further 90 min, the solution was allowed to warm to *ca.* 0° and filtered. The crude solid was recrystallized directly from 1:1 methanol–ether, furnishing 19.4 g (81%) of the nitrosated product as bright yellow crystals, mp 198–200° dec. Further recrystallization from methanol–ether gave an analytical sample of mp 198–200°; ν_{max}^{Nujol} 2700, 1680 (weak, broad) cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot HCl$: C, 57.97; H, 6.16; N, 9.01; Cl, 11.41. Found: C, 58.26; H, 6.26; N, 9.01; Cl, 11.29.

Oxime 4 Method A. Borohydride Reduction.—To a stirred solution of 9.5 g (0.0306 mol) of **2** in 100 ml of water and 25 ml of ethanol was added a solution of 2 g (0.037 mol) of potassium borohydride in 25 ml of water; the yellow color of **2** slowly disappeared during this addition. The mixture was stirred for 2 hr, 200 ml of water added, and the resulting mixture chilled and filtered, giving 7.65 g (90%) of off-white solid, mp 193–196° dec. A colorless analytical sample was obtained by two recrystallizations from acetonitrile, and had mp 191–195°; $\nu_{max}^{CHCl_3}$ 3600, 3270, 1660 (weak C=N) cm^{-1}; γ_{max}^{Nujol} 3200, 2700 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.49; H, 7.35; N, 10.38.

The hydrobromide salt was prepared by passing excess hydrogen bromide into a slurry of 6 g of the crude oxime in 50 ml of absolute ethanol. The resulting mixture was heated and diluted with more absolute ethanol to effect solution. Addition of ether to the warm solution gave 7.2 g of the salt, mp 185–189°. Two recrystallizations from methanol–ether gave 5.1 g of colorless, analytically pure material: mp 190–192°; ν_{max}^{Nujol} 3200, 2550, 2650, 2700 (NH^+) cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O_3 \cdot HBr$: C, 50.43; H, 5.92; N, 7.84; Br, 22.37. Found: C, 50.19; H, 6.02; N, 8.13; Br, 22.59, 22.36.

Method B. Catalytic Reduction.—A solution of 5 g (0.016 mol) of **2** in 300 ml of acetic acid was hydrogenated at room temperature in the presence of 0.15 g of platinum oxide catalyst at an initial pressure of 3 atm of hydrogen. After 90 min the uptake of hydrogen had stopped. The reaction mixture was filtered and evaporated. The residue was dissolved in *ca.* 100 ml of water and made basic (pH 8) with alkali. On cooling and filtering 4.0 g of crude product separated, mp 186–193°. Recrystallization from acetonitrile then furnished 2.9 g (66%) of the pure oxime **4**, mp 192–194°, identical with the material prepared by method A.

Diamine 5. By Reduction of 2.—To a solution of 12.5 g (0.0403 mol) of **2** in 300 ml of acetic acid was added 0.5 g of platinum oxide, and the resulting mixture was hydrogenated for 4 hr at 3.35 atm. A second portion of 0.2 g of platinum oxide was added and the hydrogenation continued for an additional 2 hr. The reaction mixture was filtered, the catalyst thoroughly washed with warm water, and the combined solvents were treated with 10 ml of 6 *N* hydrochloric acid and evaporated. The residue was triturated with ethyl acetate and filtered, giving 15.5 g of the crude salt of **5**. A colorless analytical sample (4.75 g) was obtained by recrystallization from aqueous isopropyl alcohol. This had mp 283–284° and retained the mole of water of crystallization after drying at 80° under high vacuum: ν_{max}^{Nujol} 3500, 3200, 2850, 2800, and 2750 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 51.29; H, 7.46; N, 7.98; Cl, 20.19. Found: C, 51.21; H, 7.49; N, 8.15; Cl, 20.01, 19.91.

The free base was obtained as a solid with mp 113–119° by treatment of an aqueous solution of the dihydrochloride with excess 10 *M* potassium hydroxide and filtration. Two recrystallizations from Skellysolve B furnished an analytical sample, mp 121–123°. This material became tan on standing for several days: $\nu_{max}^{CHCl_3}$ 2730, 2800 (Bohlmann), 3200, 1590 cm^{-1}.

The N-acetyl derivative of the 1-amino compound, prepared by treatment of the free base with acetic anhydride in pyridine and recrystallized from Skelly B, had mp 119–120°; ν_{max}^{Nujol} 3380, 1640 cm^{-1}.

Diamine 5. By Reduction of 4.—The reduction of **4** was carried out in the same way as described for reduction of **2**. The product, obtained in 58% yield, was identical with that described above.

Nitroso Adduct 7.—Enamine **6a** (37.2 g, 0.146 mol) was liberated from its quaternary bromide by treatment of an aqueous solution of 49.0 g of the salt with excess 5% sodium hydroxide solution. The precipitated base was extracted into 1 l. of ether. The solution was dried over potassium carbonate and cooled to −80°. A solution of 10.5 g (0.16 mol) of nitrosyl chloride in 200 ml of toluene was added dropwise over a 1-hr period. After stirring for a further 1 hr, the mixture was allowed to warm up to room temperature, and the yellow solid was filtered to give 45.3 g (96%) of material, mp 206–208°. A sample was recrystallized from ethanol: mp 208–210°; ν_{max}^{Nujol} 1610, 2550 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}N_2O_2 \cdot HCl$: C, 63.65; H, 6.60; N, 8.73. Found: C, 63.45; H, 6.59; N, 8.78.

Oxime 8.—The reduction of **7** was carried out with potassium borohydride as described for preparation of **4**. The yield of base once recrystallized from acetonitrile, mp 192–194°, was 85%. A sample was recrystallized again for analysis: mp 197–198°; $\nu_{max}^{CHCl_3}$ 1620, 1650 (weak, broad).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.46; H, 7.79; N, 10.10.

Diamine 9.—**9** was prepared from **7** or **8** by catalytic reduction (platinum oxide in acetic acid) as described for **5**. The dihydrobromide was obtained as a white powder, mp 279–281° after two recrystallizations from methanol: ν_{max}^{Nujol} 2550, 2675, 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}N_2O \cdot 2HBr$: C, 47.02; H, 6.04; Br, 36.80. Found: C, 47.15; H, 6.08; Br, 36.94.

The free base was obtained as white crystals which darkened on standing, mp 90–91° after recrystallization from Skellysolve B: ν_{max}^{Nujol} 3300, 1610 cm^{-1}; $\nu_{max}^{CHCl_3}$ 2780, 2710 (Bohlmann), 3250 cm^{-1}; δ (C-9) 3.5 ppm; $W^1/_2$ = 6 cps.

Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.94; H, 8.83; N, 10.42.

Bromo Salt 10a (X = Br).—Enamine **6a** (27.2 g, 0.094 mol) was liberated from its quaternary bromide (35.8 g) and extracted into 840 ml of ether as described for the preparation of **7**. The dried (potassium carbonate) ether solution was cooled to −80° and 14.4 g (0.09 mol) of bromine in 100 ml of methylene chloride was added dropwise over a 1-hr period. The yellow slurry was stirred at −80° for an additional $^1/_2$ hr, then allowed to warm to room temperature. The yellow salt was filtered and dried to give 32.5 g, 82%, mp 170–172°. A sample was recrystallized from ethanol for analysis: mp 172–173°; ν_{max}^{Nujol} 1605, 1615, 1560 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}Br_2NO$: C, 49.18; H, 5.10; Br, 38.49. Found: C, 48.98; H, 5.00; Br, 38.67.

On tlc (1-butanol–acetic acid–water, 5:2:3), the analytical material showed two spots, R_f 0.2 and 0.3, in a ratio of *ca.* 3:1.

Bromo Base 11a.—A solution of 1.0 g of salt **10a** (X = Br) in 20 ml of methanol was treated with cooling with 1.0 g of sodium borohydride in portions over 0.5 hr. The solution was diluted with 100 ml of water and the solid filtered. Two recrystallizations from acetone–water gave white needles: mp 215–216°; the material darkened on standing: $\nu_{max}^{CHCl_3}$ 2720, 2780 cm^{-1} (Bohlmann).

Anal. Calcd for $C_{17}H_{22}BrNO$: C, 60.72; H, 6.59; N, 4.17. Found: C, 60.66; H, 6.63; N, 4.42.

Acetoxy Salt 10b (X = ClO_4).—A suspension of 20.0 g (0.048 mol) of **10a** (X = Br) in 300 ml of acetic acid containing 11 g (0.112 mol) of fused potassium acetate was stirred at room temperature. The solution slowly turned orange as the salt dissolved and potassium bromide separated. After 48 hr, the solid was filtered, washed with acetic acid, and dried to afford 9.1 g (73%) of the theoretical potassium bromide. The filtrate was evaporated to dryness; the residue was dissolved in 100 ml of water and treated with excess 10% perchloric acid. After

(18) Melting points were taken on a Fisher-Johns block and are uncorrected. Ultraviolet, ir, and nmr spectra were determined on Beckman DK-1, Baird Model 455, and Varian A-60 instruments, respectively. Tlc was done on Brinkman silica gel F_{254} plates, and the spots were visualized with an iodine chamber. All samples for which analytical data are reported showed a single spot. The nmr spectra were run in $CDCl_3$ unless otherwise specified.

cooling, the water was decanted from the gum, which crystallized on scratching with ethanol to give 6.0 g (30%) of yellow solid, mp 156–160°. Two recrystallizations from ethanol gave the analytical sample: mp 160–163°; ν_{max}^{Nujol} 1605, 1745 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}ClNO_7$: C, 55.14; H, 5.85; Cl, 8.56. Found: C, 55.35; H, 5.84; Cl, 8.59.

Although subsequent work showed **10b** to be a mixture, no tlc solvent system was found which resolved the material into two spots.

Keto Salt 10d (X = ClO_4).—A solution of 8.3 g (0.02 mol) of bromo salt **10a** (X = Br) in 500 ml of acetonitrile was treated with a solution of 6.9 g (0.046 mol) of silver nitrate in 300 ml of acetonitrile. An immediate precipitate of silver bromide formed. The slurry was stirred in the dark at room temperature for three days. The silver bromide was filtered (7.52 g, 94%), and the filtrate concentrated to a dark oil. This was taken up in 100 ml of water, and a little dilute hydrochloric acid added to precipitate any remaining silver. After filtration, the clear filtrate was treated with 25 ml of 10% perchloric acid. The oily precipitate crystallized on scratching to give 5.0 g (68%) of yellow solid, mp 175–180°. A sample was recrystallized twice from methanol: mp 182–184°; ν_{max}^{Nujol} 1590, 1610, 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; N, 3.79; Cl, 9.59. Found: C, 55.21; H, 5.35; N, 3.64; Cl, 9.74.

Bromo Salt 12a (X = Br).—**12a** was prepared in the way described for bromo salt **10a** (X = Br) in 95% yield. The product was recrystallized from ethanol–ether for analysis: ν_{max}^{Nujol} 1620, 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{27}Br_2NO_3$: C, 50.32; H, 5.43; Br, 31.98. Found: C, 50.06; H, 5.53; Br, 31.94.

On tlc (1-butanol–acetic acid–water, 5:2:3), the analytical material showed two spots, R_f 0.1 and 0.2, in a ratio of *ca.*1:1.

Acetoxy Salt 12b (X = ClO_4).—**12b** was prepared as described for **10b** (X = ClO_4) in 10% yield. The crude product was recrystallized twice from ethanol: mp 173–175°; ν_{max}^{Nujol} 1550, 1600, 1735 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}ClNO_9$: C, 55.26; H, 6.05; Cl, 7.09. Found: C, 55.20; H, 6.01; Cl, 7.19.

Keto Salt 12d (X = ClO_4).—**12d** was prepared in 54% yield in the way described for **10d**. The product was recrystallized from methanol for analysis: mp 160–162°; ν_{max}^{Nujol} 1605, 1730 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}ClNO_8$: C, 55.33; H, 5.75; N, 3.07; Cl, 7.78. Found: C, 55.15; H, 5.62; N, 3.36; Cl, 7.92.

Hydroxy Bases 11c, Isomers A, B, C. By Reduction and Hydrolysis of 10b.—A solution of 11.0 g (0.0265 mol) of 11-bromo salt **10a** in 250 ml of acetic acid was mixed with a solution of 5.5 g (0.056 mol) of fused potassium acetate in 50 ml of acetic acid. The mixture was stirred for 2 days at room temperature. The mixture was evaporated to dryness, and the residue taken up in 200 ml of water and 300 ml of ethanol. Potassium borohydride (10 g) was added in portions over 1 hr at 5°. The mixture was stirred for 1 hr, then diluted with 50 ml of 20% sodium hydroxide solution, and refluxed for 1 hr. The ethanol was removed by distillation, and the oil was extracted with methylene chloride. The organic phase was washed with water, dried, and concentrated to 7.8 g of an orange semisolid residue. This was slurried in acetonitrile and filtered to give 1.6 g of off-white solid, mp 176–180°. This is almost pure isomer B.

The mother liquor was concentrated to an oil and chromatographed on 500 g of neutral alumina. The column was washed with benzene and eluted with 1 l. of anhydrous ether to give 1.8 g of yellow oil. This material showed no hydroxyl in the ir spectrum and was not investigated further. Elution with 1.5 l. of 1% ethanol in ether afforded 0.7 g of yellow oil which solidified to give isomer C mixed with a trace of isomer B. Further elution with 3% ethanol in ether gave 0.2 g of mixed isomers B and C. Elution with 8% ethanol in ether then gave 0.6 g of pure isomer A.

The solid eluted with 1% ethanol in ether was recrystallized from ethyl acetate to give pure isomer C: mp 171°; $\nu_{max}^{CH_2Cl_2}$ 2760, 2820 (Bohlmann), 2840, 3620 cm^{-1} (free OH, concentration independent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.41; H, 8.33; N, 4.95.

Isomer B, obtained by direct crystallization, was recrystallized for analysis from benzene: mp 189–190°; $\nu_{max}^{CH_2Cl_2}$ 2730, 2740, 2780 (Bohlmann), 3280–3480 cm^{-1} (bonded OH, concentration independent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.56; H, 8.52; N, 4.99.

Isomer A, obtained from the column by elution with 8% ethanol in ether, was recrystallized from benzene–Skellysolve C for analysis: mp 176–177°; $\nu_{max}^{CH_2Cl_2}$ 3623, 3130–3450 cm^{-1} (free and bonded OH, concentration dependent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C 74.69; H, 8.48; N, 5.12. Found: C, 74.47; H, 8.45; N, 5.34.

On tlc (50:50 ethyl acetate–acetone), isomers A, B, and C migrated as sharp, round spots of R_f 0.1, 0.5, and 0.6, respectively.

Hydroxy Bases 11c Isomers A and B. By Reduction of 10d.—A solution of 0.5 g of **10d** (X = ClO_4) in 25 ml of methanol was treated with 0.5 g of potassium borohydride in portions over a 1-hr period. The solution was left for 1 hr, then poured into water. The product was filtered to give 0.3 g of white solid, mp 135–145°. By tlc (see previous experiment), this material was shown to be a mixture of isomers A and B.

Hydroxy Base 13c. By Reduction of 12d.—A solution of 17.1 g of **12d** (X = ClO_4) in 1 l. of methanol was reduced as described in the previous experiment with 10 g of potassium borohydride. The methanol was evaporated, and residue was partitioned between water and ether. The ether was washed, dried, and concentrated to 12.7 g (94% yield) of off-white solid, mp 137–142°.

Recrystallization from acetonitrile furnished the analytical sample: mp 149–150°; $\nu_{max}^{CCl_4}$ 2740, 2830 (Bohlmann), 2840, 3622 cm^{-1} (free OH, concentration independent).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.16; H, 8.22; N, 4.13.

Registry No.—**2**, 17413-16-0; **4**, 17413-33-1; **4 HBr**, 17413-17-1; **5**, 17413-18-2; **5** 2HCl, 17413-19-3; **7**, 17413-34-2; **8**, 17413-20-6; **9**, 17413-21-7; **9** 2HBr, 17413-22-8; **10a** (X = Br), 17413-23-9; **10b** (X = ClO_4), 14713-24-0; **10d** (X = ClO_4), 17413-35-3; **11a**, 17413-25-1; **11c** (isomer A), 17413-26-2; **11c** (isomer B), 17413-27-3; **11c** (isomer C), 17413-28-4; **12a** (X = Br), 17413-29-5; **12b** (X = ClO_4), 17448-00-9; **12d** (X = ClO_4), 17413-30-8; **13c**, 17413-31-9; **13e**, 17413-32-0.

Acknowledgment.—The authors wish to thank Professor E. L. Eliel for his helpful suggestions. We also thank Mr. A. D. Lewis and the members of his analytical and physical chemical section, Mrs. Unni Zeek, and Dr. R. Puchalski, for the microanalyses and spectra.