2-(4-Piperidyl)ethanal and 3-(4-piperidyl)propanal

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The title aminoaldehydes were synthesized by *N*-acetylation of the corresponding amino-alcohols, Kornblum oxidation to amidoaldehydes, formation of the dimethyl acetals, alkaline amide hydrolysis, and finally acidic acetal hydrolysis. Infrared, ultraviolet, and nuclear magnetic resonance spectral examination indicates that, in solution, the aminoaldehyde hydrochlorides exist in equilibrium with *gem*-diols or hemiacetals, depending upon the solvent, but that the free bases are reversibly converted into dimeric enamines, to which structures are tentatively assigned. No evidence could be obtained for the presence of monomeric bicyclic carbinolamine tautomers of either the free amines or their salts.

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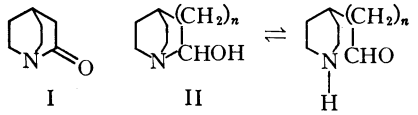
Bridged-ring bicyclic lactams with the nitrogen at a bridgehead position, e.g. 2-quinuclidone (I), are of interest as subjects for a study of the Bredt rule and the steric requirements for amide resonance (1, 2). Only within recent years have compounds of this type been prepared (3–6), although several authors have commented on their nonappearance in reaction mixtures which might have produced them (1, 7–11). As a result of steric inhibition of resonance, these compounds should have more ketonic character than simple lactams. Thus they should undergo nucleophilic attack with relative ease, and synthetic approaches to them need to minimize their exposure to nucleophiles. One such possible synthesis seemed to be through oxidation of carbinolamines such as II (cf. ref. 5). We therefore set out to learn if aminoaldehydes such as III would exist to any extent as their carbinolamine tautomers. Two representative examples (III*a* and III*b*) were prepared, but no evidence for an appreciable degree of carbinolamine formation was obtained.



I II III*a* $n=1$ III*b* $n=2$

The synthesis of the aminoaldehydes was initiated from the corresponding amino-alcohols IV. It was anticipated (correctly) that self-catalyzed aldol condensation or enamine formation would make purification of the aminoaldehydes difficult, if not impossible, and thus we felt that the reaction by which they were ultimately produced should be one in which by-product formation was minimal. Direct oxidation of the aminoalcohols was therefore not explored, but sequences were examined which culminated in the liberation of either the free amine or the free aldehyde under the mildest possible conditions in the presence of the other function. These sequences involved a series of steps which alternately protected the two functions.

O,N-Diacetylation of the aminoalcohol followed by selective saponification of ester V*a* or by acidic methanolysis of ester V*b* produced the amidoalcohol VI in each series. Surprisingly, although the amido-alcohol VI*a* was the sole product from the alkaline hydrolysis of the acetoxyamide V*a*, the homologous acetoxyamide V*b* was converted into a mixture of hydroxyamide, acetoxyamine, aminoalcohol, and acetoxy-amide under these conditions. On the other hand, acidic methanolysis of V*b* produced only the hydroxyamide VI*b*. Kornblum oxidation (12) of each amidoalcohol *p*-tol-uenesulfonate gave the amidoaldehyde VII in a good yield, provided that scrupulously dry dimethyl sulfoxide was used and the reaction time at an elevated temperature was held to the necessary minimum (10

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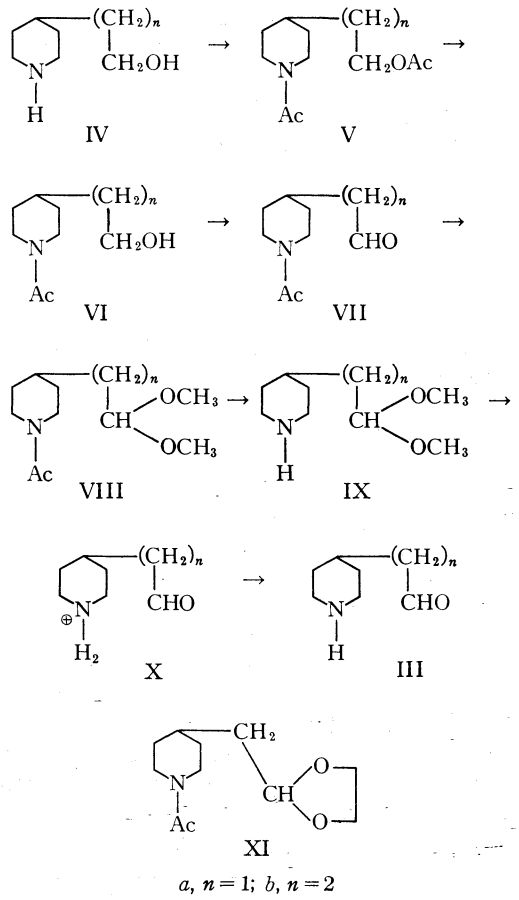
min for our tosylates). If these precautions were not taken, low and variable yields of aldehyde resulted.[3]



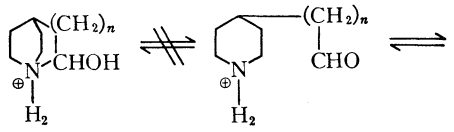
IV V VI VII VIII IX X III XI

a, $n = 1$; *b*, $n = 2$

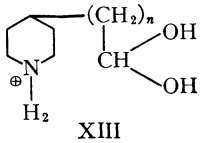
The aldehydes were protected as their dimethyl acetals VIII before saponification, which thus gave the aminoacetals IX in a moderate yield. The ethylene glycol acetal XI served equally well as a protecting group during amide hydrolysis, but was not preferred because subsequent acidic hydrolysis gave a product from which ethylene glycol was difficult to remove. Hydrolysis of the amino dimethyl acetals IX yielded the aminoaldehyde hydrochlorides X as glasses contaminated with only ammonium chloride (from neutralization of the excess hydrochloric acid), so far as nuclear magnetic resonance (n.m.r.) analysis could detect.

Before the question of aminoaldehyde–carbinolamine tautomerism in the free bases themselves was attacked, it was of interest to ascertain to which tautomeric form the salts corresponded; therefore, the hydrochlorides as well as the free bases were subjected to considerable spectral examination. Unfortunately, we were unable to obtain purified samples of the salts for this study. Attempts to free the aminoaldehyde hydrochloride X*a* from ammonium chloride by selectively dissolving the hydrochloride in propanol or butanol produced the propyl or butyl acetals, as indicated by the n.m.r. spectra of the products. No other solvent was found which would separate the hydrochloride from ammonium chloride and which could be removed completely at room temperature, and the salts underwent extensive decomposition at elevated temperatures. Solvents less polar than alcohols, such as ethyl acetate or chloroform, did not dissolve the aminoaldehyde hydrochloride, and all the more polar solvents dissolved both the hydrochloride and ammonium chloride. We were unable to induce the hydrochlorides to crystallize, and attempts to find anions which would form crystalline salts, either by metathesis of the hydrochloride or by using acids other than hydrochloric acid for the acetal hydrolysis, produced glassy salts in every instance. Since no method for obtaining purified samples of the salts could be developed, the examination of their structure was carried out on samples of the noncrystalline hydrochlorides contaminated with ammonium chloride. These crude hydrochlorides were characterized spectrally, and in no case was evidence obtained for major contamination other than ammonium chloride. Furthermore, each aminoaldehyde hydrochloride (X*a* or X*b*) was acetylated by acetic anhydride and sodium acetate in aqueous hydrochloric acid to give the amidoaldehyde VII*a* or VII*b* in excellent yield and high purity. Clearly, no unanticipated gross structural change occurred during hydrolysis of the acetals.

[3]Professor Kornblum subsequently informed us that he, too, had found these precautions necessary. We are grateful to him for information about the procedure before its publication.



XII X



XIII

a, $n=1$; *b*, $n=2$

Nuclear magnetic resonance and ultraviolet spectral analysis indicates that, in aqueous solution, the aminoaldehyde hydrochlorides X exist in equilibrium with their hydration products, the *gem*-diols XIII, but *not* with the carbinolamine salts XII. The n.m.r. spectra in deuterium oxide solution show a triplet near 0.5 τ (J = 2 c.p.s.) and a triplet near 5 τ (J = 6 c.p.s.). These triplets are equal in area, and their combined area corresponds to that expected for one proton per molecule. Both its chemical shift and its coupling constant indicate that the 0.5 τ resonance is due to aldehyde. The 5 τ resonance corresponds to a proton on a saturated carbon holding two electronegative atoms; this is considered to be the C*H*-$(OD)_2$ of *gem*-diol XIII rather than the C*H*OD($\overset{+}{N}$D) of carbinolamine hydrochloride XII for several reasons. First, this spectrum is completely analogous to that of propionaldehyde in deuterium oxide (0.45 and 5.10 τ triplets), and the aldehyde–diol equilibrium constant is known to be about 1 in that case (13). Secondly, the C*H*OD($\overset{+}{N}$D) resonance of the carbinolamine salts XII should be the X parts of ABX spectra; because of the different dihedral angle between that carbon and the adjacent methylene group in the [2.2.2] and [3.2.2] bicyclic systems, one would expect different spin-coupling patterns in the resonances for the two compounds rather than the identical triplets which are observed. Thirdly, there is no reason to expect the aldehyde–diol equilibrium X $\rightleftharpoons$ XIII to be greatly different from those of simple aldehydes (ca. 50:50 (13)) even if the aminoaldehyde is also in equilibrium with the carbinolamine. Consequently, an amount of *gem*-diol resonance equal in area to the aldehydic resonance is to be expected in the spectrum, and must be taken as the 5 τ triplet. Since the 5 τ triplet and the aldehyde triplet total one proton, there cannot be a significant amount of the carbinolamine salt in the equilibrium mixture.

Ultraviolet spectroscopy also shows that, in aqueous solution, only 50% of the aminoaldehyde salt exists as free aldehyde, in analogy with model aldehydes for which carbinolamine formation is impossible (Table I). It was assumed that the extinction coefficient of the aldehyde n $\rightarrow$ π^* absorption would be similar to those of the model compounds, since all four of the models showed very similar extinction coefficients (22 $\pm$ 1.5) in dioxane solution (where no reagent for carbonyl addition reactions is present). In ethanol, the model aldehydes slowly reach equilibrium with their hemiacetals, but the rate of approach to this equilibrium can be followed by the decrease in the optical density, and the true extinction coefficient of the aldehyde (ϵ_0) is obtained by extrapolation. These extinction coefficients (21 $\pm$ 1.7) are identical with those in dioxane. Consequently, it seems unlikely that the values would be significantly different in water (the only solvent in which the aminoaldehyde hydrochlorides could be examined conveniently). This is supported by the extinction coefficient observed for propanal in water (9.9), where other data (13) show that only 50% of the propanal exists as such. The rate of hydration of our aldehydes was so rapid that only the equilibrium value of the extinction coefficient could be observed. This was about 11 for the model compounds and for the aminoaldehyde hydrochlorides X*a* and X*b*, indicating in both cases the presence of about 50% aldehyde and 50% other material, which consequently must be the *gem*-diol.

The free aminoaldehydes were prepared by neutralization of aqueous solutions of the salts with excess 0.1 *N* sodium hydroxide, followed by immediate extraction of the organic material with chloroform. Evaporation yielded a solid containing some

TABLE I

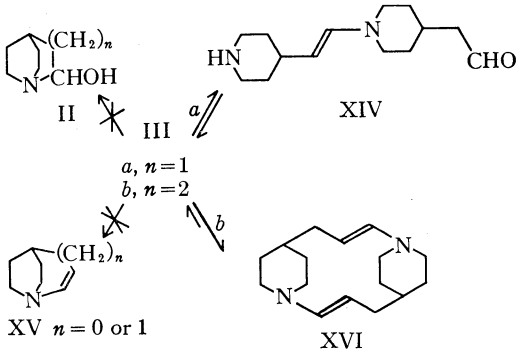
Ultraviolet absorption of aldehydes

	Dioxane		Water		Ethanol		
	λ_{max} (mμ)	ϵ	λ_{max} (mμ)	ϵ_∞*	λ_{max} (mμ)	ϵ_0*	ϵ_∞*
Propanal	288	20.1	285	9.9	286	20.5	3.0
Isopentanal	292	21.9	285	8.4	286	20.5	5.8
N-Acetyl aldehyde VII*a*†	294	21.3	285	12.3	290	21.1	2.8
Aminoaldehyde hydrochloride X*a*			285	10.2			
N-Acetyl aldehyde VII*b*†	291	23.3	282	14.6	288	23.0	4.6
Aminoaldehyde hydrochloride X*b*			280	12.4			

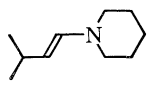
*In ethanol, ϵ_0 is the value for the extinction coefficient of the aldehyde before hemiacetal formation has started (obtained from the data by extrapolation); ϵ_∞ is the apparent extinction coefficient at equilibrium.
†The extinction coefficient has been corrected for end absorption from the amide group.

oily material in the case of the aminoaldehyde III*a*, and a gum for the aminoaldehyde III*b*. These products were very sensitive to air and heat. In both cases they darkened rapidly, and many new peaks appeared in the aromatic region of their n.m.r. spectra and as far downfield as 0.80 τ. With this limitation, no further purification was possible; thus structural examination was again limited to the freshly prepared crude material.

The "aminoaldehydes" obtained in this way are readily reconverted into their salts by extraction of the chloroform solutions with a slight excess of 5% hydrochloric acid. The crude hydrochlorides, which can be isolated in a 70% yield, have n.m.r. spectra which are nearly identical with those of the starting salts, except for the presence of very weak absorption arising from decomposition products. The large amounts of aminoaldehyde hydrochlorides which are isolated provide evidence that very little irreversible change (polymerization, etc.) takes place on formation of the free bases.



Infrared spectra of freshly prepared "aminoaldehydes" in chloroform solution show no hydroxyl absorption, indicating that no significant amount of carbinolamine II is present. However, both samples have absorption at 5.8 μ, arising from the aldehyde carbonyl, and at 6.1 μ, the position characteristic of an aldehyde enamine (6.06 μ for the model enamine XVII (14)). Comparison of the intensities of the 5.8 and 6.1 μ absorptions, assuming that the carbonyl and enamine extinction coefficients in the aminoaldehyde samples are the same as those of the amidoaldehyde VII*b* and the enamine XVII, respectively, gave an *approximate* ratio of enamine to aldehyde groups of 3:5 in the aminoaldehyde III*a*, and 6:1 in the aminoaldehyde III*b*. Thus it appears that some enamine formation occurs in both cases, but in the case of III*b* it is almost complete.



XVII

The n.m.r. spectra of the two "aminoaldehydes" also provide evidence that enamine formation occurs with both compounds, but to a much greater extent with III*b* than with III*a*. Both samples show resonance in the vinyl proton region: a doublet near 4.2 τ and a multiplet near 5.7 τ. In both cases this vinyl resonance pattern is similar to that of the model enamine XVII, except for differences in multiplicity of the β-vinyl proton resonance in the case of III*b*, as would be expected for spin

coupling with two allylic protons rather than one. In all three cases the coupling constant between the vinyl protons is 15 c.p.s. Consequently, the enamines are probably *trans* and cannot be bicyclic monomers such as XV, a conclusion which also follows from their facile hydrolysis to the aminoaldehyde salts X (17). The spectrum of III*a*, but not that of III*b*, contains an aldehyde proton resonance (0.33 τ) in addition to the enamine resonance. Unfortunately, these spectra were determined on relatively dilute solutions, and the resulting noise level precluded the detection of very weak resonances and decreased the accuracy of the integration. However, within these limits, the ratio of the aldehyde to the enamine α-proton signal in the spectrum of III*a* was approximately 50:50, whereas comparison of the area of the enamine α-proton resonance of III*b* with the rest of the spectrum showed that it corresponded to about 80% of the intensity expected for one proton per molecule. Thus, about half of the aldehyde groups in the sample of III*a* have been converted into enamines, whereas nearly all of those derived from III*b* have undergone a similar transformation. In neither aminoaldehyde spectrum does there appear any resonance which must be attributed to the carbinolamine.

The apparent molecular weights of the "aminoaldehydes" were determined osmometrically in chloroform solution. For aminoaldehyde III*a* a value of 210 was found, and for III*b* a value of 270. These approximate molecular weights are in both cases substantially higher than those expected for the monomeric structures III*a* (formula weight 127) and III*b* (formula weight 141), which is consistent with the spectral evidence for intermolecular enamine formation. Inasmuch as they are not greater than the values expected for dimers, however, the molecular weight data indicate that most of the material has not reached a very high state of polymerization. The near absence of aldehyde absorption in the infrared and n.m.r. spectra of III*b* eliminates the presence of substantial amounts of monomer III or a linear dimer analogous to XIV, and the absence of *cis*-vinyl coupling constants indicates the absence of large amounts of a bicyclic enamine monomer such as XV. Inasmuch as monomeric species are nearly absent, the molecular weight data require that little of the material exists as a greater than dimeric aggregate. Consequently, the tricyclic dimeric structure XVI is tentatively assigned to the major species present in the solution. An analogous structure for the lower homologue derived from III*a* would be of much higher energy, for, unlike XVI, it would require both piperidine rings to exist as twist conformations having all the bridging vinyl groups located axially. The molecular weight data indicate that a substantial portion of III*a* remains as the open monomer; the spectral data suggest that most of the rest exists as linear dimeric (XIV), trimeric, and perhaps polymeric species, although the data at hand do not allow the approximate amounts of these to be determined. There is no evidence, however, for the presence of significant quantities of bicyclic carbinolamines in either case.

EXPERIMENTAL

Infrared spectra were obtained on Perkin–Elmer models 21, 137, and 137G spectrophotometers, ultraviolet spectra were taken with a Cary model 14 ultraviolet spectrophotometer, and n.m.r. spectra were obtained at 31° from dilute solutions in deuteriochloroform or deuterium oxide with a Varian A-60 spectrometer. Resonance positions were determined relative to tetramethylsilane or dioxane (6.30 τ (15)) as internal standard. First-order multiplets in spectra are described by the use of the abbreviations s for singlet, d for doublet, and t for triplet; m is used for multiplets not described by other symbols. Gas chromatograms were run at 200° on an F and M model 609 hydrogen flame ionization chromatograph with nitrogen as the carrier gas, using a 6 ft $\times$ $\frac{1}{4}$ in. steel column of either 10% silicone rubber on Chromosorb W or 5% silicone rubber on Haloport F. Compositions of mixtures were estimated as the ratios of the peak areas. Melting points were taken in open capillary tubes and are uncorrected. Microanalyses were carried out by Alfred Bernhardt, Mülheim (Ruhr), Germany (designated B), or Midwest Microlab, Inc., Indianapolis, Indiana (designated M).

4-(2-Acetoxyethyl)-N-acetylpiperidine (Va)

A mixture of 30 ml (32 g, 0.32 mole) of acetic anhydride and 17.48 g (0.135 mole) of 4-(2-hydroxyethyl)piperidine (IV*a*)[4] was refluxed for 24 h and then distilled under reduced pressure to give 26.53 g

[4]We express our gratitude to Dr. F. E. Cislak of the Reilly Tar and Chemical Corporation for a generous gift of IV*a*.

(93%) of the acetoxyamide V*a* as a colorless oil, b.p. 138–143° at 0.5 mm; $\lambda_{max}^{CHCl_3}$ 5.77 and 6.15 μ; n.m.r. ($CDCl_3$) 7.97 (s), 7.93 (s), and 5.87 τ (t, J = 6 c.p.s.). Redistillation of the oil yielded the analytical sample, b.p. 108° at 0.13 mm.

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.98; N, 6.56. Found (B): C, 61.84; H, 8.92; N, 6.70.

4-(3-Acetoxypropyl)-N-acetylpiperidine (Vb)

Crude 4-(3-hydroxypropyl)piperidine hydrochloride, obtained by hydrogenation of 51.1 g (0.372 mole) of 4-(3-hydroxypropyl)pyridine in absolute ethanolic hydrogen chloride, removal of the platinum catalyst by filtration, and evaporation of all low-boiling materials *in vacuo*, was treated with 250 ml of acetic anhydride as in the previous experiment to give 80.25 g (95%) of the amidoacetate V*b* as a colorless oil, b.p. 130–150° at 0.5 mm; $\lambda_{max}^{CHCl_3}$ 5.77 and 6.14 μ; n.m.r. ($CDCl_3$) 7.93 (s), 7.97 (s), and 5.93 τ (t, J = 6 c.p.s.). The analytical sample was prepared by redistillation, b.p. 132–135° at 0.1 mm.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found (B): C, 63.24; H, 9.06; N, 6.30.

4-(2-Hydroxyethyl)-N-acetylpiperidine (VIa)

A solution of 398.4 g (1.24 moles) of 4-(2-acetoxyethyl)-*N*-acetylpiperidine (V*a*) (b.p. 135–165° at 0.7–3.0 mm) and 75 g (1.9 moles) of sodium hydroxide in 2.3 l of methanol was refluxed for 48 h, concentrated *in vacuo* until the residue became semisolid, treated with methylene chloride, and filtered, and the filtrate was concentrated *in vacuo*. The concentrate was repeatedly dissolved in methylene chloride, filtered, and concentrated until no solid precipitated from the residual oil after evaporation. The residual oils were distilled to give 264.2 g (83%) of the amidoalcohol VI*a* as a colorless oil, b.p. 173–183° at 2.0–2.5 mm; $\lambda_{max}^{CHCl_3}$ 2.90 and 6.18 μ; n.m.r. ($CDCl_3$) 7.93 (s) and 6.30 τ (t, J = 6 c.p.s.). The analytical sample was prepared by redistillation and had b.p. 155–156° at 0.8 mm.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.11; H, 10.01; N, 8.18. Found (B): C, 63.08; H, 9.97; N, 8.25.

4-(3-Hydroxypropyl)-N-acetylpiperidine (VIb)

A solution of 79.34 g (0.348 mole) of 4-(3-acetoxypropyl)-*N*-acetylpiperidine (V*b*) (b.p. 130–150° at 0.5 mm) and 5 g of *p*-toluenesulfonic acid in 500 ml of methanol was refluxed for 73 h, during which all materials boiling below 63° were distilled. The mixture was cooled, 10 g of potassium carbonate was added, and the mixture was dissolved in methylene chloride, filtered, and distilled to give 58.35 g (90%) of the amidoalcohol VI*b* as a colorless viscous oil, b.p. 140–158° at 1.5 mm; $\lambda_{max}^{CHCl_3}$ 2.90 and 6.14 μ; n.m.r. ($CDCl_3$) 6.38 (t, J = 6 c.p.s.) and 7.92 τ (s). Redistillation gave the analytical sample, b.p. 115–118° at 0.09 mm.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found (B): C, 64.87; H, 10.18; N, 7.54.

4-(2-Oxoethyl)-N-acetylpiperidine (VIIa)

A stirred solution of 25.9 g (0.151 mole) of 4-(2-hydroxyethyl)-*N*-acetylpiperidine (VI*a*) (b.p. 145–155° at 0.5–0.7 mm) in 100 ml of pyridine at 0° was treated with 35 g (0.18 mole) of *p*-toluenesulfonyl chloride, stirred at 0° for 2 h, allowed to warm to room temperature, added to 100 ml of water, and extracted with three 50 ml portions of methylene chloride. These were combined and washed with 14% aqueous hydrochloric acid until the wash solution was acidic, then with excess 5% sodium bicarbonate solution, and finally with 50 ml of water. The organic layer was dried with sodium sulfate and concentrated at reduced pressure to yield 41.9 g (88%) of the crude tosylate as a viscous oil; λ_{max}^{film} 6.15 and 8.55 μ; n.m.r. ($CDCl_3$) 7.97 (s), 7.58 (s), and 5.93 τ (t, J = 6 c.p.s.). The n.m.r. spectrum contained no other triplet near 6.3 τ.

The conditions for the oxidation were a modification of those of Kornblum (12). The crude tosylate (41.9 g, 0.129 mole) was added to a solution of 13 g (0.15 mole) of sodium bicarbonate in 100 ml of dimethyl sulfoxide which had been dried by distillation from calcium hydride, and the resulting mixture, stirred under a nitrogen atmosphere, was immersed for 15 min in an oil bath which had been preheated to 150°. The mixture was cooled immediately in an ice bath and added to 100 ml of a saturated salt solution; then enough water was added to dissolve all the solids. This solution was extracted with three 50 ml portions of methylene chloride, which were washed with 50 ml of a saturated salt solution, dried with sodium sulfate, filtered, and concentrated at reduced pressure. Distillation of the crude product gave 13.5 g (62% based on the crude tosylate) of aldehyde VII*a*, b.p. 125–140° at 0.4–0.8 mm; $\lambda_{max}^{CHCl_3}$ 5.80 and 6.15 μ; n.m.r. ($CDCl_3$) 0.28 (t, J = 2 c.p.s.) and 7.95 τ (s). Gas–liquid chromatographic analysis indicated that the purity of this material ranged from 60 to 90%, depending on the sample.

The compound could not be purified further by redistillation. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from alcohol as yellow granules, m.p. 178–179°.

Anal. Calcd. for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05. Found (M): C, 51.74; H, 5.65; N, 19.76.

The amidoaldehyde was also prepared by acetylation of the aminoaldehyde III*a*. A solution of 1.99 g (0.115 mole) of the amino dimethyl acetal IX*a* (b.p. 42–52° at 0.6 mm) in 80 ml of water was acidified with 5% hydrochloric acid to a pH of less than 2. After 4 h the reaction mixture was cooled to 0°; 10 ml of concentrated hydrochloric acid, 16 ml of acetic anhydride, and 16 g of sodium acetate trihydrate were added rapidly; and the mixture was stirred at 0° for 45 min. The solution was basified with sodium carbonate, extracted with methylene chloride, dried with magnesium sulfate, and evaporated *in vacuo* to yield 1.90 g (98%) of a crude oil. This was distilled in a microstill at an oil-bath temperature of 145° and 0.2 mm. The spectra of this sample were identical with those of the material described above; in addition, $\lambda_{max}^{dioxane}$ 294 mμ (ϵ 22.9).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.27. Found (B): C, 63.79; H, 8.95; N, 8.24.

4-(3-Oxopropyl)-N-acetylpiperidine (VIIb)

A 20.07 g (0.108 mole) sample of 4-(3-hydroxypropyl)-*N*-acetylpiperidine (VI*b*) (b.p. 140–158° at 1.5 mm) was converted into the aldehyde by the above procedure. The crude tosylate, obtained in a 99% yield, showed λ_{max}^{film} 6.1 and 8.5 μ; n.m.r. ($CDCl_3$) 7.97 (s), 7.57 (s), and 5.95 τ (t, J = 6 c.p.s.). The aldehyde, b.p. 130–150° at 1.0 mm, was obtained in a 61% yield after distillation, and was found to be approximately 65% aldehyde VII*b* by n.m.r. and gas–liquid chromatographic analysis; $\lambda_{max}^{CHCl_3}$ 5.80 and 6.15 μ; $\lambda_{max}^{dioxane}$ 291 mμ (ϵ 23.8); n.m.r. ($CDCl_3$) 7.93 (s) and 0.22 τ (t, J = 2 c.p.s.).

An analytical sample could not be prepared by redistillation or by preparation from the amino dimethyl acetal IX*b*, as was done in the preceding series. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from water–methanol to yield platelets, m.p. 115.5–116.5°.

Anal. Calcd. for $C_{16}H_{21}N_5O_5$: C, 52.88; H, 5.82; N, 19.28. Found (M): C, 53.13; H, 5.95; N, 19.14.

Ethylene Glycol Acetal of 4-(2-Oxoethyl)-N-acetylpiperidine (XI)

The procedure was adapted from Dauben *et al.* (16). To a solution of 17.5 g (0.103 mole) of 4-(2-oxoethyl)-*N*-acetylpiperidine (VII*a*) (b.p. 125–140° at 0.4–0.8 mm) in 100 ml of 2-ethyl-2-methyl-1,3-dioxalane was added a trace of *p*-toluenesulfonic acid, and the solution was refluxed for 21 h. The mixture was cooled, excess solid potassium carbonate was added, and all low-boiling compounds were removed at reduced pressure. The residue was dissolved in methylene chloride, filtered, and distilled at reduced pressure to yield 17.50 g (79%) of colorless amidoacetal XI, b.p. 131–143° at 0.7 mm; $\lambda_{max}^{CHCl_3}$ 6.15, 8.79, and 9.65 μ; n.m.r. ($CDCl_3$) 6.10 (m), 5.08 (t, J = 5 c.p.s.), and 7.93 τ (s). No analytical sample could be prepared because of partial decomposition of the compound at distillation temperatures, yielding enol ethers.

Ethylene Glycol Acetal of 4-(2-Oxoethyl)piperidine

To 15.0 g (0.070 mole) of the ethylene glycol acetal of 4-(2-oxoethyl)-*N*-acetylpiperidine (XI) (b.p. 131–143° at 0.7 mm) was added 4.5 g (0.11 mole) of sodium hydroxide in 100 ml of water, and the mixture was refluxed for 65 h. The sample was saturated with potassium carbonate, extracted with methylene chloride, dried with sodium sulfate, and distilled at reduced pressure to yield 6.9 g (57%) of the aminoacetal as a colorless liquid, b.p. 78–80° at 0.4 mm; $\lambda_{max}^{CHCl_3}$ 2.98 (weak), 8.75, and 9.67 μ; n.m.r. ($CDCl_3$) 6.12 (m) and 5.08 τ (t, J = 5 c.p.s.). The compound was extremely hygroscopic, and consequently was analyzed as its picrate, m.p. 148–149° (decomp.) after crystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{20}N_4O_9$: C, 45.00; H, 5.04; N, 14.00. Found (M): C, 45.14; H, 5.15; N, 13.99.

Dimethyl Acetal of 4-(2-Oxoethyl)-N-acetylpiperidine (VIIIa)

A solution of 12.50 g (0.074 mole) of 4-(2-oxoethyl)-*N*-acetylpiperidine (VII*a*) (b.p. 125–140° at 0.4–0.8 mm) and a trace of *p*-toluenesulfonic acid in 1.5 l of methanol was refluxed for 48 h, excess sodium carbonate was added, and the low-boiling compounds were distilled at reduced pressure. The residue was dissolved in methylene chloride, filtered, and distilled at reduced pressure to give 10.21 g (64%) of the acetal VIII*a* as a colorless oil, b.p. 135–137° at 0.8 mm; $\lambda_{max}^{CHCl_3}$ 6.15, 8.90, and 9.55 μ; n.m.r. ($CDCl_3$) 5.53 (t, J = 6 c.p.s.), 6.70 (s), and 7.93 τ (s). Redistillation yielded a sample, b.p. 112° at 0.25 mm, which contained a small amount of the vinyl ethers formed by thermal decomposition of the acetal. The decomposition products were observed in the n.m.r spectrum of the sample, and probably account for the poor analytical results.

Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found (B): C, 61.05; H, 9.22; N, 6.62.

Dimethyl Acetal of 4-(3-Oxopropyl)-N-acetylpiperidine (VIIIb)

4-(3-Oxopropyl)-*N*-acetylpiperidine (VII*b*) (b.p. 130–150° at 1.0 mm) was converted into the acetal by the same technique, which gave 60% of the acetal as a colorless oil, b.p. 130–140° at 0.4 mm; $\lambda_{max}^{CHCl_3}$ 6.14, 8.85, and 9.45 μ; n.m.r. ($CDCl_3$) 7.93 (s), 6.68 (s), and 5.63 τ (t, J = 5 c.p,s.). The analytical sample could not be prepared by fractional distillation, since the sample decomposed to yield vinyl ethers.

This amidoacetal was also prepared by refluxing 0.60 g of the amino dimethyl acetal IX*b* for 1 h in 20 ml of benzene, 2 ml of pyridine, and 1 ml of acetic anhydride. The mixture was added to 50 ml of water, saturated with sodium carbonate, extracted with two 10 ml portions of benzene, dried with magnesium sulfate, and distilled in a microstill (oil-bath temperature less than 160° and 0.1 mm) to yield a sample with the same infrared and n.m.r. spectra as those described above. The poor analytical result is probably due to contamination by starting material or enol ethers produced during distillation.

Anal. Calcd. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.10; N, 6.11. Found (B): C, 61.57; H, 9.78; N, 6.49.

Dimethyl Acetal of 4-(2-Oxoethyl)piperidine (IXa)

A solution of 12.53 g (0.0581 mole) of crude undistilled amido dimethyl acetal VIII*a* and 8.5 g (0.21 mole) of sodium hydroxide in 500 ml of water was refluxed for 63 h, cooled, saturated with potassium carbonate, and extracted with ether. The ether solution was dried with magnesium sulfate and distilled, yielding 5.72 g (57%) of the aminoacetal IX*a* as a colorless liquid, b.p. 54–55° at 0.25 mm; $\lambda_{max}^{CHCl_3}$ 8.90 and 9.52 μ; n.m.r. ($CDCl_3$) 5.53 (t, J = 6 c.p.s.) and 6.70 τ (s). The picrate, yellow prisms of m.p. 155° (decomp.), was prepared for analysis.

Anal. Calcd. for $C_{15}H_{22}N_4O_9$: C, 44.89; H, 5.28; N, 13.96. Found (B): C, 44.90; H, 5.65; N, 14.01.

Dimethyl Acetal of 4-(3-Oxopropyl)piperidine (IXb)

The dimethyl acetal of 4-(3-oxopropyl)-*N*-acetylpiperidine (VIII*b*) (b.p. 130–140° at 0.4 mm) was saponified by the same method to yield 45% of the distilled acetal IX*b* as a colorless oil, b.p. 72–78° at 0.4 mm; $\lambda_{max}^{CHCl_3}$ 3.15, 8.90, and 9.50 μ; n.m.r. ($CDCl_3$)

6.68 (s) and 5.65 τ (t, J = 5 c.p.s.). The picrate was prepared in ether and recrystallized from ethyl acetate, yielding yellow needles, m.p. 178–180° (decomp.).

Anal. Calcd. for $C_{16}H_{24}N_4O_9$: C, 46.15; H, 5.81; N, 13.46. Found (B): C, 46.43; H, 5.61; N, 13.28.

4-(ω-Oxoalkyl)piperidine Hydrochlorides (X)

A solution of 0.2 g of the aminoacetal IX*a* or IX*b* in 20 ml of water was acidified to pH 2 or less with 5% hydrochloric acid, held at room temperature for 4 h, and basified with dilute ammonia to pH 8. Water was evaporated in a rotary evaporator at reduced pressure and room temperature to yield white to light-yellow glasses which were readily soluble in water. No further purification was possible because, when the products were left in contact with air or heated slightly, they rapidly darkened, with the formation of decomposition products showing a large amount of n.m.r. absorption in the aromatic and vinyl proton regions. The n.m.r. spectra of the two crude hydrochlorides in deuterium oxide were quite similar. The 4-ethyl compound X*a* had absorption at 0.33 (t, J = 2 c.p.s.) and 4.93 τ (t, J = 6 c.p.s.), whereas the 4-propyl hydrochloride X*b* had absorption at 0.40 (t, J = 2 c.p.s.) and 5.03 τ (t, J = 6 c.p.s.). In both cases the areas under each of the triplets were about equal, and their combined area was equivalent to one proton in comparison with the rest of the spectrum. The ultraviolet spectrum in water for the 4-ethyl compound X*a* showed λ_{max} 284 mμ (ϵ 10.3), and that of the hydrochloride of X*b* showed λ_{max} 280 mμ (ϵ 12.3).

Aminoaldehydes (III)

The crude 4-(ω-oxoalkyl)piperidine hydrochloride of X*a* or X*b* was freshly prepared from 0.2 g of the corresponding aminoacetal IX*a* or IX*b*, dissolved in 20 ml of water, and diluted with 60 ml of 0.1 *N* sodium hydroxide; ther the samples were immediately extracted with chloroform, dried with sodium sulfate, and evaporated to dryness *in vacuo* at room temperature. In the case of the 4-ethyl derivative X*a*, this gave an oily solid, $\lambda_{max}^{CHCl_3}$ 6.1 and 5.8 μ; n.m.r. ($CDCl_3$) 0.33 τ (s). The spectra indicated that about 30% of the material present was in the form of the aminoaldehyde III*a*. No OH absorption was present in the infrared spectrum. The infrared spectrum of the 4-propyl derivative III*b* showed no OH absorption, very little 5.8 μ absorption, and a larger peak at 6.1 μ. The n.m.r. spectrum in $CDCl_3$ showed a doublet centered at 4.20 τ (J = 15 c.p.s.), and a multiplet at ca. 5.75 τ. No further purification of either product was successful because of rapid decomposition, as evidenced by darkening of the material; eventually, even chloroform solutions turned into a gum.

Molecular Weight Determination of the Aminoaldehydes

To 0.1 g of the amino dimethyl acetal IX*a* or IX*b* in 10 ml of water was added 5% hydrochloric acid until the pH was less than 2. After 5 h, 30 ml of 0.1 *N* sodium hydroxide was added, and the solution was extracted with four 6 ml portions of chloroform and dried with magnesium sulfate. The molal concentration of this solution was determined with a Mechrolab model 301A vapor-pressure osmometer. A 10 ml aliquot of the same solution was weighed before and after evaporation to dryness, in order to obtain the weights of both the aminoaldehyde and chloroform in the solution.

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