

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Amine Oxides. VII. The Thermal Decomposition of the N-Oxides of N-Methylazacycloalkanes^{1,2}

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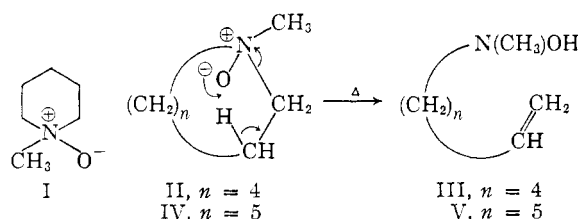
Ring cleavage of the N-oxides of N-methylazacycloalkanes by a thermal elimination reaction does not occur when the ring is six-membered and becomes progressively easier as the ring size is increased from seven to eight atoms. N-Methylpiperidine oxide gave no product from a *cis* β -elimination reaction, while pyrolysis of the homologous N-methylhexamethyleneimine and N-methylheptamethyleneimine oxides led to the unsaturated hydroxylamines in yields of 53 and 79%, respectively. These results support a planar five-membered transition state for the amine oxide pyrolysis. The unsaturated hydroxylamines were converted to unsaturated and saturated secondary amines. The thermal decomposition of a mixture of the *cis* and *trans* isomers of N-methyl- α -pipercoline oxide formed the expected N-methyl-N-5-hexenylhydroxylamine as well as a saturated bicyclic product, formulated as *cis*-N-methyl-3-oxa-2-azabicyclo[3.3.0]octane. A possible mechanism for the formation of this product is presented. The *cis* and *trans* isomers of N-methyl- α -pipercoline oxide have been separated and characterized. Each of the isomers has been pyrolyzed separately and only *trans*-N-methyl- α -pipercoline oxide formed the expected unsaturated hydroxylamine.

The thermal decomposition of aliphatic amine oxides has been shown to provide a method complementary to the Hofmann exhaustive methylation procedure for converting amines to olefins.⁴ This paper reports an extension of the amine oxide pyrolysis to heterocyclic amine oxides containing six-, seven- and eight-membered rings.

There are a number of reports of the decomposition of tertiary amine oxides resulting in the cleavage of five- and six-membered rings.⁵⁻⁸ However, these procedures were based upon the cleavage of di- and tri-alkylhydroxylamines^{5,6} or of tetrahydroisoxazines⁷ and upon oxidative cleavage with potassium dichromate.⁸ The research described in this paper shows that heterocyclic tertiary amine oxides can be thermally decomposed to unsaturated hydroxylamines if the steric configuration of the oxide permits intramolecular *cis* elimination.

N-Methylpiperidine oxide (I) showed a surprising resistance to thermal decomposition. It sublimed readily below 100° under reduced pressure and when heated to 215° decomposed explosively forming volatile decomposition products in low yield in addition to a considerable amount of black residue containing some of the undecomposed amine oxide. The volatile products contained N-methylpiperidine, identified by its picrate, and piperidine itself as shown by gas chromatography and by preparation of the benzenesulfonamide. The amine oxide also was heated in a sealed pressure vessel in a nitrogen atmosphere at 200–240°, and only N-methylpiperidine and piperidine were detected as products.

Attention was then turned to the seven- and eight-membered ring amines. N-Methylhexamethyleneimine oxide (II) decomposed smoothly



at 165° forming a fragrant basic liquid. Elemental analysis of both the base and its crystalline hydrogen oxalate was consistent with the empirical formula C₇H₁₅NO. Absorption bands characteristic of a vinyl group and a hydroxyl group were observed in the infrared spectrum. On attempted redistillation of this product, recovery was always poor, apparently because of its tendency to polymerize. The assigned structure, N-methyl-N-5-hexenylhydroxylamine (III), was confirmed by quantitative hydrogenation in the presence of palladium-on-calcium carbonate catalyst. The infrared spectrum of the reduction product did not contain the bands due to the vinyl group, but still retained absorption in the OH stretching region. An authentic sample of N-methyl-N-*n*-hexylhydroxylamine was synthesized by the pyrolysis of methyl-di-*n*-hexylamine oxide, and was shown to be identical with the hydroxylamine prepared by the hydrogenation of III.

N-Methylheptamethyleneimine also was converted to the oxide IV, which decomposed readily at 135–140°. The product, N-methyl-N-6-heptenylhydroxylamine (V), had an infrared spectrum which was very similar to that of the lower homolog III. On quantitative hydrogenation V absorbed 97.5% of one molar equivalent of hydrogen forming N-methyl-N-*n*-heptylhydroxylamine (VI) as indicated by analysis and by the infrared spectrum.

In order to utilize the amine oxide cleavage of N-methylazacycloheptanes and N-methylazacyclooctanes for degradative studies, it would be advantageous to convert the unsaturated hydroxylamines (such as III and V) to amines. As such they could be subjected once again to the amine oxide elimination reaction (after methylation), or to the Hofmann exhaustive methylation procedure. These transformations can be accomplished by employing different reduction procedures. N-Methyl-N-6-hep-

(1) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

(2) Paper VI in this series, A. C. Cope, E. Ciganek and N. A. LeBel, *THIS JOURNAL*, **81**, 2799 (1959).

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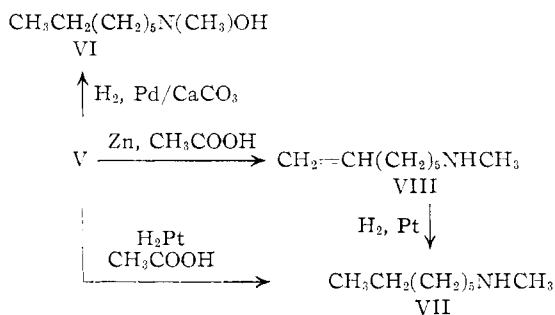
(4) For leading references see A. C. Cope, N. A. LeBel, H. H. Lee and W. R. Moore, *THIS JOURNAL*, **79**, 4720 (1957).

(5) W. Wernick and R. Wolfenstein, *Ber.*, **31**, 1553 (1898).

(6) Ya. Ya. Dodonov, *J. Gen. Chem. U.S.S.R.*, **14**, 960 (1944).

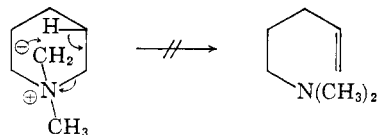
(7) C. H. Rayburn, W. R. Harlan and H. R. Hanmer, *THIS JOURNAL*, **72**, 1721 (1950).

(8) P. J. Scheuer, W. I. Kimoto and K. Ohinta, *ibid.*, **75**, 3029 (1953).



tenylhydroxylamine (V) was hydrogenated in the presence of Adams platinum catalyst in glacial acetic acid. Two molar equivalents of hydrogen was absorbed, and the product was isolated and identified as N-methyl-*n*-heptylamine (VII). The hydrogenolysis of the N-OH bond also can be accomplished without affecting the olefinic linkage, by reduction with zinc and acetic acid. The product (6-heptenylmethylamine, VIII) had infrared maxima indicative of a vinyl group and of an N-H linkage and was converted in good yield to a crystalline picrolonate. The unsaturated amine VIII was hydrogenated in the presence of platinum to N-methyl-*n*-heptylamine (VII).

A pronounced increase in the ease of elimination is noted for N-methyl heterocyclic tertiary amine oxides as the ring size is increased from six to eight. These results represent additional support for the planar quasi five-membered transition state for the amine oxide pyrolysis. For, although molecular models show that the amine oxide oxygen of N-methylpiperidine oxide (I) is in close proximity to a β -hydrogen atom, the preferred planar transition state cannot be attained because of the steric requirements of the six-membered ring. This circumstance is offered as an explanation of the fact that ring fission of I does not occur. The observation of Wittig and Polster⁹ that the N-ylide elimination of N,N-dimethylpiperidinium iodide with phenyllithium fails to take place is similar and suggests a direct analogy between the mechanism of this elimination reaction and the amine oxide decomposition.



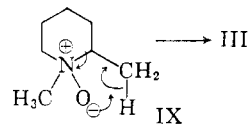
With the homologous seven- and eight-membered ring systems the planar configuration of the transition state can be attained more readily. Similar evidence for a planar quasi six-membered ring in the pyrolysis of esters forming olefins is provided by the finding that pyrolytic cleavage of lactones (the carbonyl oxygen serves a function similar to the amine oxide oxygen) occurs only with seven-membered or larger rings.¹⁰

Examination of molecular models indicates that pyrolysis of N-methyl- α -pipercoline oxide (IX), which contains a β -hydrogen atom attached to the carbon atom of the methyl group, should occur

(9) G. Wittig and R. Polster, *Ann.*, **599**, 13 (1956).

(10) W. J. Bailey, Abstracts of Papers, American Chemical Society, 131st Meeting, Miami, Fla., April 7-12, 1957, p. 44-O.

forming the unsaturated hydroxylamine III, since one of the isomers of IX can attain a planar transition state for *cis* elimination. A somewhat analogous case is the reported degradation of narcotine N-oxide.¹¹ N-Methyl- α -pipercoline was converted



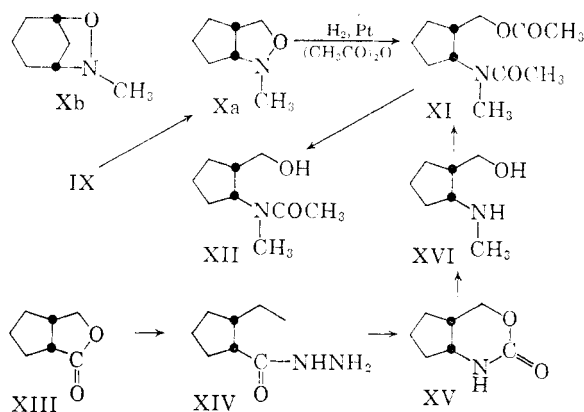
to a mixture of the *cis*- and *trans*-oxides IX. Thermal decomposition of IX formed several products that were separated by fractional distillation. N-Methyl- α -pipercoline was identified as one of them, and gas chromatography indicated the presence of a small amount of α -pipercoline as another product. An intermediate fraction (described below) was obtained in 10-14% yield. The highest boiling component had the physical properties of the expected N-methyl-N-5-hexenylhydroxylamine (III), and was identified as that compound by a comparison of infrared spectra and of the hydrogen oxalate salts. The yield of this product was quite variable and never exceeded 12%. Considerable solid material remained after fractionation of the volatile components, and was found to be undecomposed N-methyl- α -pipercoline oxide.

Final purification of the intermediate fraction from small amounts of N-methyl- α -pipercoline, α -pipercoline and several unidentified impurities was effected by gas chromatography. Elemental analysis of the pure basic liquid (X) and its hydrogen oxalate salt established the empirical formula as $\text{C}_7\text{H}_{11}\text{NO}$. The volatility of X precluded the possibility that it was dimeric. The infrared spectrum of X was rich in absorption bands, and did not contain OH, NH, carbonyl or carbon-carbon double bond stretching frequencies. Analysis confirmed the presence of one N-methyl group and the absence of C-methyl groups. No formaldehyde was obtained on acidic hydrolysis of X. Hydrogenation in the presence of platinum in glacial acetic acid resulted in the absorption of one molar equivalent of hydrogen. Reductive acetylation by hydrogenation in the presence of platinum and acetic anhydride resulted in formation of a compound containing two acetyl groups ($\text{C}_{11}\text{H}_{19}\text{NO}_3$, XI). Examination of the spectrum of XI showed that it contained an acetate group and an N,N-disubstituted acetamide function. These data are consistent with the formulation of X as a bicyclic compound containing the partial structure $-\text{CHON}(\text{CH}_3)\text{CH}-$.

Of the possible structures for X, *cis*-N-methyl-3-oxa-2-azabicyclo[3.3.0]octane (4,5-trimethyleneisoxazolidine) (Xa) and *cis*-N-methyl-3-oxa-2-azabicyclo[3.2.1]octane (2,4-trimethyleneisoxazolidine) (Xb) appeared to be the most probable formulas. Support for structure Xa was obtained by selective hydrolysis of the O-acetyl group of XI, forming the hydroxyamide XII ($\text{C}_9\text{H}_{17}\text{NO}_2$), which was oxidized with chromic anhydride. No cyclohexanone derivative which would be expected from oxidation of the reduction product of Xb was de-

(11) M. Polonovski and M. Polonovski, *Compt. rend.*, **190**, 310 (1930).

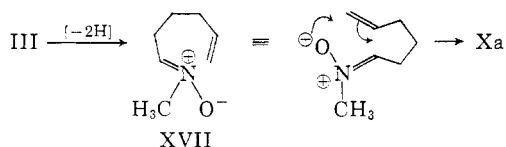
ected. The bicyclic isoxazolidine structure Xa was confirmed by synthesis of the degradation products XI and XII. The *cis*-lactone XIII, prepared from



cyclopentane-*cis*-1,2-dicarboxylic acid anhydride, was converted *via* the hydrazide XIV and a Curtius degradation to the cyclic urethan XV. Reduction of XV with lithium aluminum hydride gave N-methyl-*cis*-2-hydroxymethylcyclopentylamine (XVI). Upon acetylation this aminoalcohol gave a diacetyl derivative identical to XI derived from IX. Selective hydrolysis of this diacetyl derivative formed a hydroxyamide identical to XII derived from IX. Only structure Xa is consistent with all of these data for the product C₇H₁₃NO formed from IX.

The chemical properties of the isoxazolidine Xa are similar to the properties of the parent compound containing NH rather than NCH₃.¹²

Possible ways in which X could be formed from IX include an abnormal amine oxide elimination of IX, or formation from III by a subsequent oxidation or dehydrogenation step. Evidence concerning these possibilities was furnished by the observation that gas chromatography of III under suitable conditions led to the formation of Xa (identity confirmed by the infrared spectrum) as well as to several of the other products that appeared to contaminate Xa produced by the thermal decomposition of IX. Quantities of an amine and water which could be possible products of an oxidation-reduction reaction of III forming Xa were detected in this chromatogram. A reaction sequence resulting in the formation of Xa from IX that is consistent with these data is the dehydrogenation of the hydroxylamine III forming the nitrone XVII followed by cyclization in the concerted manner shown. A detailed study of the mechanism of ni-



trone formation from the autoxidation of aliphatic hydroxylamines has been reported recently.¹³ The products isolated in these cases were aldehydes and monoalkylhydroxylamines resulting from hy-

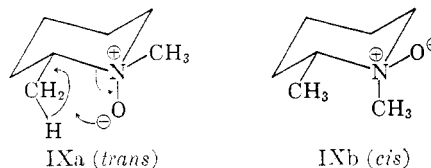
(12) H. King, *J. Chem. Soc.*, 432 (1942).

(13) D. H. Johnson, M. A. T. Rogers and G. Trappe, *J. Chem. Soc.*, 1093 (1956).

drolysis of the nitrone. It is interesting to note that monomeric aliphatic nitrones are unknown, but several monomeric alicyclic nitrones have been prepared.¹⁴

The proposed mechanism for the formation of Xa is analogous to the reaction of olefins with nitrile oxides, a general method for preparing isoxazolines.¹⁵ Moreover, the addition of carbanions to nitrones has been reported.¹⁴

The stereochemistry of N-methyl- α -pipercoline oxide should allow it to exist in two forms, the *trans* isomer (IXa, axial oxygen) and the *cis* isomer (IXb, equatorial oxygen). Because of the spatial re-



quirements for the amine oxide elimination, only the *trans* form (IXa) can undergo ring opening. Confirmatory evidence was obtained for the existence of two stereoisomers by paper strip chromatography of the amine oxide in a variety of solvent systems, which showed the presence of two components, neither of which was the original tertiary amine. When the amine oxide recovered from the decomposition of IX was examined by paper chromatography, it was found to contain a single component corresponding to the less mobile of the two that originally were present. This compound accordingly is the *cis* form IXb remaining after decomposition of the *trans* form IXa by β -elimination.

Separation of the two isomers was accomplished by decomposing IX under conditions that resulted in decomposition of part of the *trans* isomer IXa. The decomposition products were partitioned between pentane and water. A crystalline solid was obtained after concentration of the aqueous layer which gave hygroscopic needles, m.p. 109–111°, after sublimation and recrystallization. Paper strip analysis of this material indicated that it was the less mobile *cis* isomer IXb and contained only traces of IXa. This amine oxide isomer was very soluble at a concentration of 10% in carbon tetrachloride and had an infrared spectrum that showed a number of characteristic bands, including a maximum at 943 cm.⁻¹ that is assigned to the N⁺-O⁻ linkage.¹⁶ The *pK*_a of IXb was found to be 5.23 \pm 0.05.

After removal of the volatile decomposition products, the crystalline *trans* isomer IXa, m.p. 147.5–149.0° (sealed capillary), was obtained from the pentane layer. The material was shown to be homogeneous by paper chromatography and corresponded to the more mobile component of the amine oxide mixture. A *pK*_a determination gave the value 5.03 \pm 0.05 and gives further evidence

(14) R. Bonnett, R. F. C. Brown, V. M. Clark, I. D. Sutherland and A. R. Todd, *ibid.*, 2094 (1959); J. Thesing and W. Sirrenberg, *Ber.*, **92**, 1748 (1959).

(15) A. Quillico, G. S. d'Alcontres and P. Grünanger, *Gazz. chim. ital.*, **80**, 479 (1950).

(16) R. Mathis-Noël, R. Wolf and F. Gallais, *Compt. rend.*, **242**, 1873 (1956).

that this component is the *trans* isomer since IXa, with an axial oxygen atom, might be expected to be less basic than IXb. The *trans* isomer IXa is less soluble in carbon tetrachloride than IXb. Its infrared spectrum also shows a band at 943 cm^{-1} , but is not identical with the spectrum of the *cis* isomer IXb. Crystalline picrates of each of the pure isomers were prepared.

Each of the isomers of IX has been pyrolyzed separately. *trans*-N-Methyl- α -pipercoline oxide (IXa) decomposed smoothly to yield 72% of volatile products. On redistillation, pure N-methyl-N-5-hexenyl-hydroxylamine was obtained. No Xa was detected (note also that no Xa was detected in the pyrolysis of II). When IXb was heated to 190° only small amounts of volatile decomposition products were formed, containing principally N-methyl- α -pipercoline. This result supports the proposal that only the *trans* compound can undergo normal β -elimination and the assignments of structures to the amine oxide isomers.

Experimental¹⁷

N-Methylpiperidine Oxide.—N-Methylpiperidine, prepared in 86% yield¹⁸ (5 g.), was cooled to 0° and 12 g. of 30% aqueous hydrogen peroxide solution was added in small portions over a period of 30 minutes. The mixture was allowed to come to room temperature and was stirred for 24 hours, at which time it gave a negative test for the amine with phenolphthalein. The solution was allowed to stand overnight with a small amount of platinum black and then gave a negative test for hydrogen peroxide with lead sulfide paper. An aliquot of the solution was removed and added to 0.40 g. of picric acid in water. The picrate that separated was collected on a filter and washed with cold water. The yield of N-methylpiperidine oxide picrate was 0.59 g. (97%). Upon recrystallization from 95% ethanol the amine oxide picrate melted at 180–185° dec. (lit.¹⁹ 176–178°).

Thermal Decomposition of N-Methylpiperidine Oxide.—The remainder of the solution of the amine oxide described above was concentrated under reduced pressure to a viscous residue which was decomposed by heating in a nitrogen stream at atmospheric pressure in a 200-ml. round-bottomed flask connected through a short Vigreux column to two traps in series, both cooled with Dry Ice-acetone. Sublimation of the amine oxide took place at 160°. At 215°, violent decomposition occurred and some tarry residue was carried into the receivers. The heating was continued until a temperature of 240° had been reached. Ether was added to the distillate and the ethereal solution was separated, dried over potassium hydroxide pellets and concentrated. Distillation of the residue gave 1.2 g. (24%) of a product, b.p. 76–95°, which obviously was a mixture of amines. A portion of this mixture was treated with benzenesulfonyl chloride under Schotten-Baumann conditions and a crystalline benzenesulfonamide was obtained. The derivative was recrystallized from ethanol. It had m.p. 91–93° and did not depress the melting point of an authentic sample of piperidine benzenesulfonamide. The alkaline supernatant layer was extracted with ether and to this was added a saturated solution of picric acid in ether. A crystalline picrate separated and was identified as N-methylpiperidine picrate (m.p. and mixed m.p. 224–227°).

A concentrated aqueous solution of N-methylpiperidine oxide (obtained from 5 g. of amine) was placed inside the glass liner of a 330-ml. stainless steel pressure vessel with 50 ml. of tetrahydrofuran. The air was displaced by nitrogen under a pressure of 5 p.s.i. The vessel was heated at 200–240° for 3 hours. The dark viscous product was

treated with 20 ml. of dilute hydrochloric acid and concentrated to remove the tetrahydrofuran. The residue was dissolved in water, made alkaline by the addition of sodium hydroxide solution, and extracted with three 25-ml. portions of ether. The ether solutions were dried and concentrated and the residue was distilled, yielding 1.8 g. (37%) of volatile amines. Gas chromatography confirmed the presence of both N-methylpiperidine and piperidine.

N-Methylhexamethyleneimine Oxide (II).—Hexamethyleneimine²⁰ was converted to the N-methyl derivative in 86% yield.¹⁸ The latter compound (1 g.) was oxidized with hydrogen peroxide by the procedure described above for the lower homolog. The solution was treated with a warm 50% ethanolic solution of picric acid (2.2 g.), and yielded 3 g. (95%) of the amine oxide picrate, m.p. 200–202° dec. An analytical sample was recrystallized twice from 95% ethanol; m.p. 200.6–201.6° dec.

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$: C, 43.58; H, 5.06; N, 15.64. Found: C, 43.66; H, 5.03; N, 15.65.

N-Methyl-N-5-hexenylhydroxylamine (III).—The aqueous solution of N-methylhexamethyleneimine oxide obtained from 5 g. of the amine was concentrated under reduced pressure and the residue was decomposed by heating in a nitrogen stream at 5 mm. with a bath temperature of 50–200° in an apparatus similar to the one described for decomposition of N-methylpiperidine oxide. The residue solidified at 85°, then melted and began to decompose at 160–165°. The distillate was treated with 10 ml. of water and extracted with three 25-ml. portions of ether. The ether solutions were dried over anhydrous magnesium sulfate and concentrated. Distillation through a 33 × 0.6-cm. spinning band column afforded 3.04 g. (53%) of N-methyl-N-5-hexenylhydroxylamine (III), b.p. 65–66° (0.7–0.8 mm.), n_D^{20} 1.4456, d_4^{20} 0.8787, m.p. about 15°.

Anal. Calcd. for $\text{C}_7\text{H}_{15}\text{NO}$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.13; H, 12.03; N, 10.85.

The infrared spectrum of this product contained bands at 910, 991, 1639, 2990 (shoulder) and 3085 cm^{-1} characteristic of a vinyl group as well as a broad band at 3230 cm^{-1} and a band at 3620 cm^{-1} (associated and unassociated hydroxyl groups).

N-Methyl-N-5-hexenylhydroxylamine hydrogen oxalate was prepared from III and oxalic acid in ether solution, m.p. 108–111.2°. An analytical sample was recrystallized several times from dry ethyl acetate; m.p. 114.4–115.5°.

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}_3$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.14; H, 7.60; N, 6.19.

Hydrogenation of N-Methyl-N-5-hexenylhydroxylamine.—A solution of 0.50 g. of III in 13 ml. of methanol was quantitatively hydrogenated at room temperature in the presence of pre-reduced 1.5% palladium-on-calcium carbonate catalyst (0.15 g.). After 152 minutes 100% of one molar equivalent of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure (70 mm.). The crystalline residue sublimed at 0.75 mm. yielding 0.42 g. (84%) of N-methyl-N-*n*-hexylhydroxylamine, m.p. 35.0–36.5°. The infrared spectrum of this material showed that the vinyl group had been reduced.

Anal. Calcd. for $\text{C}_7\text{H}_{17}\text{NO}$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.38; H, 13.15; N, 10.79.

The hydrogen oxalate was prepared in ether (m.p. 118–119.8°) and was recrystallized from a mixture of ethanol and ether; m.p. 119.6–120.7°.

N-Methyl-N-*n*-hexylhydroxylamine—Di-*n*-hexylamine (27.8 g.) was methylated by the usual procedure,¹⁸ yielding 25.7 g. (86%) of methyl-di-*n*-hexylamine, b.p. 97–98° (4.6 mm.), n_D^{20} 1.4315 (lit.²¹ b.p. 121–122° at 19 mm.). The tertiary amine was converted to the amine oxide by the peracetic acid method²² in 98% yield as determined by isolation of the picrate, m.p. 77–79°. The remaining solution was concentrated and decomposed by heating in a nitrogen atmosphere at 4–12 mm. Decomposition occurred at 130–140° and the product was isolated by the same procedure used for III. N-Methyl-N-*n*-hexylhydroxylamine (5.07 g., 80%) was obtained, m.p. and mixed m.p. with the prod-

(17) Melting points are corrected and boiling points are uncorrected; spectra were determined with a Perkin-Elmer recording spectrophotometer, model 21, using a sodium chloride cell. We are indebted to Dr. S. M. Nagy and his associates for analyses.

(18) By essentially the procedure described in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 723.

(19) F. Hasse and R. Wolfenstein, *Ber.*, **37**, 3228 (1904).

(20) I. Ruzicka, M. Kobelt, O. Käfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(21) E. T. Burrows, *et al.*, *J. Chem. Soc.*, 197 (1947).

(22) A. C. Cope and H. H. Lee, *This Journal*, **79**, 964 (1957).

uct obtained by reduction of III, 33.0–35.3°. The infrared spectra of the two samples were identical.

N-Methyl-N-*n*-hexylhydroxylamine hydrogen oxalate was prepared in ether (m.p. 118.8–119.8°) and recrystallized twice from ethanol-ether, and had m.p. 119.8–120.8°, which was not depressed on admixture with the derivative prepared above.

Anal. Calcd. for $C_8H_{19}NO_5$: C, 48.85; H, 8.66; N, 6.33. Found: C, 49.15; H, 8.48; N, 6.21.

N-Methylheptamethyleneimine Oxide (IV).—Heptamethyleneimine²⁰ was converted to the N-methyl derivative,¹⁵ and a 12.7-g. sample of the latter compound was oxidized with hydrogen peroxide in the manner described above for the preparation of II. An aliquot of the solution was converted to the amine oxide picrate in 93% yield (m.p. 191–192°). An analytical sample was recrystallized twice from ethanol; m.p. 191.5–193°.

Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.95; H, 5.35; N, 15.16.

N-Methyl-N-6-heptenylhydroxylamine (V).—The remainder of the solution of the amine oxide described above (corresponding to 12.5 g. of the amine) was concentrated under reduced pressure and the residue was decomposed by heating at 6–7 mm. in an atmosphere of nitrogen with a bath temperature of 135–140° in the manner described for the decomposition of II. The yield of N-methyl-N-6-heptenylhydroxylamine was 11.2 g. (79%), b.p. 67–68° (1 mm.), n_D^{20} 1.4470, d_4^{25} 0.8670, m.p. 16–17°. The infrared spectrum of V was very similar to the spectrum of III.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.01; H, 11.94; N, 9.77.

N-Methyl-N-6-heptenylhydroxylamine hydrogen oxalate was prepared in ether and recrystallized for analysis from a mixture of ethanol and ether; m.p. 116–116.8°.

Anal. Calcd. for $C_{10}H_{19}NO_5$: C, 51.48; H, 8.29; N, 6.01. Found: C, 51.73; H, 8.22; N, 6.08.

N-Methyl-N-*n*-heptylhydroxylamine (VI).—N-Methyl-N-6-heptenylhydroxylamine (1.01 g.) in 15 ml. of methanol was hydrogenated at one atmosphere in the presence of 0.3 g. of pre-reduced 1.5% palladium-on-calcium carbonate catalyst. After 270 minutes, 97.5% of one molar equivalent of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was concentrated at 70 mm. The crystalline residue was sublimed at 1 mm. to give 0.86 g. (84%) of N-methyl-N-*n*-heptylhydroxylamine, m.p. 36.5–38°. The infrared spectrum of this material showed that the terminal olefin group of V had been reduced.

Anal. Calcd. for $C_8H_{19}NO$: C, 66.15; H, 13.19; N, 9.64. Found: C, 66.05; H, 13.21; N, 9.55.

N-Methyl-N-*n*-heptylhydroxylamine hydrogen oxalate, prepared in ether (m.p. 118.5–120°), was recrystallized three times from a mixture of ethanol and ether; m.p. 120.2–121.2°.

Anal. Calcd. for $C_{10}H_{21}O_5$: C, 51.05; H, 9.00; N, 5.95. Found: C, 51.02; H, 9.20; N, 6.00.

Methyl-*n*-heptylamine (VII).—Hydrogenation of VI (1.0 g.) was carried out in 13 ml. of glacial acetic acid in the presence of 0.3 g. of pre-reduced platinum oxide at room temperature. A quantitative uptake of two molar equivalents of hydrogen was complete in 270 minutes. The catalyst was separated, dilute hydrochloric acid was added and the solution was evaporated to dryness under reduced pressure, yielding 1.14 g. (97.5%) of the amine hydrochloride. The amine was recovered from the hydrochloride; 0.69 g., 77%, b.p. 100° (96 mm.), n_D^{20} 1.4207 (lit.²³ b.p. 164–166°, n_D^{20} 1.4232).

Methyl-*n*-heptylamine picrate was prepared by adding an ether solution of picric acid to an ether solution of the amine, and was recrystallized twice from ether; m.p. 97.6–98.2° (lit.²³ m.p. 96.2–97.2°). The picrolonate was prepared in ethanol and was recrystallized from the same solvent to yield orange-yellow needles, m.p. 177.5–178.5° dec. (lit.²³ m.p. 174–174.8° dec.).

6-Heptenylmethylamine (VIII).—In a 100-ml. flask equipped with a dropping funnel and a thermometer were placed 3.92 g. of zinc dust, 5 ml. of glacial acetic acid and 5 ml. of water. While the mixture was stirred, a solution of 3.45 g. of VI in 3.7 ml. of glacial acetic acid was added dropwise

over a period of 10 minutes, the temperature of the reaction mixture being maintained at 16–17°. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours, during which time it warmed spontaneously to about 60°; then it was heated at 60–70° for 1 hour. The hot solution was filtered to remove the zinc, and the residue on the filter was washed with two 5-ml. portions of 3% hydrochloric acid solution. Dilute sodium hydroxide was added to the filtrate until the precipitated zinc hydroxide had dissolved. The oily upper layer which separated was extracted with three 15-ml. portions of ether. The ethereal extracts were dried and concentrated and the residue was distilled through a semi-micro column, giving 2.2 g. (72%) of 6-heptenylmethylamine (VIII), b.p. 78–79° (36 mm.), n_D^{20} 1.4334, d_4^{25} 0.7833. Characteristic bands for the N-H stretching frequency and for the vinyl group were observed in the infrared spectrum of VIII.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.73; H, 13.49; N, 10.98.

6-Heptenylmethylamine picrolonate was prepared by adding an ethanolic solution of the amine to a 50% aqueous ethanolic solution of picrolonic acid. An analytical sample of the picrolonate was recrystallized twice from 50% aqueous ethanol; m.p. 172.5–173.4°.

Anal. Calcd. for $C_{13}H_{25}N_2O_6$: C, 55.23; H, 6.44; N, 17.89. Found: C, 55.22; H, 6.31; N, 17.95.

Hydrogenation of 6-heptenylmethylamine (VIII) (0.3 g.) in the presence of platinum (0.1 g.) in methanol (10 ml.) resulted in the uptake of 99% of one molar equivalent of hydrogen. The product was isolated as the hydrochloride (0.38 g., 97%), which was converted to the crystalline picrolonate, m.p. 176.8–177.8°. After one recrystallization from aqueous ethanol it melted at 177.8–178.8° and did not depress the melting point of an authentic sample of N-methyl-*n*-heptylamine picrolonate.

N-Methyl- α -pipercoline.—Methylation¹⁸ of α -pipercoline²⁴ (65 g.) resulted in the formation of 49 g. (87%) of N-methyl- α -pipercoline, b.p. 125–126°, n_D^{20} 1.4381 (lit.²⁵ b.p. 126–128°, n_D^{20} 1.4395).

N-Methyl- α -pipercoline Oxide (IX).—N-Methyl- α -pipercoline (1.5 g.) was converted to the oxide with aqueous hydrogen peroxide. The solution of the amine oxide was added to picric acid in water and N-methyl- α -pipercoline oxide picrate (4.6 g., 96%) was obtained, m.p. 211–215° dec. When recrystallized from dry ethyl acetate it melted at 213–217° dec. This material is a mixture of isomers, which have been separated and are reported below.

Thermal Decomposition of N-Methyl- α -pipercoline Oxide.—In a typical case, an aqueous solution of N-methyl- α -pipercoline oxide (prepared from 20 g. of the amine) was concentrated to a viscous sirup which was thermally decomposed by heating in an atmosphere of nitrogen at 10 mm. in the manner described above for N-methylhexamethyleneimine oxide. When the temperature had reached 115°, the amine oxide had solidified. The solid melted at about 140° and decomposition began soon after. At 175° the pressure was lowered to 0.3 mm. to facilitate distillation of the decomposition products and heating was continued to 185°. The contents of the receivers were combined and extracted with one 25-ml. and two 10-ml. portions of pentane. The pentane extracts were dried over anhydrous magnesium sulfate and concentrated. Distillation of the residue through a 33 × 0.6-cm. spinning-band column gave the following fractions: (1) A component, b.p. 59° (74 mm.), n_D^{20} 1.4377–1.4385 (5.8 g., 27%), which was identified as mainly N-methyl- α -pipercoline by conversion to the picrate, m.p. 240–241.5° (after recrystallization from dry ethyl acetate); gas chromatography of this fraction showed it to contain small amounts of α -pipercoline. (2) A fraction boiling at 68–70° (24 mm.), n_D^{20} 1.4483–1.4639 (3.0 g., 13.5%), the infrared spectrum of which showed no vinyl group; the purification of this material (Xa) is described. (3) A high boiling fraction (2.6 g. 12%), b.p. 60° (0.3 mm.), n_D^{20} 1.4563–1.4475, which was redistilled giving 1.01 g. of a product, b.p. 63.5° (0.9 mm.), n_D^{20} 1.4476–1.4456; the identity of this material with N-methyl-N-5-hexenylhydroxylamine (III) was established by a comparison of the infrared spectra and by preparation of the hydrogen oxalate, m.p. 113.8–114.6° after four recrystallizations from ethyl acetate and mixed m.p. 114.4–115.4° with the hydrogen oxa-

(23) N. J. Leonard, S. Swann and H. L. Dryden, *This Journal*, **74**, 2871 (1952).

(24) Kindly furnished by the Eli Lilly Co.

(25) G. Merling, *Ann.*, **264**, 339 (1891).

late of III. (4) A white crystalline hygroscopic solid (4.1 g., 20%) which formed N-methyl- α -pipercoline oxide picrate with picric acid in water, m.p. 212–214° dec.; a paper strip chromatogram of this product (described below) along with N-methyl- α -pipercoline oxide prepared from the amine showed that it was identical with the less mobile of the two components.

Purification of Xa.—The product contained in fraction 2 described above was combined with the same material from two other pyrolyses of N-methyl- α -pipercoline oxide. The neutral impurities were removed by dissolving Xa in 35 ml. of pentane and extracting with 10-ml. and 5-ml. portions of dilute hydrochloric acid. The organic base was liberated by the addition of sodium hydroxide solution and taken up in pentane. The pentane solution was dried and concentrated. Distillation of the residue produced a main fraction, b.p. 78–80° (30 mm.), n_D^{25} 1.4628–1.4635.

Analysis by gas chromatography on a column packed with 30% by weight of Dow-Corning Silicone 550 fluid impregnated on Celite (100–200 mesh) at 159° using helium as the eluent showed that the material having n_D^{25} 1.4635 or higher was more than 97% pure. Final purification was effected by collecting Xa as it emerged from the column. Distillation yielded 1.15 g. of Xa, b.p. 79–80° (30 mm.), n_D^{25} 1.4642, d_4^{25} 0.9860. The infrared spectrum of pure Xa has numerous bands including one at 943 cm^{-1} . It is characterized by the absence of -OH and -NH, carbon-carbon and carbonyl double bond stretching frequencies.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}$: C, 66.10; H, 10.30; N, 11.01; N-CH₃, 11.82; C-CH₃, 0.00. Found: C, 66.04; H, 10.31; N, 11.19; N-CH₃, 11.80; C-CH₃, 0.82.

Xa hydrogen oxalate was prepared in ether and was recrystallized from ethyl acetate, m.p. 81–81.9°. An analytical sample was recrystallized twice from a mixture of ethyl acetate and methanol, m.p. 80.9–81.9°.

Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{NO}_5$: C, 49.76; H, 6.96. Found: C, 49.70; H, 7.14.

Formation of Xa from N-Methyl-N-5-hexenylhydroxylamine (III).—Attempted gas chromatography of pure III under conditions similar to those used for Xa resulted in decomposition into more than seven products. A major component, corresponding in retention time to Xa, was collected and its identity with Xa was established by comparison of the infrared spectra. Another major component was observed which had a retention time identical with that of N-methyl- α -pipercoline, but identity was not established. Two components corresponding in retention time to water and methanol also were observed.

The diacetyl derivative of dihydro Xa (XI) was prepared by hydrogenating a solution of Xa (350 mg.) in 7 ml. of glacial acetic acid and 13 ml. of acetic anhydride in the presence of pre-reduced platinum oxide (350 mg.). A quantitative uptake of one molar equivalent of hydrogen was complete in 1 hour. The catalyst was collected on a filter and the filtrate was heated under reflux for 2 hours and then concentrated under reduced pressure. The residue was distilled at 0.03 mm., giving XI as a pale yellow oil.

Anal. Calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_4$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.17; H, 9.06; N, 6.54.

The infrared maxima of this product showed that it contained an acetate group (1738, 1236 cm^{-1}) and a tertiary acetamide linkage (1650 cm^{-1}).

N-Acetyl Derivative of Dihydro Xa (XII).—The product XI (443 mg.) from the reductive acetylation described above was dissolved in 2 ml. of water containing 1.1 equivalents of sodium hydroxide and the solution was allowed to stand overnight at room temperature. The hydroxyacetamide was extracted by means of five 5-ml. portions of ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate and concentrated. Distillation of the residue gave XII as a colorless, viscous oil (297 mg.) which showed strong hydroxyl absorption (3410 and 1028 cm^{-1}) in the infrared as well as the tertiary acetamide carbonyl stretching frequency. The absorption due to the acetate ester function had disappeared.

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}_2$: C, 63.12; H, 10.01. Found: C, 63.23; H, 10.27.

Oxidation of XII.—To the complex formed from 175 mg. of chromium trioxide and 2 ml. of pyridine was added a solution of XII (171 mg.) in 1.5 ml. of pyridine. The mixture was allowed to stand overnight and then poured into 15 ml. of

water. The aqueous solution was extracted with four 10-ml. portions of ether and the ether solutions were dried (magnesium sulfate) and concentrated. Very little product (ca. 15 mg.) was obtained. Analysis of the infrared spectrum showed that it was probably a mixture of the starting material, an aldehyde (2710, 1740 cm^{-1}) and an acid (1720, 1260, 1085 and 1015 cm^{-1}).

cis-2-Hydroxymethylcyclopentanecarboxylic Acid Lactone (XIII).²⁶—A mixture of 25 g. (0.18 mole) of cyclopentane-*cis*-1,2-dicarboxylic acid anhydride²⁷ and 6.9 g. (0.21 mole) of methanol was warmed over a steam-bath for 25 minutes, and then heated under reflux for an additional period of 30 minutes. The methanol was removed by evacuating to 0.3 mm. The viscous monomethyl ester was dissolved in 150 ml. of dry tetrahydrofuran and the solution was cooled at -30°. To this was added dropwise with vigorous stirring 227 ml. of a standardized²⁸ 0.59 *M* solution of lithium aluminum hydride in tetrahydrofuran, the temperature being maintained at -30° by external cooling. Ethyl acetate (0.5 ml.) was added to decompose the excess hydride and the mixture was allowed to warm. The solvent was removed by distillation under reduced pressure. The white residue was treated with 100 ml. of water and 150 ml. of 10% sulfuric acid, and the aqueous solution was extracted with three 100-ml. portions of ether. The ethereal solution was dried over magnesium sulfate and concentrated. The residue was boiled for 40 minutes with 30 ml. of 20% sodium hydroxide solution and the resulting alkaline solution was extracted five times with ether to remove neutral impurities. After acidification, the aqueous layer was boiled for 1 hour and the lactone was extracted with three 50-ml. portions of ether. The ethereal extracts were dried over magnesium sulfate and concentrated. The residue was distilled, giving 11.7 g. (52%) of *cis*-2-hydroxymethylcyclopentanecarboxylic acid lactone (XIII), b.p. 127–128° (19 mm.), n_D^{25} 1.4740 (absorption at 1770 cm^{-1}).

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_2$: C, 66.64; H, 7.99. Found: C, 66.48; H, 8.08.

The ethereal solution containing the neutral impurities was dried and concentrated and the residue was distilled, giving 2.95 g. (13%) of a viscous liquid. Redistillation gave pure *cis*-1,2-bis-hydroxymethylcyclopentane, b.p. 96.5° (0.3 mm.), n_D^{25} 1.4810 (lit.²⁹ b.p. 103° at 0.15 mm., n_D^{25} 1.4840).

The bis-*p*-toluenesulfonate was prepared and recrystallized from methanol; m.p. 79.5–80.5° (lit.²⁹ m.p. 82°).

cis-2-Hydroxymethylcyclopentanecarboxylic Acid Hydrazide (XIV).—A mixture of 10 g. of the *cis*-lactone XIII, 11 ml. of 95% hydrazine and 18 ml. of absolute ethanol was heated under reflux for 10 hours. After removal of the solvents under reduced pressure, the residue (XIV) was recrystallized from dry ethyl acetate; m.p. 128.5–129.5° (8.7 g., 70%).

Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{O}_2\text{N}_2$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.34; H, 9.01; N, 17.78.

2-Oxa-4-azabicyclo[4.3.0]nonan-3-one (XV).—A solution of 8.65 g. (0.055 mole) of the hydrazide XIV in 60 ml. of 1 *N* hydrochloric acid was cooled to 0° and covered with 100 ml. of ether. To this two-phase mixture was added with vigorous stirring a cold solution of 4 g. of sodium nitrite in 12 ml. of water. The addition required 20 minutes and the mixture was maintained at 0° by the addition of Dry Ice. The ether layer was separated and the aqueous solution was extracted with 25 ml. of ether. The combined ether solutions were washed with 5% aqueous sodium bicarbonate and dried over magnesium sulfate. Benzene (100 ml.) was added and the ether was removed by distillation, during which decomposition of the azide took place. The benzene solution of the urethan was heated under reflux for 2 hours and was passed through a column containing 20 g. of Merck acid-washed alumina. The column was eluted successively with 300 ml. portions of benzene, 9:1 benzene-ether, ether, 19:1 ether-methanol and methanol; fractions of 250 ml. were collected. The first two fractions contained a mobile liquid, which is undoubtedly *cis*-2-hydroxymethylcyclopentanecar-

(26) The procedure employed is similar to the one described by E. L. Eliel, A. W. Burgstahler, D. E. Rivard and L. Haefele, *THIS JOURNAL*, **77**, 5092 (1955), for the preparation of phthalide from methyl phthalate.

(27) R. C. Fuson and O. O. Cole, *ibid.*, **60**, 1237 (1938).

(28) H. Felkin, *Bull. soc. chim. France*, 347 (1951).

(29) L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 2383 (1955).

boxylic acid lactone as evidenced by a strong absorption at 1768 cm^{-1} in the infrared. Fractions 2-7 gave viscous oils which crystallized on standing in air. Crystallization from wet ether gave white needles of XV as a hydrate, m.p. 55.5-57.0°.

Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{NO}_2 \cdot \text{H}_2\text{O}$: C, 52.81; H, 8.23; N, 8.80. Found: C, 53.08; H, 8.19; N, 8.91.

Attempts to remove the water of hydration resulted in the formation of an oil.

N-Methyl-*cis*-2-hydroxymethylcyclopentylamine (XVI).—To a suspension of 1.4 g. of lithium aluminum hydride in 75 ml. of ether was added in portions a suspension of the cyclic urethan hydrate XV (2.85 g., 0.018 mole) in 75 ml. of ether. The mixture was heated under reflux for 15 hours. The excess hydride was decomposed by the successive addition of 1.5 ml. of water, 1.5 ml. of 15% sodium hydroxide and 4.5 ml. of water; the suspension was filtered. The amine was extracted from the ether with 15 ml. of 10% sulfuric acid solution. The solution was made basic and the product was isolated by continuous extraction with chloroform. After drying, the solvent was removed and the residue was flash distilled at 0.3 mm. to yield 1.42 g. (62%) of the aminoalcohol. After redistillation, b.p. 59-61° (0.7 mm.), N-methyl-*cis*-2-hydroxymethylcyclopentylamine had n_D^{25} 1.8405.

Anal. Calcd. for $\text{C}_7\text{H}_{15}\text{NO}$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.90; H, 11.62; N, 10.73.

N-Methyl-N-*cis*-2-acetoxymethylcyclopentylacetamide (XI).—The aminoalcohol XVI (250 mg.) was heated over a steam-cone with 3.0 ml. of acetic anhydride for 1 hour. The acetic anhydride was concentrated under reduced pressure and the residue was distilled at 0.3 mm., yielding 265 mg. of the diacetyl derivative XI, n_D^{25} 1.4888. The infrared spectrum of this material was indistinguishable from that of the product of the reductive acetylation of Xa.

Anal. Calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.81; H, 9.06; N, 6.63.

N-Methyl-*cis*-2-acetamidocyclopentylmethanol (XII).—A solution of 90 mg. of the diacetyl compound XI (described immediately above) in 1 ml. of 1 N sodium hydroxide was allowed to stand at room temperature for 2 hours. The hydroxyamide was extracted with five 5-ml. portions of chloroform. The chloroform solution was dried and concentrated and the residue was flash distilled at 0.3 mm., giving N-methyl-*cis*-2-acetamidocyclopentylmethanol (XII) as a viscous oil. The infrared spectrum of this product was identical with that of XII prepared from XI (derived from Xa).

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 62.96; H, 10.07; N, 8.16.

Paper Chromatography of N-Methyl- α -pipecoline Oxide.—The paper chromatography used for analytical purposes in this study was carried out by the downward flow method in a tube (51 \times 6.4-cm.). Whatman No. 1 paper, 43 \times 3.8-cm., was employed and the amount of material was restricted to 50-100 μ . The following solvent systems were employed: (1) 1-butanol-glacial acetic acid-water, 5:1:4 (upper phase); (2) 1-butanol saturated with water; (3) *sec*-butyl alcohol absolute ethanol-acetic acid-water, 15:5:1:5; (4) 1-butanol equilibrated with 450 ml. of dilute ammonia (1 part concentrated ammonia to 9 parts water); (5) *sec*-butyl alcohol-95% ethanol-dilute ammonia, 3:1:1; (6) 1-butanol-pyridine-water, 80:16:25. The material was spotted at the origin and chromatography was allowed to proceed for 12-24 hours. The chromatogram was removed and allowed to dry, and was developed by spraying with a modified Dragendorff reagent.³⁰ The compounds appeared as orange spots on a yellow background, but faded upon drying. The amine oxide isomer of highest R_f -value in each system gave a less intense spot with the reagent even when present in equal amount with the other component.

The R_f -values for the two components were highly variable in all systems and were dependent upon the temperature and flow rate. It was therefore found advisable to compare the desired sample and a parallel spot of the original amine oxide preparation on the same paper, and this was done in every case. For this reason the R_f -values are not reported, although it can be stated that all of the solvent systems employed gave approximately the same resolution (R_f of the more mobile component divided by R_f of the slower moving

was always 1.11). Solvents 1 and 2 were most commonly used.

Separation of *trans*-(IXa) and *cis*-(IXb) N-Methyl- α -pipecoline Oxide.—A concentrated solution of N-methyl- α -pipecoline oxide (prepared from 25 g. of the amine) was decomposed by heating in a nitrogen atmosphere at 10 mm. in the manner described above. When the decomposition temperature (140-150°) was reached the pressure was gradually lowered to 1 mm. Under these conditions only a small amount of the amine oxide was decomposed and much of it was carried into the receivers. The distillate was treated with 15 ml. of pentane and the layers were separated. The pentane solution was extracted with an additional 10 ml. of water, and the combined aqueous solutions were extracted with two 15-ml. portions of pentane. The aqueous layer was separated and evaporated to a viscous sirup which crystallized after being kept at 5°. Paper strip chromatography showed that this product was composed mainly of the less mobile component. It was sublimed and recrystallized twice from benzene, giving very hygroscopic, fine, white needles, m.p. 109-111° (sealed capillary, probably a hydrate), which was shown to be nearly homogeneous by paper strip chromatography. The infrared spectrum (10% in carbon tetrachloride) of the material showed bands at 908, 943, 971, 1010, 1095, 1143 and 1365 cm^{-1} . The acid dissociation constant was determined by titration of an aqueous solution with standard 0.0999 N hydrochloric acid using a Beckman pH meter (model G). Two determinations at 0.02 M (77.6 mg., 0.6 mmole in 30 ml. of water) and at 0.049 M (317 mg., 2.46 mmoles in 50 ml. of water) were conducted. The pK_a for Xb was found to be 5.25 ± 0.05 , the accuracy of this measurement being limited by the practical reproducibility of the instrument. A picrate was prepared in water and, after several recrystallizations from 50% aqueous ethanol, melted at 207-211° dec.

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}_3\text{N}_4$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.33; H, 5.29; N, 15.85.

The pentane layers obtained above were dried over magnesium sulfate and concentrated. The remaining solution was flash distilled at 0.8 mm. and the volatile decomposition products (7.2 g.) were collected in a receiver cooled with Dry Ice. The residue from this distillation (6.2 g.) was a crystalline solid which was shown to be homogeneous and to correspond to the more mobile component by paper strip chromatography. Sublimation and recrystallization from benzene gave the *trans* isomer IXa, m.p. 147.5-149° (sealed capillary). This product is barely soluble in carbon tetrachloride at a concentration of 5%. Its infrared spectrum (5% in carbon tetrachloride) shows a stronger absorption maximum at 943 cm^{-1} , but is not identical with the spectrum of IXb (915, 995 and 1020 cm^{-1}). The pK_a for IXa was found to be 5.03 ± 0.05 at a concentration of 0.02 M (127 mg., 0.98 mmole in 50 ml. of water). A picrate was prepared in water and recrystallized three times from 95% ethanol, m.p. 211-215° dec., mixed m.p. 206.5-210.0° dec. with the picrate of IXb.

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_8\text{N}_4$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.74; H, 5.25; N, 15.44.

Pyrolysis of the *trans* Isomer IXa.—A viscous aqueous sirup containing 1.65 g. of IXa was heated in a stream of nitrogen from 95-195°. Decomposition occurred at 160-165°. Distillation of the products into traps was observed and very little (0.06 g.) residue remained in the flask. The decomposition products were taken up in water and pentane. The pentane solution was concentrated yielding 1.18 g. (72%) of product, n_D^{25} 1.4382. Upon redistillation, 0.52 g. (38%) of III was obtained. No Xa was detected. The aqueous layer, after evaporation of the solvent under reduced pressure, afforded 0.28 g. (17%) of starting material IXa.

Pyrolysis of the *cis* Isomer IXb.—When 1.95 g. of nearly pure IXb was heated from 90-195°, smooth decomposition was not observed. The residue from the pyrolysis was 0.39 g. The volatile products were separated as described above and gave 0.44 g. (22%) from the pentane extract. This product was flash distilled to give 0.2 g. (10%) of a liquid, n_D^{25} 1.4418, which was mainly N-methyl- α -pipecoline. A trace of Xa was detected; however, no N-methyl-N-5-hexenylhydroxylamine was found. The aqueous layer gave 0.59 g. (30%) of pure IXb (recovered) which melted at 107-117° after sublimation and recrystallization from benzene.

(30) H. M. Bregoff, E. Roberts and C. C. Deiwiche, *J. Biol. Chem.*, **205**, 565 (1953).