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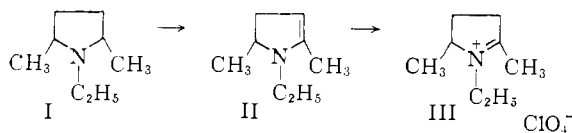
Unsaturated Amines. XIV. The Mercuric Acetate Oxidation of Substituted Pyrrolidines¹BY NELSON J. LEONARD AND A. GILBERT COOK^{2,3}

RECEIVED MAY 23, 1959

A series of methyl-substituted pyrrolidines has been used to indicate the synthetic potentialities of the mercuric acetate oxidation of saturated tertiary amines containing a five-membered ring. The 1,2-, 1,2,5-, 1,3,4- and 1,2,2,5-substituted pyrrolidines yield the corresponding Δ^2 -pyrrolines. In 1,2,2-trimethylpyrrolidine the double bond is introduced at the unsubstituted α -carbon, and the product is the dimer, 1,5,5-trimethyl-3-(1',5',5'-trimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline. 1-Methylpyrrolidine yields both dimer and trimer of the oxidation intermediate, 1-methyl- Δ^2 -pyrroline, and 1,3-dimethylpyrrolidine also yields a dimer. Reaction of the enamine dimers and trimer in solution with ethyl acetoacetate, followed by hydrolysis, furnishes new hygrine-like bases. With 1,3,4-trimethylpyrrolidine, the "dimeric" (minor) product is the result of further oxidation of one of the Δ^2 -pyrroline moieties to a pyrrole, namely, 1,3,4-trimethyl-2-(1',3',4'-trimethyl-2'-pyrrolidyl)-pyrrole.

The success of the mercuric acetate oxidation of piperidines as a synthetic route to piperidines more highly substituted, to Δ^2 -tetrahydropyridines and to Δ^2 -tetrahydroanabasines⁴ led us to test the utility of this oxidation method with cyclic tertiary amines of ring size other than six-membered. The results of the mercuric acetate oxidation of a series of substituted pyrrolidines are reported in this article, and those of the seven-, eight- and nine-membered rings in the article following.⁵

While we have concentrated on the oxidation of simple models in the five-membered ring series, Favre and Marinier⁶ have demonstrated a structural application of the mercuric acetate oxidation of the pyrrolidine moiety in conessine alkaloid derivatives. They found that dehydrogenation of dihydroheteroconessine and of dihydroconessine yielded the same ternary iminium perchlorate, showing that the two dihydro derivatives were epimeric at C-20. In the bicyclic compound somewhat related to the amine moiety in conessine, namely, 2,3-dimethyl-2-azabicyclo[3.3.0]octane, mercuric acetate introduced a double bond at the 3-position.⁷ In the simpler series^{7a} which we have been studying concurrently, the action of mercuric acetate on 2,5-dimethyl-1-ethylpyrrolidine (I) in aqueous acetic acid led to 2,5-dimethyl-1-ethyl- Δ^2 -pyrroline (II) or 2,5-dimethyl-1-ethyl- Δ^1 -pyrrolinium perchlorate (III) in the salt form. The enamine was characterized readily by the observed



shift toward higher frequency (34 cm.^{-1}) of the double bond stretching maximum in going from II

(1) For previous paper in this series, see N. J. Leonard and J. A. Adamcik, *THIS JOURNAL*, **81**, 595 (1959).

(2) Eli Lilly and Co. Fellow, 1957-1958.

(3) Monsanto Chemical Co. Fellow, 1958-1959.

(4) N. J. Leonard and F. P. Hauck, Jr., *THIS JOURNAL*, **79**, 5279 (1957).

(5) N. J. Leonard and W. K. Musker, *THIS JOURNAL*, **81**, 5631 (1959).

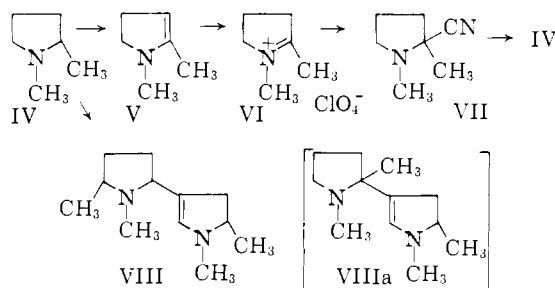
(6) H. Favre and B. Marinier, *Can. J. Chem.*, **36**, 429 (1958).

(7) R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, **42**, 121 (1959); see also J. Meinwald, *Proc. Chem. Soc.*, 286 (1958), and R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, **41**, 867 (1958).

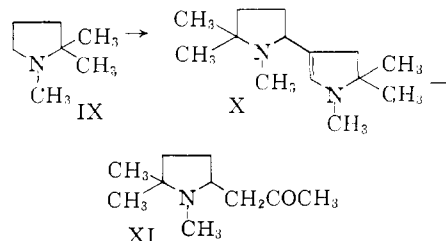
(7a) ADDED IN PROOF.—The mercuric acetate oxidation of sec-pyrrolidines has now been reported by R. Bonnett, V. M. Clark, A. Giddey and Sir Alexander Todd, *J. Chem. Soc.*, 2087 (1959).

to its protonic salt III.⁸⁻¹⁰ The yield of the 1,2,5-trisubstituted pyrroline was not as satisfactory as that obtained in the six-membered ring series, *i.e.*, 1,2,6-trimethylpiperidine \rightarrow 1,2,6-trimethyl- Δ^2 -tetrahydropyridine.⁴ The fault may be laid at least in part to the susceptibility of the initial product to further oxidation in solution and to the instability of the enamine II.

The mercuric acetate oxidation of 1,2-dimethylpyrrolidine (IV) yielded 1,2-dimethyl- Δ^2 -pyrroline (V)^{8,11-13} plus dimeric material (VIII and/or VIIIa). The monomeric enamine was converted to the known 1,2-dimethyl- Δ^1 -pyrrolinium perchlorate (VI), which reacted with potassium cyanide to give 2-cyano-1,2-dimethylpyrrolidine (VII). The cyano group in this compound was *displaced* rather than reduced on treatment with lithium aluminum hydride, in confirmation of the complete substitution on the 2-carbon⁴ and the location of the double bond as indicated in the precursor salt VI.



1,2,2-Trimethylpyrrolidine (IX) was oxidized smoothly with mercuric acetate, and the dimer of the corresponding enamine, 1,5,5-trimethyl- Δ^2 -pyr-



(8) N. J. Leonard and V. W. Gash, *THIS JOURNAL*, **76**, 2781 (1954).

(9) B. Witkop and J. B. Patrick, *ibid.*, **75**, 4474 (1953).

(10) O. E. Edwards, F. H. Clarke and B. Douglas, *Can. J. Chem.*, **32**, 235 (1954).

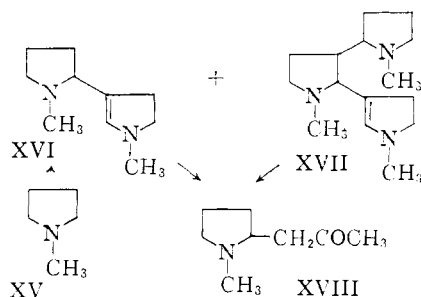
(11) R. Lukeš, *Collection Czech. Chem. Commun.*, **2**, 531 (1930).

(12) L. C. Craig, *THIS JOURNAL*, **55**, 295 (1933).

(13) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

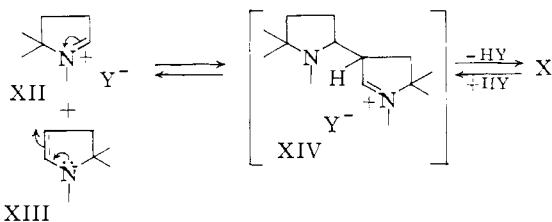
roline, was obtained in good yield. The product was recognized as the dimer by its physical properties and analysis, and the structure of the dimer could be assigned unequivocally in this case as X, 1,5,5-trimethyl-3-(1',5',5'-trimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline, since *unique* electrophilic and nucleophilic centers are available for condensation in the pyrroline monomer.¹⁴ The product was characterized further by reaction with ethyl acetoacetate, followed by hydrolysis, to give 2-acetyl-1,5,5-trimethylpyrrolidine (XI). This conversion indicates the reversibility of dimer formation under the reaction conditions.¹⁴ The mercuric acetate oxidation of 1,2,2-trimethylpyrrolidine thus provides a synthetic route not only to a representative substituted pyrrolidylpyrroline but also to a substituted hygrine.

The oxidation of the simplest member of the series, 1-methylpyrrolidine (XV), yielded two major products, one of which was the expected dimer of 1-methyl- Δ^2 -pyrroline, 1-methyl-3-(1'-methyl-2'-pyrrolidyl)- Δ^2 -pyrroline (XVI), characterized by physical properties and analysis. The other product was the trimer, of probable structure 1-methyl-3-[1'-methyl-3'-(1''-methyl-2''-pyrrolidyl)-2'-pyrrolidyl]- Δ^2 -pyrroline (XVII), according to molecular weight, analysis and analogy with the trimer of 1-methyl- Δ^2 -tetrahydropyridine.¹⁷ Both dimer and



trimer were convertible to *dl*-hygrine or 2-acetyl-1-methylpyrrolidine (XVIII), by treatment with ethyl acetoacetate in aqueous ethanol, followed by hydrolysis. Dimeric dehydrogenated product (XX) was obtained from 1,3-dimethylpyrrolidine (XIX) by mercuric acetate oxidation and was also convertible to a hygrine derivative, probably 2-acetyl-

(14) The condensation may be symbolized as taking place between the ternary iminium acetate or hydroxide form (XII) of 1,5,5-trimethyl- Δ^2 -pyrroline (XIII) and XIII, both of which may be considered to be in equilibrium with the pseudobase and *sec.*-aminoaldehyde forms of the monomer in the dilute acetic acid-acetate solution. A similar

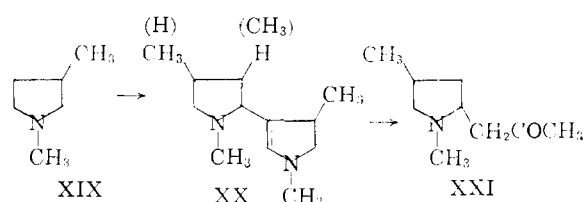


combination would represent the self-condensation of 1-methyl- Δ^2 -tetrahydropyridine,⁴ in slight variance with the concept of Schöpf.¹⁵⁻¹⁷

(15) C. Schöpf and H. L. deWaal, *Chem. Ber.*, **89**, 909 (1956).

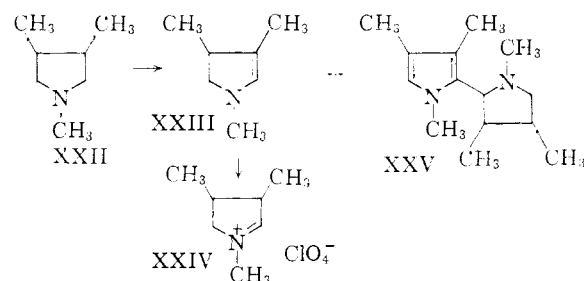
(16) C. Schöpf, G. Herbert, R. Rausch and G. Schröder, *Angew. Chem.*, **69**, 391 (1957).

(17) C. Schöpf, R. Klug, R. Rausch, H. Seubert and D. Wagner, *Ann.*, **616**, 151 (1958).



1,4-dimethylpyrrolidine (XXI) or a mixture of this and 2-acetyl-1,3-dimethylpyrrolidine.

An interesting variant in the "dimeric" product was obtained when 1,3,4-trimethylpyrrolidine (XXII) was the substrate for mercuric acetate oxidation. The major product was the expected enamine, 1,3,4-trimethyl- Δ^2 -pyrroline (XXIII), which formed a perchlorate (XXIV) of the ternary iminium type. Incidentally, the pK_a' values for 1,3,4-trimethyl- Δ^1 -pyrrolinium perchlorate, 9.6 in



water and 8.75 in 66% dimethylformamide, are very similar to those obtained for an analogous compound in the six-membered ring series, 3,5-diethyl-1-methyl- Δ^1 -tetrahydropyridinium perchlorate,⁴ pK_a' 9.47 (water) and 8.46 (66% DMF),¹⁸ and the acid strengths of both conjugate acids are greater than those for cyclic ternary iminium salts substituted on the α -carbon.^{18,19,20} The minor product from 1,3,4-trimethylpyrrolidine (XXII) had elemental analysis and molecular weight consistent with the molecular formula $C_{14}H_{24}N_2$. Since the intermediate 1,3,4-trimethyl- Δ^2 -pyrroline would not be expected to undergo self-condensation on the β -carbon, we assumed that overoxidation might have occurred to give some 1,3,4-trimethylpyrroline, which could then have undergone condensation with XXIII on the α -carbon of the pyrrole to yield 1,3,4-trimethyl-2-(1',3',4'-trimethyl-2'-pyrrolidyl)-pyrrole (XXV). Exact analogy is found in the work of Fuhlhage and VanderWerf²¹ on the reaction of Δ^1 -pyrroline and Δ^1 -tetrahydropyridine with pyrroles. The presence of the pyrrole moiety was confirmed by the strong pine splint test (in the cold) which was given by the $C_{14}H_{24}N_2$ compound, but not by representative enamines among those described above, and by the possibility of introducing an aldehyde group into the molecule by the method usually used for making pyrrolealdehydes, so that the structural assignment XXV has a sound basis.

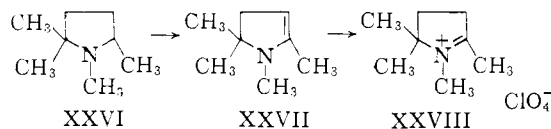
(18) N. J. Leonard, K. Conrow and R. R. Sauer, *THIS JOURNAL*, **80**, 5185 (1958).

(19) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *ibid.*, **77**, 439 (1955).

(20) N. J. Leonard, P. D. Thomas and V. W. Gash, *ibid.*, **77**, 1532 (1955).

(21) D. W. Fuhlhage and C. A. VanderWerf, *ibid.*, **80**, 6249 (1958).

The most highly substituted pyrrolidine investigated²² as an oxidation substrate was 1,2,2,5-tetramethylpyrrolidine (XXVI), which was converted to 1,2,5,5-tetramethyl- Δ^2 -pyrroline (XXVII), iso-



lated as 1,2,5,5-tetramethyl- Δ^1 -pyrrolinium perchlorate (XXVIII) in 78% yield.

In summary, the extension of the mercuric acetate oxidation reaction to five-membered ring compounds affords a route to variously substituted pyrrolines and pyrrolidines and to "dimeric" and "trimeric" products of unusual composition. The pyrrolines which can be produced by the mercuric acetate oxidation suggest applications in various enamine condensations.²³ From the representative pyrrolidine examples here provided, it is now possible for us to predict the site of oxidation of almost any alkyl-substituted pyrrolidine.

Experimental²⁴

Saturated Amines.—The following known saturated tertiary amines were used as precursors: 1-methylpyrrolidine,²⁵ b.p. 75–78° (750 mm.), n_D^{25} 1.4222; picrate,²⁶ m.p. 223–225°; 1,2-dimethylpyrrolidine,^{27–29} b.p. 94–96°, n_D^{25} 1.4205; picrate,³⁰ m.p. 236–239° dec.; 1,2,2-trimethylpyrrolidine,^{11,27,31} b.p. 118–120°, n_D^{27} 1.4299; picrate, m.p. 268° dec.; 1,3-dimethylpyrrolidine,^{30,32,33} b.p. 95–97°, n_D^{25} 1.4192; picrate, m.p. 183–184°; 2,5-dimethyl-1-ethylpyrrolidine,³⁴ b.p. 130.5–134°, n_D^{25} 1.4334; picrate, m.p. 187.5–191.5°; 1-methyl-1-azacycloheptane,³⁵ b.p. 141–144°, n_D^{25} 1.4510; picrate, m.p. 220.5–221.5° dec.

Mercuric Acetate Oxidation of 2,5-Dimethyl-1-ethylpyrrolidine. **General Procedure for Mercuric Acetate Oxidations.**—A mixture of 12.3 g. (0.10 mole) of 2,5-dimethyl-1-ethylpyrrolidine and 130 g. (0.50 mole) of mercuric acetate in 500 ml. of 5% acetic acid (95% water) was heated on the steam-bath with stirring for 2 hours. The first precipitate appeared 17 minutes after heating was begun. The reaction mixture was cooled, and the precipitated mercurous acetate was collected by filtration and washed with 5% acetic acid (washings added to filtrate), then with acetone (washings discarded). The precipitate, dried by suction on the filter, weighed 31 g. (60% of theoret.). The filtrate was saturated with hydrogen sulfide, the mercuric sulfide was removed, and basification with potassium carbonate was followed by ether extraction, as in the general directions for the oxidation of substituted piperidines.⁴ The ether was removed by slow distilling through a helices-packed column, and the re-

sidual liquid was distilled from sodium under nitrogen through a Holzman column, yielding 2.80 g. (23%) of 2,5-dimethyl-1-ethyl- Δ^2 -pyrroline, b.p. 41° (29 mm.), n_D^{25} 1.4421, $\nu_{\text{max}}^{\text{liquid film}}$ 1644 cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{N}$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.80; H, 12.12; N, 11.26.

2,5-Dimethyl-1-ethyl- Δ^1 -pyrrolinium perchlorate crystallized from ethanol as colorless needles, m.p. 244–245.5°, $\nu_{\text{max}}^{\text{solid}}$ 1678 cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{ClNO}_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 42.42; H, 7.42; N, 6.10.

Mercuric Acetate Oxidation of 1,2-Dimethylpyrrolidine.—For the oxidation of 10 g. (0.10 mole) of 1,2-dimethylpyrrolidine with mercuric acetate the general procedure was followed except that after the removal of mercuric sulfide the aqueous filtrate was extracted with several portions of chloroform. However, no product appeared in these extracts. The aqueous residue was basified, extracted, and dried in the usual manner. Distillation of the ether extracts gave 2.9 g. (34%) of a mixture of 1,2-dimethyl- Δ^2 -pyrroline³⁶ and 1,5-dimethyl-3-(1',5'(and/or 1',2')-dimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline, the boiling point of the mixture ranging from 105° (750 mm.) to 148° (16 mm.). The fact that the product was a mixture was indicated by the infrared spectrum (liquid film) which showed strong maxima at 1640 cm^{-1} (1,2-dimethyl- Δ^2 -pyrroline)³⁶ and at 1658 cm^{-1} (1,5-dimethyl-3-(1',5'(and/or 1',2')-dimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline) as well as weak maxima at 1700 and 1757 cm^{-1} , the latter two maxima possibly being due to hydrolysis of the enamines to the amino-ketone and aminoaldehyde, respectively.³⁶ The anomalous boiling point may be due to the reversible dimerization of 1,2-dimethyl- Δ^2 -pyrroline as described by Craig.^{12,13} For this reason as well it was very difficult to separate pure components by fractional distillation, and vapor phase chromatography was not successful. Hence, the yield of each product could not be determined. Nevertheless, infrared spectra indicated that the lower boiling fractions were richer in 1,2-dimethyl- Δ^2 -pyrroline while the higher boiling fractions were richer in dimeric material.

1,2-Dimethyl- Δ^1 -pyrrolinium perchlorate,³⁶ formed by adding perchloric acid to an ether solution of the lower boiling fractions, crystallized from ethanol as colorless plates, m.p. 239–240.5° dec., $\nu_{\text{max}}^{\text{solid}}$ 1701 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_{12}\text{ClNO}_4$: C, 36.46; H, 6.12; N, 7.09. Found: C, 36.32; H, 6.32; N, 7.00.

1,2-Dimethyl- Δ^2 -pyrroline was obtained from the perchlorate by basification and extraction with pentane, and then by distillation, b.p. 58–59° (98 mm.), $\nu_{\text{max}}^{\text{film}}$ 1640 cm^{-1} . Because of the instability of this compound, it was difficult to obtain the free base analytically pure.

Anal. Calcd. for $\text{C}_6\text{H}_{11}\text{N}$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.34; H, 11.39; N, 14.51.

Dimeric material, 1,5-dimethyl-3-(1',5'(and/or 1',2')-dimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline was obtained by redistillation at 126–130° (22 mm.), n_D^{27} 1.4983, $\nu_{\text{max}}^{\text{film}}$ 1658 cm^{-1} , but decomposed rapidly.

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{N}_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.26; H, 10.90; N, 14.43.

Reaction of 1,2-Dimethyl- Δ^1 -pyrrolinium Perchlorate with Potassium Cyanide.—To a solution of 3.8 g. (0.02 mole) of 1,2-dimethyl- Δ^1 -pyrrolinium perchlorate in 25 ml. of water was added 3.5 g. (0.054 mole) of potassium cyanide and a portion of ether. The mixture was shaken and extracted with further portions of ether. The combined ether extracts were dried and concentrated, and the residual 2-cyano-1,2-dimethylpyrrolidine³⁷ was distilled, b.p. 77° (22 mm.), n_D^{25} 1.4440, $\nu_{\text{max}}^{\text{film}}$ 2220 cm^{-1} , yield ca. 70%.

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{N}_2$: C, 67.70; H, 9.74. Found: C, 67.60; H, 9.79.

Reaction of 2-Cyano-1,2-dimethylpyrrolidine with Lithium Aluminum Hydride.—A slurry of 2.4 g. (0.063 mole) of lithium aluminum hydride in 200 ml. of dry ether was stirred while a solution of 1.9 g. (0.016 mole) of 2-cyano-1,2-dimethylpyrrolidine in 50 ml. of anhydrous ether was added dropwise, and the mixture was then heated at reflux for 5 hours. Excess reagent was decomposed by the cautious

(36) R. Lukeš, V. Dědek and L. Novotný, *Chem. Listy*, **52**, 634 (1958).

(37) W. Hertler, Ph.D. Thesis, University of Illinois, 1958.

(22) Cf. C. Sandris and G. Ourisson, *Bull. soc. chim. France*, 345 (1958), for 2,2,5,5-substitution.

(23) E.g., R. E. Ireland, *Chemistry & Industry*, 979 (1958).

(24) All melting points are corrected. We are indebted to Mrs. Maria Stingl, Miss Claire Higham and Mr. Josef Nemeth for the microanalyses. We also thank Mr. James Brader and Mr. Brian Clooney for the determination of the infrared absorption spectra.

(25) S. Searles, M. Tamres, F. Block and L. A. Quarterman, *THIS JOURNAL*, **78**, 4917 (1956).

(26) J. P. Wibaut, *Rec. trav. chim.*, **44**, 1101 (1925).

(27) R. B. Moffett, *Org. Syntheses*, **33**, 32 (1953).

(28) R. L. Frank, W. R. Schmitz and B. Zeidman, *ibid.*, Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 328.

(29) Yu. K. Yur'ev, *Zhur. Obshch. Chim.*, **8**, 1934 (1938).

(30) K. Löffler, *Ber.*, **43**, 2035 (1910).

(31) R. Lukeš, V. Dienstbierová and O. Červinka, *Chem. Listy*, **52**, 1137 (1958).

(32) F. F. Blicke and C.-J. Lu, *THIS JOURNAL*, **74**, 3933 (1952).

(33) H. T. Clarke and L. D. Behr, "Org. Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 562.

(34) N. J. Leonard, J. Curry and J. Sagura, *THIS JOURNAL*, **75**, 6249 (1953).

(35) R. Lukeš and J. Málek, *Coll. Czech. Chem. Commun.*, **16**, 23 (1951).

dropwise addition of a saturated aqueous solution of potassium carbonate. The entire solution then was extracted several times with ether. The combined ethereal filtrates were concentrated, and the residual oil was converted to the picrate of 1,2-dimethylpyrrolidine²⁹; m.p. 240° dec., yield 8.5 g. (60%).

Mercuric Acetate Oxidation of 1,2,2-Trimethylpyrrolidine.—Oxidation of 9.4 g. (0.083 mole) of 1,2,2-trimethylpyrrolidine by the general procedure described gave 6.89 g. (74%) of 1,5,5-trimethyl-3-(1',5',5'-trimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline, b.p. 125–127° (15 mm.), n_D^{25} 1.4790; ν_{\max}^{film} 1648(s), 1757(w) cm^{-1} (latter band possibly due to hydrolysis of some enamine to aminoaldehyde).³⁶

Anal. Calcd. for $\text{C}_{14}\text{H}_{26}\text{N}_2$: C, 75.61; H, 11.79; N, 12.60; mol. wt., 222.4. Found: C, 75.29; H, 11.58; N, 12.52; mol. wt., 236 \pm 11.

Condensation of 1,5,5-Trimethyl-3-(1',5',5'-trimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline with Ethyl Acetoacetate.—A solution of 2.6 g. (0.012 mole) of 1,5,5-trimethyl-3-(1',5',5'-trimethyl-2'-pyrrolidyl)- Δ^2 -pyrroline and 65 g. of ethyl acetoacetate in 65 ml. of 50% aqueous ethanol was allowed to stand in the dark under nitrogen at about 25° for several days. Then 105 ml. of 12 *N* hydrochloric acid was added, and the resulting solution was heated on a steam-bath for 5 hours. The solution was reduced to a small volume under vacuum, and the residue was washed with ether to remove non-basic material. The aqueous layer was basified with potassium carbonate and extracted exhaustively with ether. The combined basic ether extracts were dried, filtered, and concentrated. The residue was fractionally distilled to give 1.3 g. (33%) of a colorless liquid, 2-acetyl-1,5,5-trimethylpyrrolidine, b.p. 95° (16 mm.), n_D^{25} 1.4539, ν_{\max}^{film} 1708(s) cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.94; H, 11.36; N, 8.42.

The picrate crystallized from ethanol as fine yellow needles, m.p. 157–158°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_6$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.09; H, 5.63; N, 14.33.

The perchlorate crystallized from ethanol as colorless prisms, m.p. 127.5–129°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{ClNO}_5$: C, 44.53; H, 7.47; N, 5.19. Found: C, 44.83; H, 7.23; N, 5.13.

Mercuric Acetate Oxidation of 1-Methylpyrrolidine.—Oxidation of 20 g. (0.235 mole) of 1-methylpyrrolidine²⁵ by the general procedure yielded two major products: (a) Dimer: 1-methyl-3-(1'-methyl-2'-pyrrolidyl)- Δ^2 -pyrroline, ^{37a} b.p. 103° (21 mm.), n_D^{25} 1.4945, yield 5.1 g. (25%), ν_{\max}^{film} 1645 cm^{-1} . (The crude material had a very weak infrared band at 1690 cm^{-1} , which could be indicative of a trace amount of 1-methyl-2-pyrrolidone.³⁸)

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{N}_2$: C, 72.24; H, 10.91; N, 16.85; mol. wt., 170.3. Found: C, 72.05; H, 10.87; N, 16.48; mol. wt., 169 \pm 8 (cryoscopic).³⁹

(b) Trimer: 1-methyl-3-[1'-methyl-3'-(1''-methyl-2''-pyrrolidyl)-2'-pyrrolidyl]- Δ^2 -pyrroline, b.p. 173° (21 mm.), n_D^{25} 1.5072, ν_{\max}^{film} 1645(s) cm^{-1} ; yield 5.1 g. (25%).

Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{N}_3$: C, 72.24; H, 10.91; N, 16.85; mol. wt., 249.4. Found: C, 71.71; H, 10.76; N, 16.65; mol. wt., 246 \pm 12 (cryoscopic).

Condensation of 1-Methyl- Δ^2 -pyrroline Dimer and Trimer with Ethyl Acetoacetate.—A solution of 3.0 g. (0.023 mole) of the dimer of 1-methyl- Δ^2 -pyrroline and 65 g. of ethyl acetoacetate in 65 ml. of 50% aqueous ethanol was allowed to stand in the dark under nitrogen at 25° for 11 days. The product, 2-acetyl-1-methylpyrrolidine or *dl*-hygrine, following isolation in the manner described above for 2-acetyl-1,5,5-trimethylpyrrolidine, was fractionally distilled, b.p. 83° (19 mm.), n_D^{25} 1.4552, yield 0.55 g. (13%), ν_{\max}^{film} 1708 cm^{-1} ; picrate, m.p. 149.5–151° (reported 148°–149°).

[37a] ADDED IN PROOF.—See also R. Lukeš, J. Iešek and J. Trojánek, *Collection Czech. Chem. Commun.*, **24**, 1987 (1959).

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[39] F. Pregl, "Quantitative Organic Microanalysis," 5th English edition, J. and A. Churchill, Ltd., London, 1951.

[40] E. F. L. J. Anet, G. K. Hughes and E. Ritchie, *Austral. J. Sci. and Res.*, **2**, 617 (1949).

151, ⁴¹ 155°⁴²). The condensation of the trimer of 1-methyl- Δ^2 -pyrroline with ethyl acetoacetate under the same conditions yielded *dl*-hygrine in approximately the same amount. We have not studied variations in the conditions for the purpose of obtaining a maximum yield.

Mercuric Acetate Oxidation of 1,3-Dimethylpyrrolidine.—Oxidation of 20 g. (0.20 mole) of 1,3-dimethylpyrrolidine with mercuric acetate according to the general procedure gave 8.4 g. (43%) of the dimer, 1,4-dimethyl-3-[1',4' (and/or 1',3')-dimethyl-2'-pyrrolidyl]- Δ^2 -pyrroline, b.p. 111–113° (22 mm.), n_D^{25} 1.4879, ν_{\max}^{film} 1638 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{N}_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.38; H, 11.21; N, 14.17.

Condensation of "1,4-Dimethyl- Δ^2 -pyrroline Dimer" with Ethyl Acetoacetate.—A solution of 0.52 g. (0.011 mole) of "1,4-dimethyl- Δ^2 -pyrroline dimer" and 20 g. of ethyl acetoacetate in 17 ml. of 50% aqueous ethanol was allowed to stand in the dark under nitrogen at about 25° for 13 days. The product was 0.39 g. (47%) of 2-acetyl-1,4-dimethylpyrrolidine (or a mixture of this and 2-acetyl-1,3-dimethylpyrrolidine), b.p. 80° (15 mm.), n_D^{25} 1.4499, ν_{\max}^{film} 1708 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{NO}$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.66; H, 10.74; N, 8.99.

The picrate crystallized from ethanol as fine yellow needles, m.p. 141–143.5°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_6$: C, 46.87; H, 5.25; N, 14.58. Found: C, 46.66; H, 5.08; N, 14.87.

1,3,4-Trimethylpyrrolidine.—The general procedure for reducing imides to amines with lithium aluminum hydride in ether was used to reduce 1,3,4-trimethylsuccinimide⁴³ (n_D^{25} 1.4698) to 1,3,4-trimethylpyrrolidine in 78% yield, b.p. 114–115°, n_D^{25} 1.4209.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{N}$: C, 74.27; H, 13.36; N, 12.37. Found: C, 73.95; H, 13.50; N, 12.55.

The picrate crystallized from ethanol as yellow needles, m.p. 203–204°.

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_7$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.40; H, 5.41; N, 16.23.

The picronate crystallized from aqueous ethanol as yellow-orange needles, m.p. 183.5–184.5°.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{N}_3\text{O}_6$: C, 54.10; H, 6.14; N, 18.56. Found: C, 54.22; H, 6.26; N, 18.42.

Mercuric Acetate Oxidation of 1,3,4-Trimethylpyrrolidine.—Oxidation of 10 g. (0.088 mole) of 1,3,4-trimethylpyrrolidine by the general procedure described gave two major products: (a) 1,3,4-Trimethyl- Δ^2 -pyrroline, b.p. 40° (30 mm.), n_D^{25} 1.4382, ν_{\max}^{film} 1648 cm^{-1} , yield 5.2 g. (52%). Instability of this product and possibly codistillation with solvent interfered with the analysis.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{N}$: C, 75.61; H, 11.79; N, 12.60. Found: C, 74.38; H, 11.48; N, 12.22.

The perchlorate crystallized from ethanol as colorless needles, m.p. 101–102°, $\nu_{\max}^{\text{Nujol}}$ 1693 cm^{-1} , pK'_a 9.6 (water), 8.75 (66% dimethylformamide), mol. wt. 211 \pm 2 (theor. 211).⁴⁴

Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{ClNO}_4$: C, 39.72; H, 6.67; N, 6.62. Found: C, 39.98; H, 6.95; N, 6.95.

(b) 1,3,4-Trimethyl-2-(1',3',4'-trimethyl-2'-pyrrolidyl)-pyrroline, b.p. 120–125° (19 mm.), n_D^{25} 1.5031, yield 1.07 g. (11%); $\nu_{\max}^{\text{Cl}_4}$ 2760(s), 1530(m) cm^{-1} ; $\lambda_{\max}^{\text{EtOH}}$ 220–230 μ (plateau), ϵ 6950. The compound gave a strong pine splint test in the cold, whereas representative enamines herein described did not give a good pine splint test under the same conditions.

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_2$: C, 76.31; H, 10.98; N, 12.71; mol. wt., 220. Found: C, 76.44; H, 11.04; N, 12.97; mol. wt., 223 \pm 11 (cryoscopic, with camphor).

(41) F. Galinovsky, A. Wagner and R. Weiser, *Monatsh. Chem.*, **82**, 551 (1951).

(42) F. Šorm, *Coll. Czech. Chem. Commun.*, **12**, 245 (1947).

(43) C. A. Miller and L. M. Long, *This Journal*, **75**, 373 (1953); see G. E. McCasland and S. Proskow, *ibid.*, **76**, 6087 (1954); see also J. Trojánek and J. Pospíšek, *Coll. Czech. Chem. Commun.*, **24**, 307 (1959).

(44) The authors express their sincere appreciation to Dr. Harold Bonz, Eli Lilly and Co., Indianapolis, Ind., for making these figures available to us.

Using the general method of introducing an aldehyde function on pyrrole,⁴⁶ compound (b) was converted to 1,3,4-trimethyl-2-(1',3',4'-trimethyl-2'-pyrrolidyl)-5-pyrrolicarboxaldehyde, b.p. 90° (1.9 mm.), n_{D}^{25} 1.5438, $\nu_{\text{max}}^{\text{C=O}}$ 1650 cm^{-1} ; $\lambda_{\text{max}}^{\text{EOM}}$ 272 (ϵ 9000), 304 $\text{m}\mu$ (ϵ 6830).⁴⁶

2,2,5-Trimethylpyrrolidine,⁴⁷ b.p. 113–114°, n_{D}^{24} 1.4212, was converted to the hydrochloride, m.p. 185–187.5°, colorless prisms from ether-ethanol.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{ClN}$: C, 56.17; H, 10.78; N, 9.36. Found: C, 56.28; H, 10.56; N, 9.57.

1,2,2,5-Tetramethylpyrrolidine.—Methylation of 2,2,5-trimethylpyrrolidine in the usual manner with formic acid and formalin produced 1,2,2,5-tetramethylpyrrolidine, b.p. 128–130°, n_{D}^{27} 1.4273.

Anal. Calcd. for $\text{C}_8\text{H}_{17}\text{N}$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.65; H, 13.61; N, 11.22.

The picrate crystallized from ethanol in the form of yellow needles, m.p. 241–241.5° dec. (reported⁴⁸ 224–226°).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.22; H, 5.55; N, 15.78.

The perchlorate crystallized from isopropyl alcohol as colorless needles, m.p. 223.5–225°.

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{ClNO}_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.22; H, 7.70; N, 6.00.

The hydrochloride separated from ethanol-ether as colorless prisms, m.p. 212–213°.

(45) R. M. Silverstein, E. E. Ryskiewicz and C. Willard, *Org. Syntheses*, **36**, 74 (1956).

(46) See W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958).

(47) R. B. Moffett and J. L. White, *ibid.*, **17**, 407 (1952).

(48) R. Lukeš and M. Vecerá, *Coll. Czech. Chem. Commun.*, **19**, 263 (1954).

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{ClN}$: C, 58.70; H, 11.08; N, 8.56. Found: C, 58.64; H, 10.89; N, 8.50.

Mercuric Acetate Oxidation of 1,2,2,5-Tetramethylpyrrolidine.—Oxidation of 9.0 g. (0.071 mole) of 1,2,2,5-tetramethylpyrrolidine was carried out in the usual manner except that the final ethereal solution was treated dropwise with a solution of 1:1 70% perchloric acid:ethanol until the mixture was acid to congo red. Recrystallization of the precipitated salt from isopropyl alcohol yielded 12.45 g. (78%) of 1,2,5,5-tetramethyl- Δ^1 -pyrrolinium perchlorate, colorless needles, m.p. 189–191°, $\nu_{\text{max}}^{\text{N}^+\text{O}^-}$ 1677 cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{ClNO}_4$: C, 42.57; H, 7.15; N, 6.21; O, 28.23. Found: C, 42.53; H, 7.06; N, 6.15; O, 28.15.

The corresponding base, 1,2,5,5-tetramethyl- Δ^2 -pyrrolidine, was distilled under nitrogen, b.p. 89° (120 mm.), n_{D}^{24} 1.4639, but decomposed rapidly, $\nu_{\text{max}}^{\text{C=C}}$ 1635(s) ($\text{C}=\text{C}$) and 1695(vw) cm^{-1} (possible hydrolysis of some of the enamine by water vapor to the aminoketone).³⁸

The picrate crystallized from ethanol as yellow-orange needles, m.p. 223–224° dec., $\nu_{\text{max}}^{\text{N}^+\text{O}^-}$ 1677 cm^{-1} ($>\text{C}=\text{N}^+<$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.62; H, 5.04; N, 15.72.

Mercuric Acetate Oxidation of 1-Methyl-1-azacycloheptane.⁴⁹—Oxidation of 14.2 g. (0.13 mole) of 1-methyl-1-azacycloheptane³⁶ with mercuric acetate and isolation by the general procedure yielded 3.89 g. of crude product, $\nu_{\text{max}}^{\text{C=C}}$ 1655 cm^{-1} . On distillation, 0.9 g. of starting material was recovered but no enamine. The distillation residue was hard and resinous.

(49) See also ref. 5.

URBANA, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Unsaturated Amines. XV. The Mercuric Acetate Oxidation of Medium Rings Containing Tertiary Nitrogen¹

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The major product of mercuric acetate oxidation of 1-methyl-1-azacyclooctane (I), then a treatment with hydrogen sulfide and hydrochloric acid, has been shown to be 2,4,6-tris-(6'-methylaminoheptyl)-trithiane trihydrochloride (II). The corresponding products, 2,4,6-tris-(7'-methylaminoheptyl)-trithiane trihydrochloride and 2,4,6-tris-(5'-methylaminopentyl)-trithiane trihydrochloride, are obtained from 1-methyl-1-azacyclononane and 1-methyl-1-azacycloheptane, respectively. The conversions indicate that cyclic amines of ring size seven to nine (and higher) undergo ring opening under conditions which permit equilibration between open and closed forms. As a result of the experiments described herein, the main course of the mercuric acetate oxidation of medium-ring tertiary amines may be predicted and conditions may be selected so as to effect over-all—when a final Raney nickel desulfurization step is included—a carbon-nitrogen hydrogenolytic scission.

A logical extension of the study of the mercuric acetate oxidation of monocyclic tertiary amines, which thus far has dealt mainly with five-¹ and six-membered ring compounds,³ was to determine the course of the oxidation with seven-, eight- and nine-membered rings, since unusual behavior could be predicted for the tertiary amines of medium ring size. Indeed, we were not disappointed, since the major products obtained from the mercuric acetate oxidation of 1-methyl-1-azacycloheptane, 1-methyl-1-azacyclooctane and 1-methyl-1-azacyclononane were unlike those obtained from the amines of classical ring size.

Some variation in the usual conditions³ was necessary in order to obtain identifiable products.

(1) For article XIV in this series, see preceding paper by N. J. Leonard and A. G. Cook, *THIS JOURNAL*, **81**, 5627 (1959).

(2) USI (U. S. Industrial Chemicals Co.) Fellow, 1958–1959.

(3) N. J. Leonard and F. P. Hauck, Jr., *THIS JOURNAL*, **79**, 5279 (1957).

Thus, since the treatment of 1-methyl-1-azacycloheptane with excess mercuric acetate in 5% acetic acid for 2 hours on the steam-bath, followed by the normal sequence of filtration, precipitation with hydrogen sulfide, basification and ether extraction, yielded no monomeric material,¹ we modified the isolation procedure with a termination sequence of hydrochloric acid treatment and evaporation following the hydrogen sulfide reaction. Well-characterized products were obtained from the seven-, eight- and nine-membered ring compounds by this means. The product from 1-methyl-1-azacyclooctane (I) under the modified conditions will be discussed first. The reaction involved essentially two stages, mercuric acetate oxidation at 45–48° during 50 hours and hydrogen sulfide-hydrochloric acid treatment. The crystalline organic product, m.p. 236–239° dec., contained chlorine, nitrogen and sulfur in a ratio of unity, corresponding to an em-