Using the general method of introducing an aldehyde function on pyrrole,[45] compound (b) was converted to **1,3,4-trimethyl-2-(1′,3′,4′-trimethyl-2′-pyrrolidyl)-5-pyrrolecarboxaldehyde**, b.p. 90° (1.9 mm.), $n^{25}\mathrm{D}$ 1.5438, $\nu_{\max}^{\mathrm{CCl_4}}$ 1650 cm.$^{-1}$; $\lambda_{\max}^{\mathrm{EtOH}}$ 272 (ϵ 9000), 304 mμ (ϵ 6830).[46]

2,2,5-Trimethylpyrrolidine,[47] b.p. 113–114°, $n^{24.5}\mathrm{D}$ 1.4212, was converted to the **hydrochloride**, m.p. 185–187.5°, colorless prisms from ether–ethanol.

Anal. Calcd. for $C_7H_{16}ClN$: 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°, $n^{27.5}\mathrm{D}$ 1.4273.

Anal. Calcd. for $C_8H_{17}N$: 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. (reported[48] 224–226°).

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: 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 $C_8H_{18}ClNO_4$: 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°.

Anal. Calcd. for $C_8H_{18}ClN$: 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°, $\nu_{\max}^{\mathrm{Nujol}}$ 1677 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}ClNO_4$: 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-pyrroline, was distilled under nitrogen, b.p. 89° (120 mm.), $n^{24}\mathrm{D}$ 1.4639, but decomposed rapidly, $\nu_{\max}^{\mathrm{film}}$ 1635(s) (C=C) and 1695(vw)cm.$^{-1}$ (possible hydrolysis of some of the enamine by water vapor to the aminoketone).[36]

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

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: 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-azacycloheptane[35] with mercuric acetate and isolation by the general procedure yielded 3.89 g. of crude product, $\nu_{\max}^{\mathrm{film}}$ 1655 cm.$^{-1}$. On distillation, 0.9 g. of starting material was recovered but no enamine. The distillation residue was hard and resinous.

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[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. Večeřa, *Coll. Czech. Chem. Communs.*, **19**, 263 (1954).

[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 Nitrogen[1]

BY NELSON J. LEONARD AND W. KENNETH MUSKER[2]

RECEIVED MAY 23, 1959

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′-methylaminohexyl)-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 conditions[3] was necessary in order to obtain identifiable products. 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-

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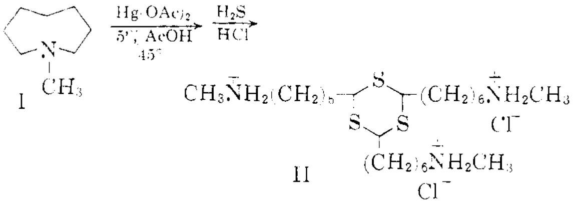
[1] For article XIV in this series, see preceding paper by N. J. Leonard and A. G. Cook, THIS JOURNAL, **81**, 5627 (1959).

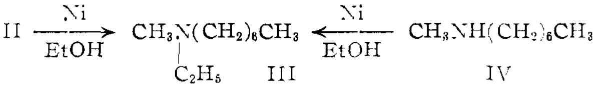
[2] USI (U. S. Industrial Chemicals Co.) Fellow, 1958–1959.

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

pirical formula $C_8H_{18}ClNS$. The chlorine was ionic, and the infrared absorption maxima at 1600 and 2435 cm.$^{-1}$ were indicative of the grouping $>\overset{+}{N}H_2$-Cl^- and therefore of a structure in which the original eight-membered ring had been opened. The incorporation of sulfur in the product suggested a thioaldehyde group at the end of the chain opposite the disubstituted ammonium chloride group, and recollection of the tendency of the thioaldehydes to trimerize[4,5] led us to postulate structure II, $C_{24}H_{54}Cl_3N_3S_3$, for this product.

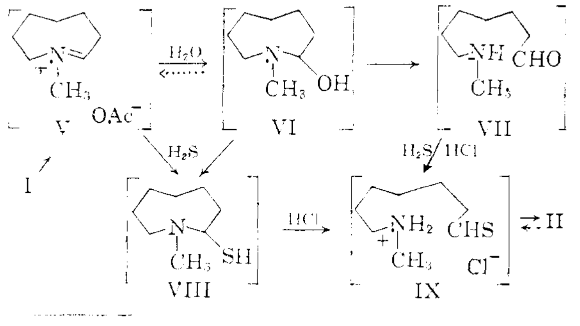


The cyclic trimer of 7-methylaminothioheptanal hydrochloride, or 2,4,6-tris-(6′-methylaminohexyl)-trithiane trihydrochloride (II), should possess an ultraviolet spectrum indicative of the trithiane moiety. In confirmation, the maximum at 238 mμ (log ε 3.05) for the reaction product in ethanol corresponds to that observed for trithiane, 240 mμ (log ε 3.16).[6] The infrared spectrum was also consistent with the presence of the trithiane moiety in II. The rest of the molecule was characterized by treatment with Raney nickel, which effected hydrogenolysis of the carbon–sulfur bonds[7] and, since aqueous ethanol was used as a solvent, ethylation[8,9] of the secondary amine intermediate to yield ethylmethylheptylamine (III). The tertiary amine, identified by the picrate which formed readily, was also produced by treatment of methylheptylamine (IV) with Raney nickel in aqueous ethanol.



$$\mathrm{II} \xrightarrow[\mathrm{EtOH}]{\mathrm{Ni}} \underset{\underset{\mathrm{III}}{C_2H_5}}{CH_3N}(CH_2)_6CH_3 \xleftarrow[\mathrm{EtOH}]{\mathrm{Ni}} \underset{\mathrm{IV}}{CH_3NH(CH_2)_6CH_3}$$

The formation of II (yield 40%) from 1-methyl-1-azacyclooöctane (I) can be explained satisfactorily by alternative pathways, such as those presented in the accompanying diagram. It is reasonable to expect the saturated tertiary amine I to be oxidized by mercuric acetate to the ternary iminium salt V, just as in the examples of the five- and six-membered cyclic tertiary amines.[1,3] However, unlike these rings, the equilibrium for the eight-membered ring case between cyclic ternary iminium form V, cyclic pseudobase VI and sec.-aminealdehyde form VII would be expected to lie preponderantly with the ring-opened form VII, due to the possibility of relieving the ring strain resulting from non-bonded interactions in the medium ring. Hydrogen sulfide and hydrochloric acid, used in the second stage of the reaction, would convert the aminoaldehyde to the aminothioaldehyde (hydrochloride) IX and thence to the trimer II. If any 2-mercapto-1-methyl-1-azacyclooöctane (VIII) were produced from V or VI, it would also tend to exist in the ring-opened aminothioaldehyde form and would eventually yield the substituted trithiane II or linear analogs thereof.



The conversion of I to II may be taken as a firm indication that the eight-membered ring containing nitrogen undergoes ring opening under conditions which permit equilibration between open and closed forms. The same tendency toward ring opening has been recognized earlier in the reactions of Grignard reagents with seven-, eight- and nine-membered lactams[10,11] and in the Clemmensen and Wolff–Kishner reductions of eight-membered ring α-aminoketones.[12,13]

The nine-membered ring is opened similarly, as shown by the conversion of 1-methyl-1-azacyclononane to 2,4,6-tris-(7′-methylaminoheptyl)-trithiane trihydrochloride (37%) using mercuric acetate followed by hydrogen sulfide and hydrochloric acid treatment. The same ring opening reaction is predicted for the ten-membered ring compound. Finally, returning to the seven-membered ring system, 1-methyl-1-azacycloheptane was converted to 2,4,6-tris-(5′-methylaminopentyl)-trithiane trihydrochloride in somewhat lower yield (23%) than that obtainable in the analogous conversion from 1-methyl-1-azacyclooöctane, which is in line with previous experience.[11] The six-membered ring compound, 1-methylpiperidine, did not yield a ring-opened product. As a result of the present experiments, the course of the mercuric acetate oxidation of medium-ring tertiary amines may be predicted and a reaction sequence may be followed so as to effect, over-all, a carbon–nitrogen hydrogenolytic scission.

Experimental[14]

Saturated Amines.—Methylation of azacycloheptane, azacyclooöctane and azacyclononane[15] with formaldehyde–formic acid[16] yielded the known tertiary amines: 1-methyl-1-azacycloheptane,[11] b.p. 141–144° (746 mm.), n^{26}D 1.4510;

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[4] H. Klinger, *Ber.*, **11**, 1023 (1878).

[5] E. Baumann and E. Fromm, *ibid.*, **22**, 2600 (1889).

[6] E. A. Fehnel and M. Carmack, THIS JOURNAL, **71**, 84 (1949).

[7] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *ibid.*, **65**, 1013 (1943).

[8] G. N. Kao, B. D. Tilak and K. Venkataraman, *J. Sci. Ind. Research India*, **14B**, 624 (1955).

[9] R. G. Rice and E. J. Kohn, THIS JOURNAL, **77**, 4052 (1955).

[10] R. Lukeš and J. Dobáš, *Coll. Czech. Chem. Communs.*, **15**, 303 (1950).

[11] R. Lukeš and J. Málek, *ibid.*, **16**, 23 (1951); *Chem. Listy*, **45**, 72 (1951).

[12] N. J. Leonard and R. C. Sentz, THIS JOURNAL, **74**, 1704 (1952).

[13] N. J. Leonard and S. Gelfand, *ibid.*, **77**, 3269 (1955).

[14] All melting points are corrected. We are indebted to Miss Claire Higham and Mr. Josef Nemeth for the microanalyses. We also thank Miss Mary E. Demott and Mr. Paul McMahon for the determination of the infrared absorption spectra.

[15] L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

[16] H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

picrate, m.p. 220.5–221.5° dec.; 1-methyl-1-azacyclooöctane,[11] b.p. 157–160°, n^{25}D 1.4581; picrate, m.p. 206–208° dec.; 1-methyl-1-azacyclononane,[11] b.p. 180–181°, n^{25}D 1.4640; picrate, m.p. 199–201° dec.

Mercuric Acetate Oxidation of 1-Methyl-1-azacyclooöctane, General Procedure for the Mercuric Acetate Oxidations.—A mixture of 3.95 g. (0.031 mole) of 1-methyl-1-azacyclooöctane and 48 g. (0.185 mole) of mercuric acetate in 130 ml. of 5% acetic acid (95% water) was heated with stirring at 45–48° for 50 hours. 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 dried mercurous acetate weighed 11.4 g. (71% of theoret.). The filtrate was saturated with hydrogen sulfide and the resulting mixture was filtered through a mat of Filter-Cel in a large Büchner funnel. The mercuric sulfide was washed several times with dilute acetic acid, and the combined filtrates were resaturated with hydrogen sulfide. After a second filtration 12 *N* hydrochloric acid (50 ml.) was added to the filtrate. Most of the water was removed under vacuum, 100 ml. of ethanol was added and the ethanolic solution was concentrated to 25 ml. The precipitate which formed on cooling was recrystallized from absolute ethanol to give 2.36 g. (40%) of colorless product, m.p. 236–239° dec., the trimer of 7-methylaminothioheptanal hydrochloride or 2,4,6-tris-(6′-methylaminohexyl)-trithiane trihydrochloride (II), $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ε 3.05); $\nu_{\max}^{\mathrm{Nujol}}$ 725, 1160 and 1375 cm.$^{-1}$ (trithiane) and 1045, 1600 and 2435 cm.$^{-1}$ ($>\overset{+}{N}H_2Cl^-$). The same product was obtained when the oxidation conditions were 3 hours at steam-bath temperature and the same isolation procedure was employed.

Anal. Calcd. for $C_{24}H_{54}Cl_3N_3S_3$: C, 49.10; H, 9.27; Cl, 18.11; N, 7.15; S, 16.36; mol. wt., 587.4 (undissociated). Found: C, 48.99; H, 9.22; Cl, 18.20; N, 6.98; S, 16.96; mol. wt., 214 (ebullioscopic in ethanol).

Raney Nickel Desulfurization–Alkylation of 2,4,6-Tris-(6′-methylaminohexyl)-trithiane Trihydrochloride. General Procedure for Desulfurization–Alkylation Reactions.—Pyrophoric nickel was prepared from commercial Raney nickel by washing several times with absolute ethanol, centrifuging and then refluxing 3 hours in absolute ethanol. A mixture of 19 g. of nickel and 0.6 g. (1.1 mmoles) of 2,4,6-tris-(6′-methylaminohexyl)-trithiane trihydrochloride in 50 ml. of 70% ethanol was heated at reflux for 2 days. The mixture was centrifuged, and the liquid was decanted from the nickel, which was washed twice with hot ethanol and once with water. The washings were combined and acidified with 12 *N* hydrochloric acid. Most of the ethanol was removed under reduced pressure, and the acidic solution was extracted with ether to remove non-basic materials. The solution was basified with potassium hydroxide and extracted three times with ether. The dried ethereal solution was treated with picric acid in ethanol. Partial evaporation and then the dropwise addition of water yielded crystalline material, and recrystallization from aqueous ethanol furnished **ethylmethylheptylamine picrate**, yellow needles, m.p. 60–62.5° (after solidification and remelting, at 57.5–58.5°), yield 0.6 g. (49%). No depression in melting point was observed on admixture with an authentic sample (see below).

Anal. Calcd. for $C_{16}H_{26}N_4O_7$: C, 49.73; H, 6.78; N, 14.50. Found: C, 49.65; H, 6.66; N, 14.67.

When methylheptylamine[17] in aqueous ethanol was treated with Raney nickel as described above, ethylmethylheptylamine picrate was isolated, m.p. 60–62.5° (after solidification and remelting, at 57–58°).

Mercuric Acetate Oxidation of 1-Methyl-1-azacyclononane.—Oxidation of 4.38 g. (0.031 mole) of 1-methyl-1-azacyclononane following the directions given above yielded 2.4 g. (37%) of the trimer of 8-methylaminothioöctanal hydrochloride, or 2,4,6-tris-(7′-methylaminoheptyl)-trithiane trihydrochloride, recrystallized from absolute ethanol, m.p. 234.5–236° dec., $\lambda_{\max}^{\mathrm{EtOH}}$ 238 mμ (log ε 3.06), infrared spectrum like that of the lower homolog.

Anal. Calcd. for $C_{27}H_{60}Cl_3N_3S_3$: C, 51.53; H, 9.61; Cl, 16.90; N, 6.68; S, 15.28. Found: C, 51.29; H, 9.85; Cl, 16.79; N, 6.48; S, 14.83.

Raney Nickel Desulfurization–Alkylation of 2,4,6-Tris-(7′-methylaminoheptyl)-trithiane Trihydrochloride.—Treatment of tris-(7′-methylaminoheptyl)-trithiane trihydrochloride in aqueous ethanol with Raney nickel gave **ethylmethyloctylamine**, isolated as the **picrolonate**, m.p. 101–102° dec., yellow prisms from aqueous methanol, yield 52%.

Anal. Calcd. for $C_{21}H_{33}N_5O_5$: C, 57.91; H, 7.64; N, 16.08. Found: C, 58.13; H, 7.71; N, 16.24.

Mercuric Acetate Oxidation of 1-Methyl-1-azacycloheptane.—Oxidation of 5.70 g. (0.05 mole) of 1-methyl-1-azacycloheptane, followed by the isolation procedure described above, gave 1.65 g. (23%) of the trimer of 6-methylaminothiohexanal hydrochloride, or 2,4,6-tris-(5′-methylaminopentyl)-trithiane trihydrochloride, recrystallized from absolute ethanol, m.p. 223–225° dec., $\lambda_{\max}^{\mathrm{EtOH}}$ 237 mμ (log ε 3.09), infrared spectrum very similar to those of the higher homologs.

Anal. Calcd. for $C_{21}H_{48}Cl_3N_3S_3$: C, 46.28; H, 8.88; Cl, 19.50; N, 7.71; S, 17.64. Found: C, 46.12; H, 8.58; Cl, 19.59; N, 7.49; S, 17.91.

Raney Nickel Desulfurization–Alkylation of 2,4,6-Tris-(5′-methylaminopentyl)-trithiane Trihydrochloride.—Treatment of tris-(5′-methylaminopentyl)-trithiane trihydrochloride in aqueous ethanol with Raney nickel gave **ethylmethylhexylamine**, isolated as the **picrolonate**, m.p. 79.5–81°, yellow needles from aqueous methanol, yield 41%.

Anal. Calcd. for $C_{19}H_{29}N_5O_5$: C, 56.00; H, 7.17; N, 17.09. Found: C, 56.09; H, 7.02; N, 16.80.

Mercuric Acetate Oxidation of 1-Methylpiperidine.—When the mercuric acetate oxidation of 1-methylpiperidine, followed by product isolation, was carried out according to the directions described above rather than following the conditions used previously for the oxidation of this substrate,[3] which had yielded (67%) 1,1′-dimethyl-Δ^2-tetrahydroanabasine, no product was obtained corresponding to opening of the six-membered ring.

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[17] N. J. Leonard, S. Swann, Jr., and H. L. Dryden, This Journal, **74**, 2871 (1952).