Synthesis and Properties of 2-Piperidinemethanethiol, 2-Pyrrolidinemethanethiol, and 1-Ethyl-2-pyrrolidinemethanethiol[1,2]

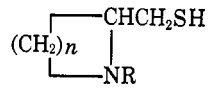
SCOTT SEARLES, JR., GLENN E. ROELOFS, MILTON TAMRES, AND RICHARD N. MCDONALD

Department of Chemistry, Kansas State University, Manhattan, Kansas

Received April 8, 1965

2-Pyrrolidinemethanethiol (I), its 1-ethyl derivative (II), and 2-piperidinemethanethiol (III) were synthesized by the reaction of the hydrobromides of the corresponding 2-bromomethyl compounds with thiourea, followed by cleavage of the resulting crystalline thiouronium salts with tetraethylenepentamine. Compounds I and II were crystalline, sublimable solids with mainly polar solubility properties, and the infrared spectrum of solid I showed it to be largely in the dipolar ion form, while in chloroform solutions the nonionic form predominated in mobile equilibrium with the dipolar form. The basicity of III was unusually high for a β-mercaptoethylamine and greater than that of I, in reverse of the usual effect of ring size on the basicity of cyclic imines. This changed situation is probably associated with protonation on the sulfur atom, rather than the nitrogen atom.

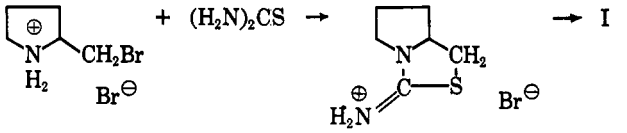
α-Mercaptomethyl cyclic imines are of potential interest as possible radiation-protective drugs, because of the greater basicity of 4-, 5-, and 6-membered cyclic imines relative to comparable acyclic imines.[3] Radiation-protective activity of mercaptans appears to require the presence of a strongly basic function[4-6] and in the case of β-mercaptoamines to depend on its basicity.[7] In the present work, 2-pyrrolidinemethanethiol (I), 1-ethyl-2-pyrrolidinemethanethiol (II), and 2-piperidinemethanethiol (III) were synthesized and their properties were examined.



I, $n = 3$; R = H
II, $n = 3$; R = C_2H_5
III, $n = 4$; R = H

Most of the usual synthetic approaches to β-mercaptoamines, such as the reaction of ethylene sulfides with amines,[8-13] and that of ethylenimines with hydrogen sulfide, mercaptans, or carbon disulfide[14,15] were not applicable because of the cyclic structure required. Several other possible methods, such as reaction of 2-bromomethylpyrrolidine hydrobromide (IV) with sodium benzylmercaptide and with sodium thiolacetate, proved to be unsatisfactory.

The reaction of thiourea with IV, however, gave an isothiouronium salt, which could be isolated in crystalline state in 75% yield. The elemental analysis showed an empirical formula of $C_6H_{11}BrN_2S$, in agreement with the bicyclic structure (V). This is of particular interest, since Piper and Johnson recently reported that they were unable to obtain an isothiouronium salt from the reaction of thiourea with 2-chloromethylpyrrolidine hydrochloride.[16]



The isothiouronium salt (V) was readily cleaved with tetraethylenepentamine in refluxing alcoholic solution,[17] and 2-pyrrolidinemethanethiol (I) was obtained in 75% yield as a white crystalline low-melting solid, which was easily purified by sublimation.

The structure (I) was supported by the elemental analysis and molecular weight determination, as well as the infrared spectrum, which showed both N–H and S–H functionality. Further evidence for the presence of amine and thiol groups was provided by observation of formation of a crystalline hygroscopic hydrochloride, formation of an N,S-diacetyl derivative, and formation of the crystalline benzenesulfonamide (VI) of the corresponding disulfide under Schotten–Baumann conditions.[18] The separation of deeply colored complexes when III was added to solutions of cobaltous and nickel salts, and of a white precipitate when added to a cadmium chloride solution, provided additional evidence for a β relationship for the amino and mercaptan groups, since similar behavior has been observed for β-mercaptoethylamine.[19]

There remained the possibility of isomerization, especially since 2-chloromethyl-1-ethylpyrrolidine hydrochloride has been found to undergo rearrangement with ring enlargement when treated with base.[20] In order to establish the ring skeleton of I, Raney nickel

(1) Abstracted from the Ph.D. Dissertation of G. E. R., Kansas State University, 1965. Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) This work was supported in part by U. S. Army Medical Command Contract MD-2026 and National Institutes of Health Grant RH-00300-02.

(3) S. Searles, M. Tamres, L. Quarterman, and F. Block, *J. Am. Chem. Soc.*, **78**, 4917 (1956).

(4) Z. M. Bacq and P. Alexander, "Fundamentals of Radiobiology," Pergamon Press Ltd., London, 1961, p. 460.

(5) D. G. Doherty, W. T. Bennett, Jr., and R. Shapira, *Radiation Res.*, **7**, 13 (1957); R. Shapira, D. G. Doherty, and W. T. Bennett Jr., *ibid.*, **7**, 22 (1957).

(6) D. G. Doherty, *Intern. Ser. Monographs Pure Appl. Biol., Mod. Trends Physiol. Sci. Div.*, **7**, 45 (1960).

(7) D. P. Jacobs, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962.

(8) H. Gilman and L. A. Woods, *J. Am. Chem. Soc.*, **67**, 1843 (1945).

(9) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *ibid.*, **69**, 2672 (1957).

(10) Y. K. Yur'ev and S. V. Dyatlovitskaya, *Zh. Obshch. Khim.*, **27**, 1787 (1957); *Chem. Abstr.*, **52**, 4603 (1958).

(11) F. Y. Rachinskii and N. M. Slavachevskaya, *Tiolovye Soedin. v. Med. Ukr. Nauchn. Issled. Sanit. Khim. Inst. Tr. Nauchn. Konf., Kiev*, 1957, 23 (1959); *Chem. Abstr.*, **54**, 25368 (1960). F. Y. Fachinskii, N. M. Slavachevskaya, and D. V. Jaffe, *Zh. Obshch. Khim.*, **28**, 2998 (1958).

(12) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5125 (1961).

(13) R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *ibid.*, **27**, 4222 (1962).

(14) H. Bestian, *et al.*, *Ann.*, **566**, 210 (1950).

(15) M. Boese, *Ber.*, **53**, 2000 (1920).

(16) J. R. Piper and T. P. Johnson, *J. Org. Chem.*, **28**, 981 (1963).

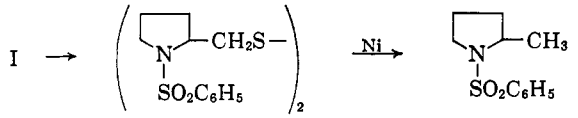
(17) A modification of the method of B. C. Cossar, J. O. Fournier, D. L. Fields, and D. D. Reynolds, *ibid.*, **27**, 93 (1962).

(18) The disulfide formation can no doubt be attributed to air oxidation in the basic medium: D. S. Tarbell ("Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., p. 101) states that "Oxidation of thiols proceeds more rapidly at higher pH and hence probably involves the ion RS^-."

(19) D. C. Jicha and D. H. Busch, *Inorg. Chem.*, **1**, 872 (1962).

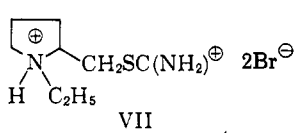
(20) R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760 (1948).

desulfurization of the derivative VI was carried out. The product was identical in all respects with an authentic sample of 1-benzenesulfonyl-2-methylpyrrolidine. Had rearrangement with ring enlargement occurred, the desulfurization product would have been 1-benzenesulfonylpiperidine, which has very different spectral and melting point properties.

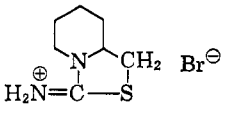


VI

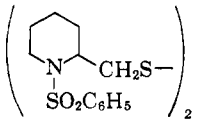
The syntheses of II and III were achieved by synthetic sequences analogous to that described for I The intermediate isothiouronium salts were isolated in crystalline state, the one in the sequence to III being obtained as the 1:1 adduct of VII with thiourea, according to the elemental analysis. The intermediate isothiouronium salt in the synthesis of II was, of course, of the normal type (VII), because of the tertiary-amino structure present. 1-Ethyl-2-pyrrolidinemethanethiol (II) was obtained as a liquid in 49% yield by cleavage of VII with tetraethylenepentamine. 2-Piperidinemethanethiol (III) was obtained as a white crystalline solid from the similar cleavage of VIII.



VII



VIII

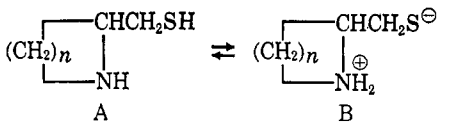


IX

The assignment of structure for II and for III was supported by the elemental analyses and the infrared and n.m.r. spectra. The ring skeleton of III was established in the same way as for I, with the bis(benzenesulfonamide) (IX) of the disulfide, obtained by Schotten–Baumann benzenesulfonation of III being desulfurized with Raney nickel to give 1-benzenesulfonyl-2-methylpiperidine identical with an authentic sample. This method was not applicable to II because of its tertiary-amine nature and the complexity of the reaction of Raney nickel with the aminomercaptans themselves, but the n.m.r. spectrum was sufficiently well resolved, so that a practically complete assignment could be made, showing two methylene and one methine hydrogen atoms in the ring α to the nitrogen atom. Had rearrangement to a piperidine structure, analogous to that observed with the corresponding chloromethyl hydrochloride,[20] occurred, the integration as well as the band splitting would have been significantly different.

Both 2-pyrrolidinemethanethiol (I) and 2-piperidinemethanethiol (III) are low-melting solids, which are very soluble in water but quite insoluble in nonpolar solvents, unless heated. In these respects they differ markedly from their open-chain analogs, the 2-(primary alkylamino)-1-alkanethiols, which are high-boiling liquids of nonpolar character,[12,13,21,22] but they resemble 2-aminoethanethiol,[23] which has been described by Reid[24] as an "inner salt."

Many of the properties of 2-aminoethanethiol and of I and III, however, are quite unlike those for well-recognized inner salt compounds such as α-amino acids, *e.g.*, the relatively low melting points and volatility at moderate temperatures. It seemed of interest, therefore, to investigate the matter further. The infrared spectrum of solid I, both in a Nujol mull and in a potassium bromide disk, showed broad absorption in the 3.5–4.5-μ region and a band of moderate intensity at 6.4 μ, both of which are reported to be characteristic of salts of secondary amines[25] and were seen in the spectrum of the hydrochloride of I. Absorption bands for normal N–H and S–H groups were, however, also present in the spectrum of solid I, although at lower intensities than usual. Whether both forms A and B are present in the crystal is not known, as sample preparation may have caused formation of some of the covalent form. There is undoubtedly an easily displaced equilibrium between the two forms, with the dipolar ion favored in the solid in special cases, such as



A B

I, III, and 2-aminoethanethiol, perhaps because of crystal lattice forces.[26] The very easy air oxidation of I and III to disulfides in the solid state also suggests the presence of the dipolar ion, since mercaptides are much more readily oxidized than mercaptans.[27]

One might expect the nonpolar form (A) to be favored in solvents of low polarity. Solutions of III in chloroform or methylene chloride showed no NH_2^+ absorption bands in the infrared spectrum, and the n.m.r. spectra of chloroform solutions showed the normal chemical shifts for the hydrogen atoms α to the sulfur and nitrogen atoms in covalent amines and mercaptans. There was a single peak in the n.m.r. spectrum for both the N–H and S–H protons, which was shifted by addition of dioxane, indicating that rapid exchange of these protons occurs even in nonpolar solvents. The above equilibrium is no doubt very important even when the nonpolar form is predominant.

Basicity measurements in aqueous solution showed that compound III was an unusually basic β-aminomercaptan, more basic, in fact, than 2-aminoethylmercaptan. The pyrrolidine analog I, however, was considerably less basic than III, although, in general, pyrrolidines tend to be more basic than piperidines,

(21) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, pp. 407–409.

(22) A few crystalline N-alkylaminoethylmercaptans are known, but in these either the alkyl group is secondary or tertiary or additional functionality is present [*e.g.*, *t*-butylaminoethylmercaptan, m.p. 46–48°, and 2-(6′-aminohexyl)aminoethylmercaptan, m.p. 38–40°, reported in ref. 13].

(23) S. Gabriel and J. Coleman, *Ber.*, **45**, 1643 (1912).

(24) E. E. Reid, ref. 21, p. 399.

(25) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962, p. 39.

(26) The presence of hydrogen-bonded species intermediate between A and B is also possible, as there was a weak band in the infrared spectrum of solid III at 0.2 μ greater wave length than the normal S–H vibration at 3.8 μ. The infrared spectra of chloroform and methylene chloride solutions, however, showed no evidence of hydrogen bonding. Hydrogen bonding of mercaptans has been indicated to be weak in other work: D. Plant, D. S. Tarbell, and C. Whiteman, *J. Am. Chem. Soc.*, **77**, 1572 (1955); L. D. Colebrook and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **47**, 993 (1961).

(27) D. S. Tarbell, ref. 18.

TABLE I

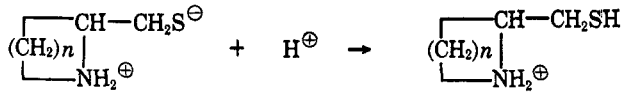
pK_a VALUES OF RELATED β-AMINOMERCAPTANS, β-AMINO ALCOHOLS, AND AMINES

Compd.	pK_a (25°)
2-Pyrrolidinemethanethiol (I)	8.15
2-Piperidinemethanethiol (III)	8.85
2-Aminoethanethiol	8.10[a]
2-*sec*-Butylaminoethanethiol	8.10
2-Pyrrolidinemethanol	10.09
2-Piperidinemethanol	10.00
2-Aminoethanol	9.45[b]
2-Ethylpyrrolidine	10.75
2-Methylpiperidine	10.71
Pyrrolidine	11.27[c]
Piperidine	11.23[c]
Diethylamine	10.98[d]
1-Ethyl-2-pyrrolidinemethanethiol (II)	8.01
1-Ethyl-2-pyrrolidinemethanol	9.60
1-Methylpyrrolidine	10.46[c]
1-Methylpiperidine	10.08[c]
1,2-Diethylpiperidine	10.15

[a] Ref. 28. [b] H. K. Hall, Jr., *J. Am. Chem. Soc.*, **78**, 2570 (1956). [c] Ref. 3. [d] N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932).

as shown by the data in Table I for such cyclic imines and their 2-hydroxymethyl derivatives.

This unusual ring-size effect must be due to the site of protonation of I and III being principally on the mercaptide sulfur atom of the dipolar ion, rather than on the ring nitrogen atom of the aminomercaptan form. One would expect that the dipolar ion form would be favored by solvation in water solution, and there is



evidence for such a situation in related compounds. Comparison of titrimetric data[28] with spectral changes with pH[29] for 2-mercaptoethylamine shows that this compound exists in water solution as the dipolar ion to the extent of over 80%, and protonation of cysteine has been found to involve both sulfur and nitrogen sites, the former apparently predominating.[29-32]

Since there is probably no significant change in the hybridization with ring size in the present cases, the difference in basicity probably indicates a smaller decrease in solvation accompanying the protonation of III than that of I. Differences in solvation of I and III could arise from conformational effects in their chelated forms.[33] Models indicate that the dipolar ions of both I and III could have feasible chelated structures, but there is greater steric hindrance for the sulfur atom in III than in I, due to hydrogen at position 6. Thus, it seems reasonable that protonation of III would be accompanied by less solvation decrease than that of I, resulting in greater basicity of the former.

(28) J. P. Danehy and C. F. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

(29) R. E. Benesch and R. Benesch, *ibid.*, **77**, 5877 (1955).

(30) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1958, pp. 496–504.

(31) D. Garfield and J. T. Edsall, *J. Am. Chem. Soc.*, **80**, 3823 (1958).

(32) M. A. Grafius and J. B. Neilands, *ibid.*, **77**, 3389 (1955).

(33) That such chelation may be quite important in the dipolar ion forms of β-mercaptoamines may be deduced from the relatively low entropy effect observed in the reaction of 2-mercaptoethylamine with ethylene oxide.[28] Such chelation, which presumably occurs by $-NH_2^+-H\cdots S^-$ hydrogen bonding, would necessarily reduce the degree of solvation of the dipolar ion.

Experimental Section

2-Bromomethylpyrrolidine Hydrobromide (IV).—Hydrogen bromide gas was bubbled into a cooled solution of 5.0 g. (0.05 mole) of 2-hydroxymethylpyrrolidine[34] for 20 min. On removal of the solvent *in vacuo* a yellowish orange syrup was obtained. To this syrup was added directly 6.8 g. (0.025 mole) of phosphorus tribromide and within a few minutes an exothermic reaction commenced with evolution of dense hydrogen bromide fumes. After the gas evolution ceased, the volatiles were removed *in vacuo*, the syrupy residue was washed with ether, and the resulting solid was recrystallized from absolute alcohol to afford 9.1 g. of the product in 75% yield, m.p. 123–124°.

Anal. Calcd. for $C_5H_{11}Br_2N$: C, 24.49; H, 4.49; N, 5.71. Found: C, 24.68; H, 4.50; N, 5.65.

3,4-Trimethylene-2-iminothiazolidine Hydrobromide (V).—A solution of 5.0 g. (0.021 mole) of 2-bromomethylpyrrolidine hydrobromide (IV) and 1.9 g. (0.025 mole) of thiourea in 50 ml. of absolute alcohol were refluxed for 5 hr. with stirring. Upon adding cold ether to the cooled mixture, a white crystalline product separated. This material, was recrystallized several times from absolute alcohol, furnishing 4.0 g. (75%) of product: m.p. 243–244°; λ_{max}^{KBr} 3.15 (NH_2^+), 6.05 (C=N), and 6.20 μ (NH_2). The analysis indicates the probable presence of a small amount of thiourea, which seems prone to cocrystallize and difficult to remove completely.

Anal. Calcd. for $C_6H_{11}BrN_2S$: C, 32.30; H, 4.93; Br, 35.8; N, 12.5. Found: C, 31.41; H, 4.61; Br, 35.2 (as AgBr); N, 13.3 (Kjeldahl).[35]

2-Mercaptomethylpyrrolidine (I).—To a solution of 2.5 g. (0.01 mole) of V in 25 ml. of absolute alcohol was added 2.0 g. of tetraethylenepentamine. The mixture was refluxed for 1 hr., and the alcohol was removed by distillation.[17] The distilling head was replaced with a short reflux condenser which was connected to a vacuum system. Upon heating the pot residue to 130° at 0.1 mm., a white solid material sublimed and collected in the reflux condenser. The solid was purified by resublimation at 50° (0.1 mm), affording 0.75 g. (75%) of product, m.p. 65–66°. (A small amount of a solid phase sometimes remained in the melt until about 92–93°; it is presumed to be disulfide due to air oxidation prior to or during the determination of the melting point, but it was not successfully isolated.) The infrared spectrum in a potassium bromide disk showed maxima at 3.0 (NH), 3.4–4.5 (NH_2^+), 3.75 (w, SH), 4.25 (w, SH···N), and 6.40–6.50 μ (NH_2^+). The n.m.r. spectrum of a deuteriochloroform solution showed well-resolved peaks centered at δ 1.6 (multiplet, CH_2CH_2), 2.6 (doublet, CH_2S), 2.9 (triplet, CH_2N), 3.2 (multiplet, CHN), and 1.8 (singlet, NH and SH).

Anal. Calcd. for $C_5H_{11}NS$: C, 51.27; H, 9.41; S, 27.34. Found: C, 51.11; H, 9.45; S, 27.47.

Addition of hydrogen chloride gas to a chloroform solution of I gave a hydrochloride which was too hygroscopic to obtain crystalline, but which showed infrared absorption at 3.4–4.2 (NH_2^+), 3.9 (SH), and 6.3 μ (NH_2^+). The diacetyl derivative, obtained by treatment of I with acetic anhydride was a viscous liquid showing strong carbonyl absorption at 5.9 ($SCOCH_3$) and 6.05 μ ($NCOCH_3$) and lack of the N–H and S–H bands.

Metal complexes of I were prepared by a modification of the procedure used by Jicha and Busch[18] to form complexes of 2-mercaptoethylamine. An alcoholic solution of cobaltous chloride, cuprous chloride, cadmium chloride hydrate, or nickel nitrate hexahydrate was added with stirring to an alcoholic solution of I until reaction was complete. The precipitate formed in each case (except that of nickel) was filtered and washed with alcohol and ether. The appearance of the cobalt complex, a dark green solid, and the cadmium complex, a white solid, resembled that of the analogous metal complexes with 2-mercaptoethylamine. The copper complex was a light green solid; formation of a copper complex of 2-mercaptoethylamine has been reported,[36] but not its color or other properties. The nickel complex of I was dark green in color but did not precipitate from alcohol, whereas a nickel complex of 2-mercaptoethylamine was a dark green precipitate. The infrared spectra of the solid complexes all showed fairly sharp N–H-type absorptions at 2.8–2.9 μ but no S–H band in the 3.8–4-μ region. In addition, there were well-defined bands at 3.2 and 6.2 μ.

(34) O. Vogl and M. Pohm, *Monatsch.*, **83**, 541 (1952).

(35) The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(36) R. V. G. Evans and G. S. Gibson, *J. Chem. Soc.*, 431 (1949).

1-Benzenesulfonyl-2-piperidinomethyl Disulfide (VI).—Using normal Schotten–Baumann conditions, 2-mercaptomethylpyrrolidine on treatment with benzenesulfonyl chloride in sodium hydroxide solution gave a white crystalline compound, m.p. 126°, on recrystallization from absolute alcohol.

Anal. Calcd. for $C_{11}H_{14}NO_2S_2$: C, 51.56; H, 5.46. Found: C, 51.26; H, 5.25.

Desulfurization of VI.—A solution of 0.44 g. of the disulfide product, in 25 ml. of absolute alcohol was refluxed for 2 hr. in the presence of a threefold excess of Raney nickel. Upon cooling, filtering, and removing the solvent, a small amount of a clear, syrupy liquid was obtained. The infrared and n.m.r. spectra of this product were identical with an authentic sample, prepared by benzenesulfonation of 2-methylpyrrolidine: λ_{max} 3.40, 3.48, 6.88, 7.45, 8.05, 9.10, 10.15, 13.45, and 14.35 μ; n.m.r., δ 1.1 (doublet, CH_3), 2.7–3.6 (multiplet, CH_2N and CHN), and 7.4 (doublet, phenyl).

2-Methylpyrrolidine.—A solution of 19.0 g. of 1,4-dibromopentane[37] and 30 ml. of liquid ammonia were heated to 200° for 3.5 hr. in an autoclave. After cooling, the excess ammonia was allowed to evaporate, the remaining mixture was poured into ether, and the ammonium bromide was filtered off. After drying the ether filtrates over sodium sulfate, the ether was removed and the residue was distilled to give 0.95 g. (13.5%) of 2-methylpyrrolidine, b.p. 90–91° (730 mm.), $n^{25}D$ 1.4350 (lit.[38] b.p. 96–98°, $n^{16}D$ 1.4296).

1-Ethyl-2-hydroxymethylpyrrolidine.—To a suspension of 8.0 g. (0.21 mole) of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran was added 11.0 g. (0.07 mole) of N-acetylproline.[39] The mixture was refluxed for 8 hr., and, after the usual work-up, 7.0 g. (77.5%) of product was obtained, b.p. 86° (14 mm), $n^{26}D$ 1.4650 (lit.[20] b.p. 78–79° (17 mm.), $n^{25}D$ 1.4659).

1-Ethyl-2-bromomethylpyrrolidine Hydrobromide.—From 7 g. of 1-ethyl-2-hydroxymethylpyrrolidine, treated with hydrogen bromide and phosphorus tribromide by the same procedure as described for the preparation of IV, was obtained 11.4 g. (77%) of white crystals, m.p. 165–166° from absolute ethanol.

Anal. Calcd. for $C_7H_{15}Br_2N$: C, 30.76; H, 5.53; N, 5.12. Found: C, 31.05; H, 5.39; N, 5.14.

1-Ethyl-2-pyrrolidinylmethylisothiouronium Dibromide (VII).—A solution of 3.97 g. (0.015 mole) of 1-ethyl-2-bromomethylpyrrolidine hydrobromide and 1.1 g. (0.015 mole) of thiourea in 35 ml. of dry alcohol were refluxed with stirring for 3 hr. On cooling the solution, a white crystalline solid separated out. After filtering and recrystallization from alcohol, 3.2 g. (62%) of product was obtained: m.p. 209–210°; λ_{max}^{KBr} 3.05 (broad, NH_2, NH_2^+), 6.05 (C=N), 2.15 and 6.25 μ (NH_2).

Anal. Calcd. for $C_8H_{19}Br_2N_3S$: C, 27.50; H, 5.44; N, 12.03. Found: C, 27.50; H, 5.39; N, 11.96.

1-Ethyl-2-mercaptomethylpyrrolidine (III).—A solution of 3.1 g. (0.009 mole) of the isothiouronium salt (VII) and 3 g. of tetraethylenepentamine in 25 ml. of absolute alcohol was refluxed for 1 hr., the solvent was distilled, and the residue was distilled to give 0.63 g. (49%) of product, b.p. 65° (9.5 mm.), $n^{25}D$ 1.4080, λ_{max} 3.90 μ (w, SH). The n.m.r. spectrum of a carbon tetrachloride solution showed the following peaks: a triplet centered at δ 1.0 (area 3, ethyl CH_3), a quartet centered at 2.35 (area 2, ethyl CH_2), a triplet centered at 2.78 (area 2, ring CH_2N), a multiplet centered at 1.5–2.2 (area about 7, other ring CH_2 groups + CH_2S + SH), and a multiplet centered at 3.1 (area about 1, ring CHN).

Anal. Calcd. for $C_7H_{15}NS$: C, 57.93; H, 10.34; N, 9.65. Found: C, 57.75; H, 10.22; N, 9.80.

2-Hydroxymethylpiperidine.—Following the procedure for the reduction of proline,[34] 19.5 g. (0.15 mole) of piperidine-2-carboxylic acid[40] was added to a suspension of 14.3 g. (0.375 mole) of lithium aluminum hydride in 500 ml. dry tetrahydrofuran. After refluxing for 8 hr. and processing in the usual manner, 12.5 g. (73%) of product was obtained, b.p. 100–101° (8.5 mm.), m.p. 68–69° [lit.[39] b.p. 104–106° (10 mm.), m.p. 67–69°].

2-Bromomethylpiperidine Hydrobromide.—Conversion of 8.5 g. of 2-hydroxymethylpiperidine to its hydrobromide was accomplished in the usual manner, and treatment of the resulting syrup with 9.7 g. of phosphorus tribromide afforded 10.2 g. (54%) of white crystals, m.p. 191–192° (from alcohol, lit.[16] m.p. 192–193°).

3,4-Tetramethylene-2-iminothiazolidine Hydrobromide (VIII).—A mixture of 6.4 g. (0.025 mole) of 2-bromomethylpiperidine hydrobromide and 1.9 g. (0.025 mole) of thiourea in 100 ml. of dry alcohol was refluxed for 4 hr. with stirring. This was processed in the same way as II, to give 3.5 g. of white crystalline solid: m.p. 153–153.5°; λ_{max}^{KBr} 3.0 and 3.15 (NH_2 and $\overset{+}{N}H_2$), 6.05 (C=N), and 6.25 μ (NH_2). The elemental analysis does not agree with either the normal isothiouronium salt or the bicyclic form (VIII), but shows good agreement with a 1:1 ratio of VIII and thiourea.

Anal. Calcd. for $C_8H_{17}BrN_4S_2$: C, 30.67; H, 5.40; N, 17.88. Found: C, 30.52; H, 5.43; N, 17.82.

2-Mercaptomethylpiperidine.—The reaction of 3.6 g. of the above isothiouronium salt and 3 g. of tetraethylenepentamine by the procedure used for I and II gave 0.8 g. (43%) of a white solid: m.p. 55–56°; λ_{max}^{melt} 3.10 (NH) and 3.90 μ (w, SH); n.m.r., δ 1.5 (multiplet, $CH_2CH_2CH_2$), 1.8 (NH and SH), 2.50 (triplet, CH_2S), 3.0 (multiplet, CH_2N).

Anal. Calcd. for $C_6H_{13}NS$: C, 54.98; H, 9.92; S, 24.42. Found: C, 55.19; H, 9.67; S, 24.20.

(1-Benzenesulfonyl)-2-piperidinomethyl Disulfide (IX).—Treatment of 2-mercaptomethylpiperidine with benzenesulfonyl chloride in sodium hydroxide solution gave a white crystalline solid, m.p. 165–166°, on recrystallization from absolute alcohol.

Anal. Calcd. for $C_{24}H_{32}N_2S_4O_4$: C, 53.40; H, 5.93. Found: C, 53.64; H, 5.96.

Desulfurization of VIII.—A solution of 0.13 g. of the disulfide and a threefold excess of Raney nickel were refluxed in 25 ml. of absolute alcohol for 1.5 hr. After cooling, filtering the solution, and removal of the solvent *in vacuo*, 0.08 g. of a sirupy product was obtained. Attempts to crystallize this product failed. The infrared and n.m.r. spectra of this product were identical with that of authentic 1-benzenesulfonyl-2-methylpiperidine, prepared by benzenesulfonation of 2-methylpiperidine (obtained from Eastman Kodak Co.): λ_{max} 3.5, 6.90, 7.04, 8.10, 9.10, 13.65, and 14.40 μ; n.m.r., δ 0.9 (CH_3), 1.35 (broad singlet, $CH_2CH_2CH_2$), 7.5 (multiplet, phenyl), and a complex series of peaks from 2.8–4.1 (protons α to nitrogen).

1-Acetyl-2-ethylpiperidine.—A solution of 6.1 g. (0.054 mole) of 2-ethylpiperidine was refluxed for 1 hr. in 35 ml. of dry pyridine and 35 ml. of acetic anhydride. The excess solvents were evaporated *in vacuo* and distillation of the dark red residual liquid afforded 5.6 g. (68%) of product, b.p. 106–108° (6.5 mm.).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.67; H, 10.96. Found: C, 69.46; H, 10.92.

1,2-Diethylpiperidine.—A solution of 5.6 g. (0.036 mole) of 1-acetyl-2-ethylpiperidine in 75 ml. of dry ether was added slowly to a stirred suspension of 0.9 g. (0.024 mole) of lithium aluminum hydride in 75 ml. of dry ether. After addition was complete, the mixture was refluxed for 1 hr., cooled, and hydrolyzed with water. The solution was filtered, the precipitates were boiled once with ether, and the combined ether filtrates were dried over sodium sulfate. On evaporation of the ether and distillation of the residual liquid, 2.6 g. (51%) of product was obtained, b.p. 100–104° (78 mm.), $n^{28}D$ 1.4510.

Anal. Calcd. for $C_9H_{19}N$: C, 76.59; H, 13.47. Found: C, 76.33; H, 13.45.

2-(*sec*-Butyl)aminoethanethiol.—A solution of 8.0 g. of ethylene sulfide and 18.9 g. of *sec*-butylamine in 30 ml. of benzene was heated in a sealed tube on a steam cone for 20 hr. Upon removal of the solvent and distillation of the remaining liquid, 9.5 g. (55%) of product was obtained, b.p. 88–89° (22 mm.), $n^{26}D$ 1.4660 [lit.[12] b.p. 83° (33 mm.), $n^{25}D$ 1.4676], λ_{max} 3.0 (w, NH) and 3.95 μ (w, SH).

2-Mercaptoethylamine Hydrochloride.—Electrometric titrations were carried out with glass electrodes and a Radiometer pH meter, Model 4. The solutions of amines in aqueous solution in a water-jacketed vessel maintained at 25° were titrated with approximately 0.1 *N* hydrochloric acid, delivered from a microburet.

Acknowledgment.—We wish to acknowledge a helpful conversation with Dr. George Gorin and a grant from the National Science Foundation which aided in the purchase of the n.m.r. spectrometer used in this work.

(37) M. Okawara, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **54**, 132 (1951).
(38) R. Paul and H. Cottin, *Bull. soc. chim. France*, **7**, 626 (1940).
(39) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **74**, 2859 (1947).
(40) C. M. Stevens and P. B. Ellman, *J. Biol. Chem.*, **182**, 75 (1950).