SYNTHESIS AND REACTION OF 2-MERCAPTO-5,5-DIMETHYLPYRROLIDINE
HYDROCHLORIDE AND 2-MERCAPTO-1-ACETYL-5,5-DIMETHYLPYRROLIDINE

by

HYOUN SOO PARK

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Department of Chemistry

KANSAS STATE UNIVERSITY

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Approved by:

Scott Searles, Jr.
Major Professor

TO MY PARENTS

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INTRODUCTION

Historical

Since β-mercaptoethylamine[1] and its derivatives[2] show significant
antiradiation activity in animals, it was of interest to prepare ali-
phatic α-mercaptoamines for testing. Heterocyclic α-mercaptoamines are
known in which the nitrogen atom is part of a heterocyclic ring, as in
α-mercaptopyridine[3], but no aliphatic α-mercaptoamine appears to have
been described in the literature.

Various kinds of mercaptans have been reported to undergo addition
to acyclic Schiff bases[4] and oxazolones[5,6]. $\underline{N}$-Benzylideneanthranilic
acid (I) gave addition products (II) and (III) with thiolacetic acid and
mercaptoacetic acid[7]. The latter did not cyclize to a thiazolidone,

(II)   (I)   (III)
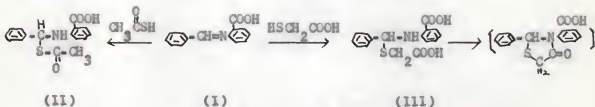
although Schiff bases (IV), which were obtained from the condensation of
benzaldehyde and the secondary-primary diamine, where n=2,3 or 6, reacted
with methylthioglycolate to give 4-thiazolidone[8] (V).

(IV)

(V)
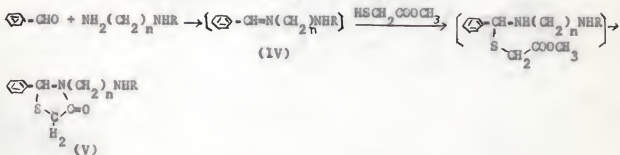
The reaction of N-benzylideneaniline (VI) with p-toluenethiol in equimolar amounts gave an addition product (VII), while reaction with an excess of the thiol gave as reduction products N-benzylaniline (VIII) and di-p-tolyl disulfide (IX). When the produce (VII) was heated with an excess of thiol, compounds (VIII) and (IX) were formed.
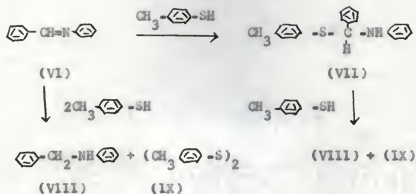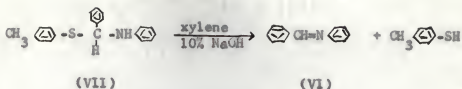

It was also reported that in the presence of moisture, cleavage of the Schiff base (I) by p-thiocresol occured to give mercaptal (X) and aminobenzoic acid (XI)[4] instead of the reduction observed under anhydrous
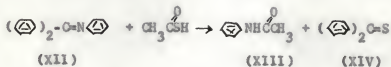

conditions.

When the pure product (VII) was washed with 10% of sodium hydroxide solution, decomposition of the adduct to the starting material was observed[4].

$$CH_3 \langle \rangle -S- \overset{O}{\underset{H}{C}} -NH\langle \rangle \xrightarrow[\text{10\% NaOH}]{\text{xylene}} \langle \rangle CH=N\langle \rangle + CH_3\langle \rangle -SH$$

$$\text{(VII)} \qquad\qquad\qquad \text{(VI)}$$

It was recently reported that benzophenoneanil (XII) in the absence of oxygen did not give an addition product with thiolacetic acid, as reported for N-benzylideneanthranilic acid[7]; instead, it formed acetanilide (XIII) and thiobenzophenone (XIV) as cleavage products[9].

$$(\langle \rangle)_2 -C=N\langle \rangle + CH_3\overset{O}{C}SH \rightarrow \langle \rangle NH\overset{O}{C}CH_3 + (\langle \rangle)_2 C=S$$

$$\text{(XII)} \qquad\qquad\qquad \text{(XIII)} \qquad \text{(XIV)}$$

Hydrogen sulfide adds to oxazolone[5] and 2-(p-dimethylaminophenyl-amino)-3-coumaranone (XV) to give 2-mercapto-2-(p-dimethylaminoanilino)-3-coumaranone (XVI)[10] but benzophenoneanil, which is stable toward

$$\text{(XV)} \qquad\qquad\qquad\qquad \text{(XVI)}$$
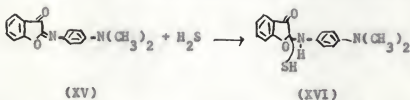
hydrolysis in water even at 180°, was cleaved, however, by gaseous hydrogen sulfide to aniline and thiobenzophenone[11] (XVII).

$$(\langle \rangle)_2 C=N\langle \rangle + H_2S \rightarrow (\langle \rangle)_2 C=S + \langle \rangle \overset{NH_2}{}$$

$$\text{(XII)} \qquad\qquad\qquad \text{(XVII)}$$
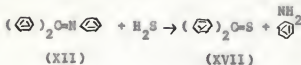
The S-acetyl derivative of 2-mercapto-5,5-dimethylpyrrolidine would also be of interest. An understanding of the chemical and physical properties of the thioester may aid in elucidation of some biological mechanism involving reaction between a certain coenzyme with an active carbonyl group. Intramolecular acetyl transfer from sulfur to nitrogen in $CH_3COS(CH_2)_n NH_3^-$, where n = 2,3 has been reported[12]. A mechanism for S-N transfer reaction, which accounted for the ester disappearance, the reaction was first order.
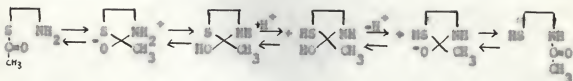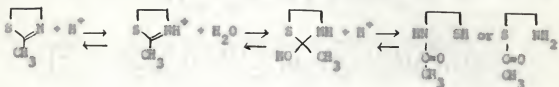

Base hydrolysis of the thioester indicates that the hydrolysis is negligible compared to the rapid S-N transfer reaction[13]. The rate of hydrolysis of 2-methylthiazoline as function of pH, assuming hydrothiasilidine as an intermediate, was studied by following the appearance of N or S-acetyl-β-mercaptoethylamine, which one depending on the conditions[16].

It was recently reported that β-mercaptoethylamine may act as an inhibitor of the decarboxylation of amino acids, involving the formation of a thiazolidine ring by condensation with pyridoxal phosphate linked coenzyme, or the formation of mercaptals, depending on the reaction

conditions[15].

$$RC\underset{H}{\overset{=O}{\longleftarrow}} + HSCH_2CH_2NH_2 \rightarrow RC\underset{SH}{\overset{H}{\underset{|}{\longleftarrow}}}SCH_2CH_2NH_2 \rightarrow HN\underset{R}{\overset{}{\boxed{}}}S \xrightarrow[+H_2O]{HSCH_2CH_2NH_2} R-\underset{SCH_2CH_2NH_2}{\overset{H-SCH_2CH_2NH_2}{\underset{|}{C}}}$$
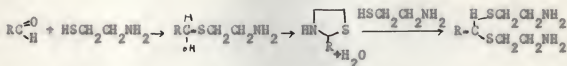
Statement of the Problem

The compound chosen in this work for attempted preparation was
2-mercapto-5,5-dimethylpyrrolidine. 5,5-Dimethyl-1-pyrroline is a well
characterized, unusually stable cyclic imine[16], and it was hoped that
hydrogen sulfide and thiolacetic acid could be added to it, and that
subsequent acidic or basic hydrolysis of the latter adduct would give
2-mercapto-5,5-dimethylpyrrolidine or its salt.

RESULTS AND DISCUSSION

It was found that the nucleophilic addition of hydrogen sulfide
to 5,5-dimethyl-1-pyrroline (XVIII) in aqueous sodium hydrosulfide so-
lution proceeded easily, and the colorless 2-mercapto-5,5-dimethyl-
pyrrolidine hydrochloride (XIX) was obtained by using excess of hydro-
chloric acid. Evidence for the structure (XIX) was provided by its
infrared spectra (Plate 1), showing S-H, N-H and -NH$^+_2$Cl$^-$ bands, and by
its elemental analysis, which was in excellent agreement with the
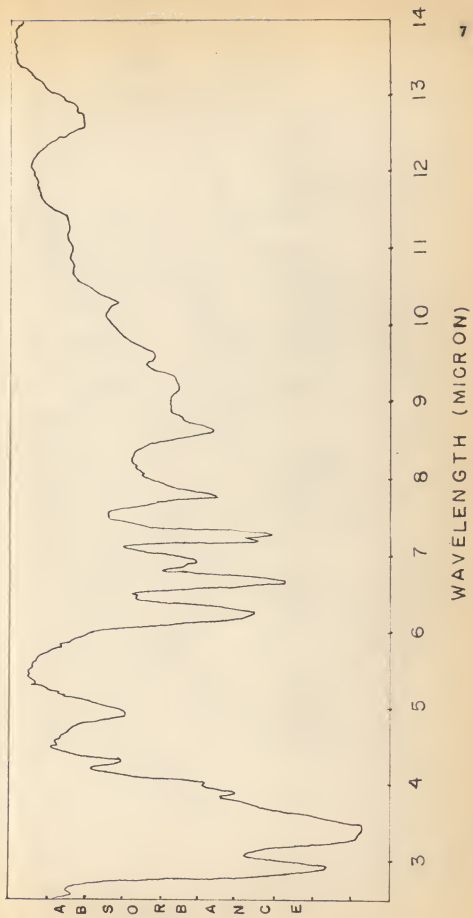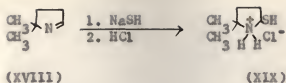theoretical.

EXPLANATION OF PLATE (I)

Infrared Spectrum of

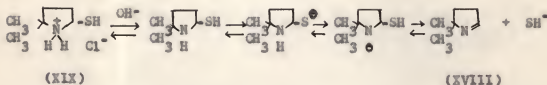2-Mercapto-5,5-dimethylpyrrolidine Hydrochloride (XIX)

(KBr Pellet)

PLATE I

WAVELENGTH (MICRON)

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$$\underset{\text{(XVIII)}}{\overset{CH_3}{\underset{CH_3}{\diagdown}}\!\!N} \quad \xrightarrow[\text{2. HCl}]{\text{1. NaSH}} \quad \underset{\text{(XIX)}}{\overset{CH_3}{\underset{CH_3}{\diagdown}}\!\!\overset{SH}{\underset{H\ H}{N}}Cl^-}$$
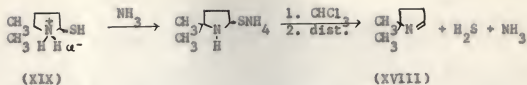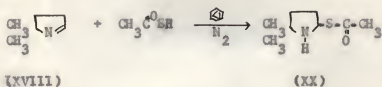
Free 2-mercapto-5,5-dimethylpyrrolidine was isolated by extracting
with ether the reaction mixture from the addition of an equimolar amount
of hydrogen sulfide to (XVIII), with sodium hydrosulfide as catalyst.
Evidence for the existence of free mercaptoamine is the positive nitro-
prusside test in base[17], as well as an S-H band in the infrared spectra.
Comparison of the infrared spectrum with that for (XIX), showed the lack
of $-NH_2^+Cl^-$ band. No distillation was attempted, because of the products
instability. This compound (XIX) was decomposed exothermally in warm
dilute sodium hydroxide solution and the pyrroline (XVIII) which separated
from solution was identified. It is apparent that the addition of hydro-
gen sulfide to (XVIII) is reversible.

$$\underset{\text{(XIX)}}{\overset{CH_3}{\underset{CH_3}{\diagdown}}\!\!\overset{SH}{\underset{H\ H\quad Cl^-}{N}}} \underset{\xrightarrow{\quad}}{\overset{OH^-}{\rightleftharpoons}} \underset{CH_3}{\overset{CH_3}{\diagdown}}\!\!N\!-\!SH \underset{\leftarrow}{\rightarrow} \underset{CH_3}{\overset{CH_3}{\diagdown}}\!\!N\!-\!S^{\bullet} \underset{\leftarrow}{\rightarrow} \underset{CH_3}{\overset{CH_3}{\diagdown}}\!\!N\!-\!SH \rightleftharpoons \underset{\text{(XVIII)}}{\overset{CH_3}{\underset{CH_3}{\diagdown}}\!\!N} \quad + \quad SH^-$$

In order to try the effect of a weak base, compound (XIX) was dis-
solved in liquid ammonia. After evaporation of the ammonia, chloroform
extraction gave a liquid, which was distilled, and seemed to be an azeo-
tropic mixture of chloroform and the pyrroline (XVIII), according to
infrared and gas chromatographic evidence. It is thought that the free
mercaptoamine decomposed during the distillation.

$$\underset{\text{(XIX)}}{\overset{CH_3}{\underset{CH_3}{\bigcup}}}\text{-SH} \xrightarrow{NH_3} \underset{CH_3}{\overset{CH_3}{\bigcup}}\text{-SNH}_4 \xrightarrow[\text{2. dist.}]{\text{1. CHCl}_3} \underset{\text{(XVIII)}}{\overset{CH_3}{\underset{CH_3}{\bigcup}}} + H_2S + NH_3$$

Addition of thiolacetic acid to (XVIII) in anhydrous benzene proceeded smoothly to give 2-acetylmercapto-5,5-dimethylpyrrolidine (XX), (Plate II).

$$\underset{\text{(XVIII)}}{\overset{CH_3}{\underset{CH_3}{\bigcup}}} + CH_3C \overset{O}{\underset{}{}} SH \xrightarrow[N_2]{\bigcirc} \underset{\text{(XX)}}{\overset{CH_3}{\underset{CH_3}{\bigcup}}}\text{-S-C-CH}_3$$

This compound was very hard to purify, decomposing on attempted distillation at 10^{-3} mm, and an attempted crystallization in absolute alcohol in room light decomposing to elemental sulfur (m.p. 118-9°), however this decomposition did not occur in the dark. Various nonaqueous solvents, such as chloroform, carbon tetrachloride, Skelly B and C were tried, but no success was had in crystallization. Fortunately, however, the crude material was purified sufficiently by merely washing with solvents, to give an elemental analysis that was fairly satisfactory, being only 0.47% high on carbon and very acceptable on nitrogen and hydrogen. The infrared spectra showed the -C-S- stretch band in the -C -S- linkage at 9μ.

Compound (XX) was hydrolyzed with hydrochloric acid under nitrogen to give 50% yield of compound (XIX); when hydrolysis was done in air, the disulfide was obtained. Compound (XIX) and the disulfide of (XIX) have similar infrared spectra, except that the disulfide does not give a sodium
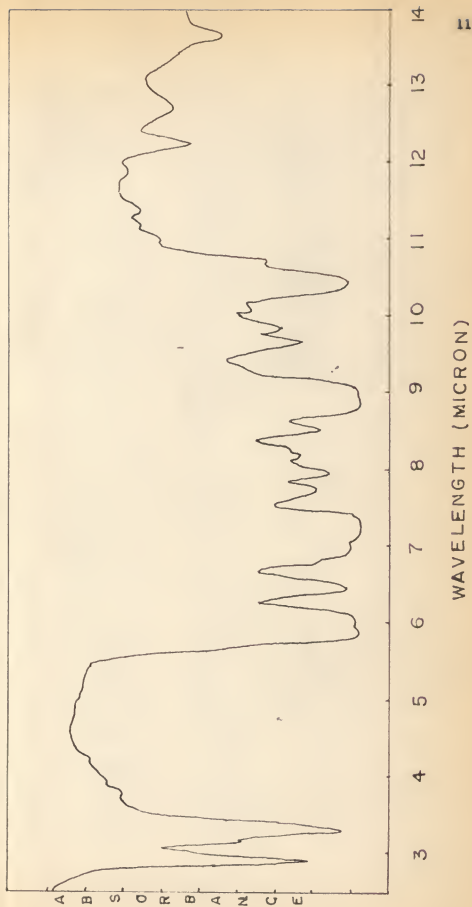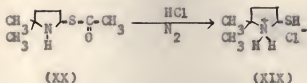
EXPLANATION OF PLATE II

Infrared Spectrum of

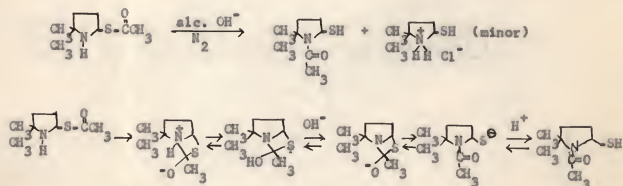2-Acetylmercapto-5,5-dimethylpyrrolidine (XX)

(NaCl Plate)

PLATE II

ABSORBANCE

WAVELENGTH (MICRON)

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nitroprusside test, and shows no S-H band.

$$CH_3 \underset{H}{\overset{CH_3}{\diagup}} N-S-\overset{O}{\underset{O}{C}}-CH_3 \xrightarrow[N_2]{HCl} CH_3 \underset{H}{\overset{CH_3}{\diagup}} N \overset{SH}{\underset{H}{\diagup}} Cl^-$$

$$(XX) \qquad\qquad\qquad (XIX)$$

Compound (XX) was hydrolyzed with alcoholic base under nitrogen to give a 22% yield of (XXII) with 8% of residue from which some disulfide was identified. In the remaining solution, about 10% of compound (XIX) were also obtained. The new compound, (XXII), was isomeric with compound (XX), as shown by an excellent elemental analysis. It dissolved in water and most organic solvents with a resulting garlic smell. The infrared spectra of this compound showed no N-H and -C-S- stretch band, but had S-H and amide carbonyl bands (Plate III). Accordingly, it must be 2-mercapto-1-acetyl-5,5-dimethylpyrrolidine (XXII). This may have resulted from either an intramolecular or intermolecular rearrangement process. The former would be analogous to the well known intramolecular S-N acetyl transfer previously mentioned and would be interesting example, as it would involve a four membered ring reaction intermediate.

$$CH_3 \underset{H}{\overset{CH_3}{\diagup}} N-S-\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[N_2]{alc.\ OH^-} CH_3 \underset{\overset{|}{C}=O}{\overset{CH_3}{\diagup}} N \overset{SH}{\diagup} + CH_3 \underset{H\ H\ Cl^-}{\overset{CH_3}{\diagup}} N \overset{SH}{\diagup} (minor)$$

$$CH_3 \underset{H}{\overset{CH_3}{\diagup}} N-S-\overset{O}{\overset{\|}{C}}CH_3 \rightarrow CH_3 \overset{CH_3}{\diagup} \rightleftharpoons CH_3 \overset{CH_3}{\diagup} \rightleftharpoons CH_3 \overset{CH_3}{\diagup} \rightleftharpoons CH_3 \overset{CH_3}{\diagup} \overset{H^+}{\rightleftharpoons} CH_3 \overset{CH_3}{\diagup} N \overset{SH}{\diagup}$$
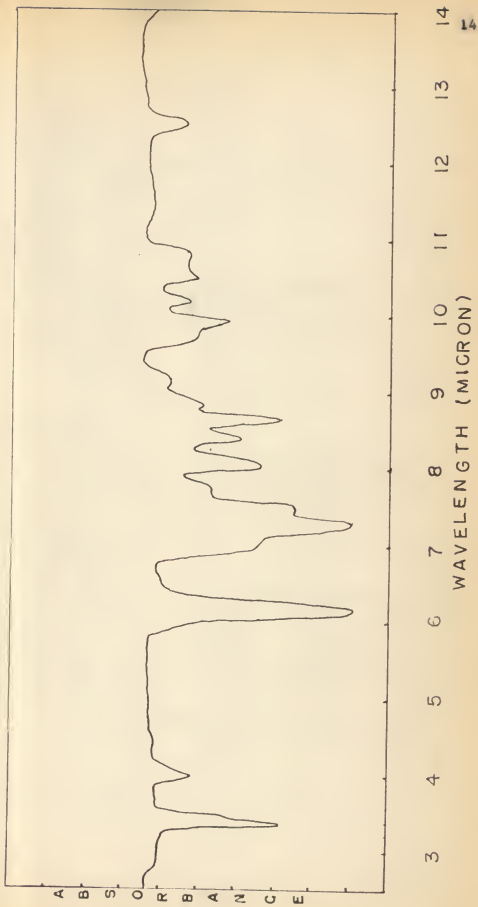
EXPLANATION OF PLATE III

Infrared Spectrum of

2-Mercapto-1-Acetyl-5,5-dimethylpyrrolidine (XXII)

(KBr Pellet)

PLATE III

ABSORBANCE

WAVELENGTH (MICRON)

(XXIII)

(XXII)   (XXIV)

(XIX)
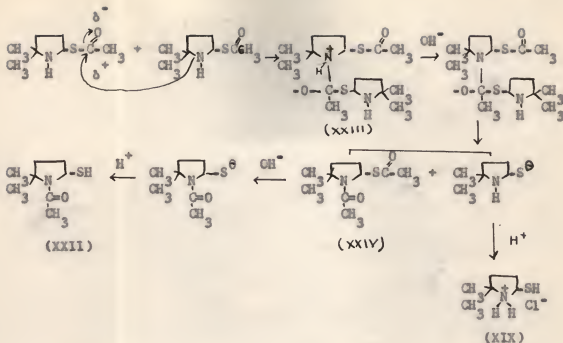
The intermolecular process would involve the acetylation of one molecule by another and would involve intermediate formation of (XXIII). The presence of compound (XIX) is understandable by this process. The anion of compound (XIX) must be reasonably stable at the room temperature or lower. The N,S-diacetyl compound (XXIV), then would hydrolyze readily in base to (XXII). Thus if this mechanism is correct, the maximum yield of (XXII) would be 50%. This is in accord with the observed yield of 22%.

(XXII)   (XXV)
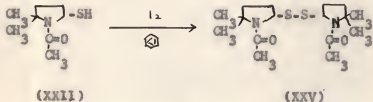
Also, if the intramolecular mechanism were true, it should occur in the absence of base, although perhaps slowly. It was observed that heating the compound (XX) gave N,S-diacetyl derivative (XXIV), according to

the infrared spectra (Plate IV). This compound was hydrolyzed in al-
coholic base to give the N-acetyl derivative (XXII) also. During the
recrystallization this became oxidized to the disulfide (XXV).

Compound (XXII) was also oxidized to disulfide (XXV) by iodine,
the reaction mixture showing loss of the S-H band in the infrared
spectra.

EXPERIMENTAL

5,5-Dimethyl-1-pyrroline[16] (XVIII)

Compound (XVIII) was prepared by nucleophilic condensation of 2-
nitropropane with acrolein with sodium methoxide catalyst and the re-
sulting 4-methyl-4-nitropentane-1-al was converted to the dioxolane with
ethylene glycol. Hydrogenation of 2-(3-methyl-3-nitrobutyl)-1,3-dioxolane
and subsequent cyclization by hydrochloric acid gave compound (XVIII),
n^{19}_D 1.450, Yield, 17 g. (32%). The infrared spectrum shows a C≡N band
at 6.05μ, but no N-H band at around 2.9μ.

2-Mercapto-5,5-dimethylpyrrolidine Hydrochloride (XIX)

Aqueous sodium hydrosulfide solution was prepared by bubbling hy-
drogen sulfide gas into a 20% sodium hydroxide solution until no more gas
was absorbed. The temperature was kept under 65°. To 22 ml. (0.13 mol)
of sodium hydrosulfide solution, 30 ml. of water and 9.7 g. (0.1 mol) of
compound (XVIII), 70 ml. of 6 N hydrochloric acid was added slowly in an
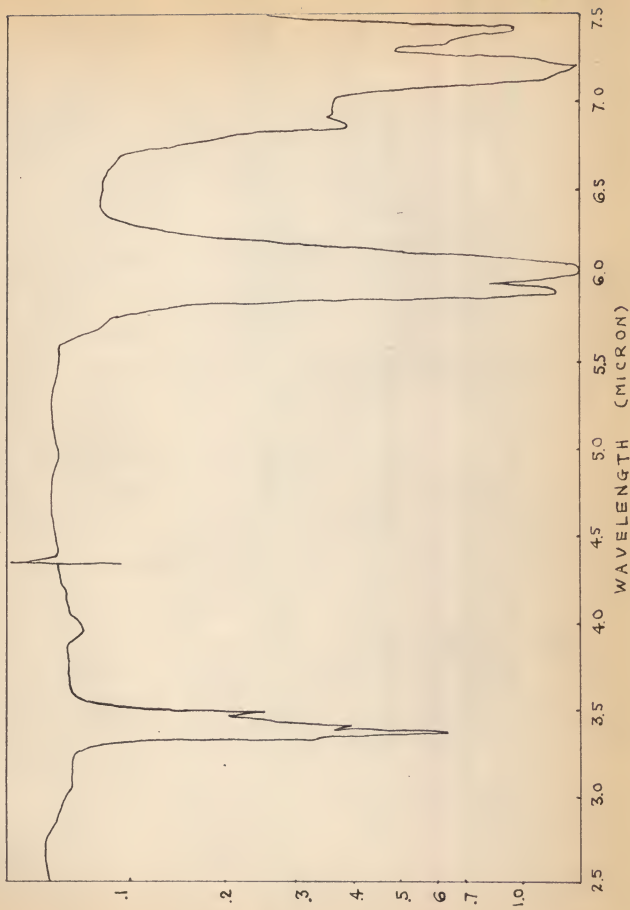ice bath during a four hour period, with stirring at 0-5° under nitrogen.
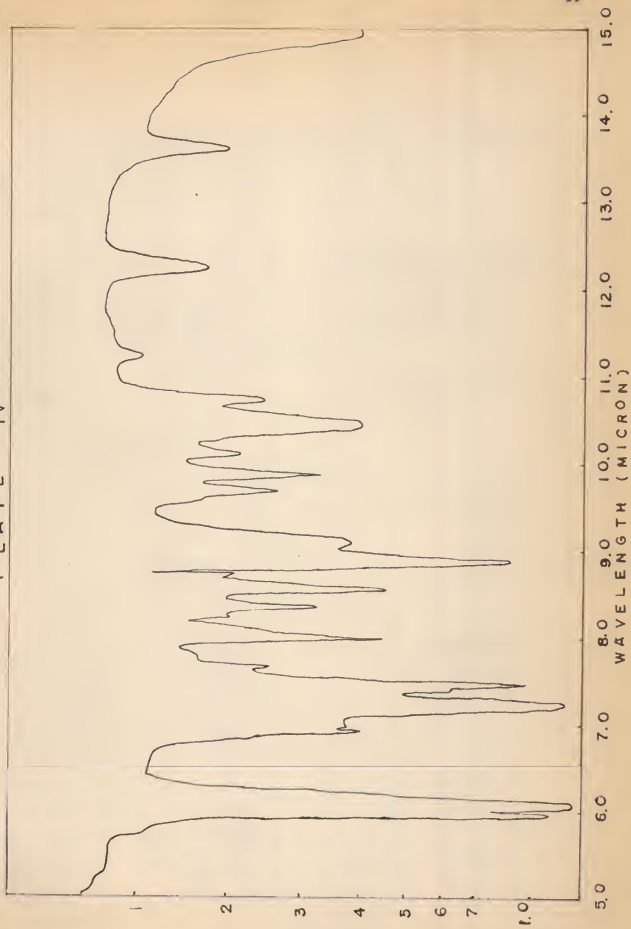
EXPLANATION OF PLATE IV

Infrared Spectrum of

2-Acetylmercapto-1-Acetyl-5,5-dimethylpyrrolidine (XXIV)

(NaCl Plate)

PLATE IV

WAVELENGTH (MICRON)

PLATE IV

After five hours additional stirring, the water was removed under reduced pressure with warming, and the residue was completely dried under vacuum. Sodium chloride was then filtered off after dissolving the mixture in the absolute alcohol. The filtrate was dried again under reduced pressure, finally over P_2O_5. The characteristic $-NH_2^+Cl^-$ bands were similar to those for β-mercaptoethylamine HCl[18]. Compound (XIX) decomposed in dilute sodium hydroxide solution, slowly at lower temperatures, and it gave a positive sodium nitroprusside test in base. The yield was 16 g. (96%). The product showed a decomposition range beginning at 210°C. The infrared spectra show N-H bands at 2.9μ and 6.2μ; $-NH_2^-Cl^-$ at 3.7μ, 3.9μ, 4.9μ, and 6.7μ; S-H band at around 4μ.

Anal. Calcd. for C_6H_4NSCl: C, 42.97; H, 8.41; N, 8.35. Found: C, 43.09; H, 8.48; N, 8.12.

Elimination of Hydrogen Sulfide from 2-Mercapto-5,5-dimethylpyrrolidine Hydrochloride

To 25 g. of compound (XIX), 70 ml. of liquid ammonia was added, and 8 g. of black green residue was filtered out. As the ammonia evaporated off, the mixture was extracted with a small portion of chloroform. The extract was then distilled up to 106° and about 14 g. of distillate was collected between 62°-106°. The mixture was identified by vapor chromatograph, as a simple distillation could not separate the azeotropic mixture of compound (XVIII) and chloroform. The infrared spectrum of the distillate, except for a C-Cl band at around 13.8μ, was the same as the infrared spectrum of compound (XVIII).

2-Acetylmercapto-5,5-dimethylpyrrolidine (XX)

To 29 g. (0.3 mol) of compound (XVIII) and 108 ml. of anhydrous benzene, 22.5 g. (0.3 mol) of thiolacetic acid was added slowly for three hours at room temperature under nitrogen and stirred another three hours. The produce was isolated by removal of solvent and unreacted material under reduced pressure, followed by washing with dry ether and refrigeration in 30 ml. of benzene over night, then careful decantation of the solvent and drying. The yield was 45 g. of viscous oil (87-90%). Upon drying under vacuum, it solidified. However, it could not be re-crystallized from chloroform, carbon tetrachloride or Skelly B and C. The infrared spectra show an N-H band at 2.9μ and $5.8-6.1\mu$ which overlaps the carbonyl band, and a -C-S- stretch band at 9μ.

Anal. Calcd. for $C_8H_{15}NSO$: C, 55.45; H, 8.73; N, 8.08. Found: C, 55.92; H, 8.90; N, 7.74.

Distillation of 20 g. of compound (XX) in an alembic at 10^{-3}mm, re-sulted in much decomposition. About 1.5 g. of distillate in the third distillation fraction had no N-H band at around 2.9μ and 6.5μ, however two bands at $5.9-6.1\mu$ was formed which may be due to N and S-acetyl carbonyl bands, with an unchanged -C-S- stretch band at 9μ. The second fraction of the distillate, which was similar to the first, shows a weak N-H band at 2.9μ and 6.5μ, with a weak S-H band at 4μ, and some change of the carbonyl band at $5.9-6.1\mu$. The third fraction of the distillate (0.3 g.) was hydrolyzed in about 50% alcoholic base by heating on the steam cone for ten minutes, acidification with 6 N hydrochloric acid to

pH 3, and extracted with ether; the ether extract was recrystallized from Skelly B. The infrared spectrum shows the same absorption bands as compound (XXII) and after repetition of the recrystallization several times it changed to the disulfide (XXVI).

Acid Hydrolysis of 2-Acetylmercapto-5,5-dimethylpyrrolidine

To 10 g. (0.058 mol) of compound (XX), 70 ml. of 6 N hydrochloric acid was added and refluxed for five hours on a steam cone under nitrogen. Water was removed under reduced pressure, and the product was washed with benzene, then ether, and dried under vacuum. About 5 g. (50%) of compound (XIX) was obtained. The infrared absorption bands are the same as in the compound obtained by hydrogen sulfide addition to compound (XVIII).

Basic Hydrolysis of 2-Acetylmercapto-5,5-dimethylpyrrolidine

A solution of 40 g. (0.23 mol) of compound (XX) and 28 g. of potassium hydroxide in 120 ml. of 95% ethanol and 200 ml. of water, was refluxed on the steam cone for thirty minutes under nitrogen. The ethanol was completely removed under reduced pressure, and then all unreacted basic compounds was washed out by ether three times. Removal of the ether gave 15-18 g. of heavy oil, which was discarded. The aqueous solution of potassium mercaptide was acidified with 6 N hydrochloric acid in an ice bath to pH 5, then extracted with three 100 ml. portions of ether and dried over sodium sulfate. The ether was evaporated on a steam cone, leaving about 15 g. of residue, which distilled at 93-4° (0.6 mm.). Obtained were 8.5 g. (22%) of colorless compound (XXII), n^{20}_D 1.5150, and 3.5 g. of residue from

which was obtained some disulfide by recrystallization. Compound (XXII), which crystallized on standing and was recrystallized from Skelly B, had a m.p. 42-42.5°. The infrared absorption bands of the liquid compound (XXII) were clear; however, the crystal compound (XXII) showed diffused bands and carbonyl shifting, due to the phase change was observed[19].

Anal. Calcd. for $C_8H_{15}NSO$: C, 55.45; H, 8.73; N, 8.08; S, 18.51. Found: C, 55.68; H, 8.92; N, 8.24; S, 18.61.

The remaining solution was acidified with more 6 N hydrochloric acid to pH 3. Removal of water under vacuum gave 4 g. (10%) of compound (XIX). The infrared spectrum of this compound was compared to the hydrogen sulfide adduct of (XVIII), and found to be identical.

Oxidation of 2-Mercapto-1-Acetyl-5,5-dimethylpyrrolidine

To a solution of 0.8 g. of compound (XXII) in 10 ml. of water and 15 ml. of benzene, a 15% solution of iodine in benzene was added without shaking to the mixture, until no more iodine was absorbed. The mixture was washed with dilute sodium hydroxide solution and the benzene layer was separated. The solvent was evaporated after drying over sodium sulfate, and the crude solid was recrystallized from Skelly B, to give about 0.3 g. of colorless crystal, m.p. 142-3°, uncorrected. The infrared spectrum shows no S-H band, but other absorption bands are very similar to compound (XXII), except for two new bands at 13.8μ and 14.8μ.

Anal. Calcd. for $C_{16}H_{28}N_2S_2O_2$: H, 8.17; N, 8.13. Found: H, 7.87; N, 7.85.

SUMMARY

It was of interest to prepare α-mercaptoamines as possible anti-
radiation compounds. A review of the literature indicated that no
aliphatic α-mercaptoamine has been reported, and this work was carried
out to synthesize an α-mercaptoamine in the pyrrolidine series.

2-Mercapto-5,5-dimethylpyrrolidine hydrochloride was synthesized
in 96% yield by addition of hydrogen sulfide to 5,5-dimethyl-1-pyrroline.
This compound was reasonably stable, but the corresponding free base was
decomposed with loss of hydrogen sulfide to the starting pyrroline on
heating or treating with aqueous base. The cyclic imine ring is not
cleaved therefore.

2-Acetylmercapto-5,5-dimethylpyrrolidine was prepared in 87-90%
yield by addition of thiolacetic acid to 5,5-dimethyl-1-pyrroline in
benzene. Acid hydrolysis of 2-acetylmercapto-5,5-dimethylpyrrolidine
which was obtained by addition of thiolacetic acid to 5,5-dimethyl-1-
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Basic hydrolysis of 2-acetylmercapto-5,5-dimethylpyrrolidine gave
an isomer of the former, 2-mercapto-1-acetyl-5,5-dimethylpyrrolidine
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Two possible mechanisms were suggested, either by the well known
S-N intramolecular or intermolecular rearrangement. If the rearrange-
ment proceeded by intramolecular S-N acetyl transfer, the intermediate
would involve a four membered ring. The intermolecular rearrangement
process may involve two molecules of aminothioester in formation of an

intermediate, which was also obtained from the distillation of 2-acetyl-mercapto-5,5-dimethylpyrrolidine, according to the infrared spectra. The subsequent basic hydrolysis and acidification of their intermediate results in formation of 2-mercapto-1-acetyl-5,5-dimethylpyrrolidine. This is converted then to the disulfide during the recrystallization process.

The disulfide of 2-mercapto-1-acetyl-5,5-dimethylpyrrolidine was obtained by oxidation of pure 2-mercapto-1-acetyl-5,5-dimethylpyrrolidine with iodine in benzene solution.

The structures of 2-mercapto-5,5-dimethylpyrrolidine hydrochloride, 2-acetylmercapto-5,5-dimethylpyrrolidine, 2-mercapto-1-acetyl-5,5-dimethyl-pyrrolidine and the disulfide of 2-mercapto-1-acetyl-5,5-dimethylpyrroli-dine were proven by the elemental analysis, infrared spectra and chemical tests.

BIBLIOGRAPHY

1. R.L. Mundy and M.H. Heiffer, _Radiation Research_, 13, 381-394 (1960).

2. T.P. Johnston and A. Gallagher, _J. Org. Chem._, 27, 2452 (1962).

3. M.P.V. Boarland and J.F.W. McOmie, _J. Chem. Soc._, 1218 (1951).

4. G.W. Stacy, R.I. Day and R.J. Morath, _J. Am. Chem. Soc._, 77, 3869 (1955).

5. H.T. Clarke, J.R. Johnson and R. Robinson, "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1949, p. 737.

6. A. Mustafa and M.M.M. Sallam, _J. Org. Chem._, 27, 2406 (1962).

7. G.W. Stacy and R.J. Morath, _J. Am. Chem. Soc._, 74, 3885 (1952).

8. A.R. Surrey, _ibid._, 71, 3354 (1949).

9. B.M. Mikhailov and I.S. Saveleva, _Bulletin of the Academy of Science of U.S.S.R._, No. 7, p.1255 (July, 1959).

10. K. Fries, A. Hasselbach and L. Schröder, _Ber._, 47, 1640 (1914).

11. C.M. Rosser and J.J. Ritter, _J. Am. Chem. Soc._, 59, 2179 (1937).

12. R.B. Martin and R.I. Hedrick, _ibid._, 84, 104 (1962).

13. L.H. Noda, S.A. Kuby and H.A. Lardy, _ibid._, 75, 913 (1953).

14. R.B. Martin, S. Lowey, E.L. Elson and J.T. Edsall, _ibid._, 81, 5089 (1959).

15. L.A. Semina and S.R. Mardashev, _Biochemistry_, Vol. 26, 921 (1962).

16. R. Bonnett, V.M. Clark, A. Giddey and Sir A. Todd, _J. Chem. Soc._, 2087 (1959).

17. N.D. Cheronis and J.B. Entrickin, Semimicro Qualitative Analysis, 2nd Ed., Interscience Publishers Inc., New York, N.Y., 1957, p. 275.

18. The Sadtler Standard Spectra, Sadtler Research Laboratories, No. 7233, Philadelphia, Penn., 1956 Ed.

19. A.D. Cross, "An Introduction to Practical Infrared Spectroscopy", Butterworths Scientific Publications, London, 1960, p. 29.

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SYNTHESIS AND REACTION OF 2-MERCAPTO-5,5-DIMETHYLPYRROLIDINE
HYDROCHLORIDE AND 2-MERCAPTO-1-ACETYL-5,5-DIMETHYLPYRROLIDINE

by

HYOUN SOO PARK

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AN ABSTRACT OF A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

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KANSAS STATE UNIVERSITY

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It was of interest to prepare α-mercaptoamines as possible anti-radiation compounds. A review of the literature indicated that no aliphatic α-mercaptoamine has been reported, and this work was carried out to synthesize an α-mercaptoamine in the pyrrolidine series.

2-Mercapto-5,5-dimethylpyrrolidine hydrochloride was synthesized in 96% yield by addition of hydrogen sulfide to 5,5-dimethyl-1-pyrroline. This compound was reasonably stable, but the corresponding free base was decomposed with loss of hydrogen sulfide to the starting pyrroline on heating or treating with aqueous base. The cyclic imine ring is not cleaved therefore.

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