Rearrangements of the Aminoalkylation Products of Tetrahydro-2*H*-1,3-oxazine-2-thione

Richard C. Clapp and Louis Long, Jr.

Pioneering Research Laboratory, U. S. Army Natick Laboratories

The nature of the compounds afforded by the rearrangement of the aminopropylation and aminoethylation products of tetrahydro-2*H*-1,3-oxazine-2-thione (I) has been investigated. In both instances compounds that can be considered to result from ring opening at either the C—O or C—S bond of a hypothetical bicyclic intermediate of structure IV were obtained. The compounds required for identification of the rearrangement products have been prepared by the reaction of the 2-methylthio derivatives of 2-thiazoline, 5,6-dihydro-4*H*-1,3-thiazine, and 5,6-dihydro-4*H*-1,3-oxazine with the appropriate hydroxyalkylamine or mercaptoalkylamine.

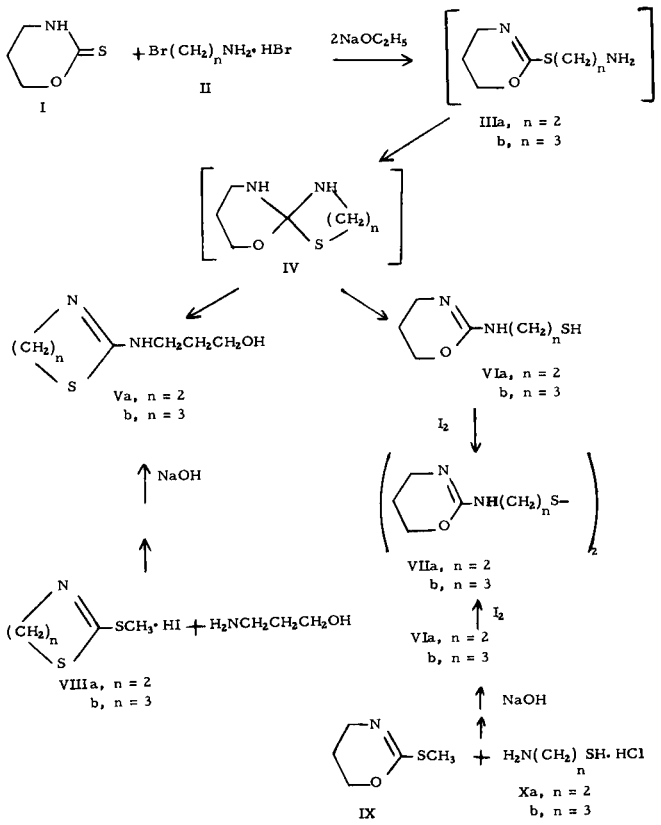
In a previous paper (1), the conversion of several 2-(2-aminoethylthio)-2-oxazolines to the corresponding 2-(2-mercaptoethylamino)-2-oxazolines, through a postulated bicyclic intermediate, has been reported. Similar rearrangements involving the aminoalkylthio derivatives of 2-thiazoline (2-4), 2-imidazoline (4-6), 5,6-dihydro-4*H*-1,3-thiazine (3) and tetrahydropyrimidine (6) have been described. These reactions are analogous to the conversion, by transguanylation through a proposed cyclic intermediate, of the radioprotective agent 2-(2-aminoethyl)-2-thiopseudourea (AET) to 2-mercaptoethylguanidine reported by Doherty, *et al.* (7). In the present paper, the products resulting from the rearrangements of the aminoalkylthio derivatives of 5,6-dihydro-4*H*-1,3-oxazine (structure III) are considered.

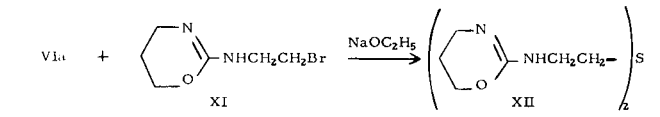
The hypothetical bicyclic intermediate that would be involved in the rearrangement of the aminoalkylthio derivatives of 5,6-dihydro-4*H*-1,3-oxazine is represented by IV. As indicated in Scheme I, either a 2-(3-hydroxypropylamino)heterocycle of structure V or a 2-mercaptoalkylamino-5,6-dihydro-4*H*-1,3-oxazine (VI) can be formed from this intermediate. In the case of the 2-(2-aminoethylthio)-2-oxazolines (1), the rearrangements afforded only the 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfide dipicrates in 10-15% yield.

As in the investigation of the oxazolidinethiones (1), attempts to carry out the aminoalkylation of tetrahydro-2*H*-1,3-oxazine-2-thione (I) with bromoalkylamine hydrobromides did not yield identifiable products, and it was necessary to effect the aminoalkylations in the presence of equivalent quantities of sodium ethylate. From the reaction of I and 3-bromopropylamine under these conditions were obtained both 2-(3-hydroxypropylamino)-5,6-dihydro-4*H*-1,3-thiazine (Vb), separated by column chromatography and isolated as the picrate (22% yield), and 2-(3-mercaptopropylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIb), isolated as the dipicrate of the disulfide VIIb (9.4% yield).

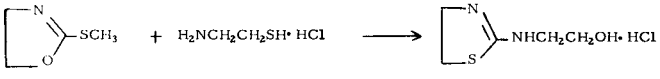
The structures of the rearrangement products were established by alternative synthesis. The reaction of

SCHEME I





XI XII



XIII XIV

2-methylthio-5,6-dihydro-4*H*-1,3-thiazine hydroiodide (VIIIb) and 3-amino-1-propanol afforded Vb. The disulfide VIIb was obtained by iodine oxidation of the mercaptan VIb, which was prepared from 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (IX) and 3-aminopropanethiol hydrochloride (Xb).

The aminoethylation of tetrahydro-2*H*-1,3-oxazine-2-thione (I) by 2-bromoethylamine hydrobromide with two equivalents of sodium ethylate was carried out similarly. Again, two products were obtained that could be considered to come from ring opening at either the C–O bond or the C–S bond of an intermediate of structure IV (n=2) formed from the aminoethylation product IIIa. 2-(3-Hydroxypropylamino)-2-thiazoline (Va) was isolated as the picrate in 27% yield, and its structure was confirmed by its synthesis from 2-methylthio-2-thiazoline hydroiodide (VIIIa) and 3-amino-1-propanol.

Although the second product from the aminoethylation showed spectral properties that were similar to those of the disulfide of 2-(2-mercaptoethylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIIa), which was prepared from 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (IX) and 2-aminoethanethiol hydrochloride, it proved to be different from the disulfide. That the new compound retained the oxazine ring was demonstrated by its infrared and nmr spectra. The analyses and properties of the compound indicated that it might be the sulfide XII, and confirmation of this structure was provided by its nmr spectrum. The signals in the spectrum were similar to those in the spectrum of the disulfide VIIa and represented the same number of protons, but the triplet for the methylene adjacent to sulfur was displaced to higher field by 0.15 ppm. A like displacement has been observed for sulfide-disulfide pairs in other cases (8,9). The expected smaller displacement for the resonance of the methylene β to sulfur was also indicated by the spectrum of XII.

The sulfide XII, isolated as the picrate in 12% crude yield, can result from the reaction of 2-(2-mercaptoethylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIa) with 2-(2-bromoethylamino)-5,6-dihydro-4*H*-1,3-oxazine (XI). The latter can be formed during the reaction from IIIa and 2-bromoethylamine. Thin-layer chromatography indicated that the reaction mixture might also contain some of the disulfide VIIa, but attempts to isolate it by column chromatography were unsuccessful.

The reaction of 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (IX) with aminoethanethiol hydrochloride (Xa), as the first step in the preparation of disulfide VIIa, contrasted to the reaction of 2-methylthio-2-oxazoline (XIII) with aminoethanethiol hydrochloride that had previously been carried out (1,10). In refluxing methanol the latter afforded 2-(2-hydroxyethylamino)-2-thiazoline hydrochloride (XIV) in 55% yield, presumably by rearrangement through a bicyclic intermediate of type IV, whereas under similar conditions IX and Xa gave 2-(2-mercaptoethylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIa) in 85-90% yield, rather than 2-(3-hydroxypropylamino)-2-thiazoline (Va). The failure of this mercaptoethylamino heterocycle to undergo rearrangement may suggest a greater stability for the tetrahydrooxazine ring of the intermediate, or it may indicate that the intermediate is not formed under the conditions of the reaction in this case, perhaps because a fast reaction of IX and Xa to form a compound containing a single basic function may rapidly reduce the likelihood of a base-catalyzed ring closure to the intermediate. In previous work on the 2-methylthio derivatives of the analogous thiazines and thiazolines (3), the six-membered heterocycle was found to react more readily with amines than the five membered.

Although chromatographic procedures such as were used in the present work were not applied to the rearrangement products from the 2-(2-aminoethylthio)-2-oxazolines (1), it seems clear that the rearrangement of 2-(2-aminoethylthio)-5,6-dihydro-4*H*-1,3-oxazine (IIIa) is distinguished from the rearrangements of the 2-(2-aminoethylthio)-2-oxazolines by the isolation from it, in relatively good yield, of a hydroxyalkylamino derivative. This result would be anticipated from the greater stability observed for 2-(3-hydroxypropylamino)-2-thiazoline (Va) compared to 2-(2-hydroxyethylamino)-2-thiazoline. Thus, whereas the rearrangement of the latter compound to 2-(2-mercaptoethylamino)-2-oxazoline takes place in neutral solution and proceeds more rapidly in alkaline solution (1,10), the 3-hydroxypropylamino derivative Va was recovered from 0.35 *N* sodium hydroxide after standing for about 24 hours. The comparative stability of the 3-hydroxypropylamino derivative reflects the greater difficulty of ring closure to form a six-membered ring, rather than a five-membered ring, in an intermediate of type IV. The difference in the ease of ring closure to five- and six-membered rings (11) has previously been cited (3) to account for the products obtained from rearrangements involving analogous intermediates.

EXPERIMENTAL

Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer, the picrates in potassium bromide pellets and the bases in chloroform. The nmr spectra were determined in deuteriochloroform at 100 MHz with a Varian HA-100 spectrometer with tetramethylsilane as an internal standard. Plates of silica gel G were used for thin-layer chromatography with visualization by iodine vapor. Concentrations were carried out under reduced pressure in a rotary evaporator.

2-(3-Hydroxypropylamino)-5,6-dihydro-4*H*-1,3-thiazine (Vb).

A solution of 4.13 g. (0.015 mole) of 2-methylthio-5,6-dihydro-4*H*-1,3-thiazine hydroiodide (VIIIb) (12) and 1.13 g. (0.015 mole) of 3-amino-1-propanol in 80 ml. of ethanol was refluxed for 21 hours. The solution was concentrated, and the cloudiness was removed from a solution of the concentrate in 40 ml. of water by extraction with ether. To 20 ml. of the aqueous solution was added a solution of 1.5 g. of picric acid in 30 ml. of ethanol. The supernatant liquid was decanted from some tacky precipitate, and addition of 60 ml. of water to the decantate yielded 1.50 g. (50%) of crystalline picrate, m.p. 130-133°. Crystallization from ethyl acetate afforded 1.04 g. of yellow needles, m.p. 134-136°. The analytical sample melted at 136-137.5°.

Anal. Calcd. for $C_{13}H_{17}N_5O_8S$: C, 38.71; H, 4.25; N, 17.36. Found: C, 38.62; H, 4.30; N, 17.28.

A solution of 0.635 g. of the picrate in 50 ml. of chloroform was shaken with three 20-ml. portions of 0.5 *N* sodium hydroxide. After the chloroform solution had been dried (anhydrous sodium sulfate) and concentrated, crystallization of the residue from 1:1 hexane-ethyl acetate afforded 0.233 g. (71%) of colorless Vb, m.p. 76-78°. Recrystallization gave prismatic crystals, m.p. 77-78.5°; ir 6.10 μ (N=C–N) (13).

Anal. Calcd. for $C_7H_{14}N_2OS$: C, 48.24; H, 8.10; N, 16.08. Found: C, 48.41; H, 7.94; N, 15.59.

2-(3-Mercaptopropylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIb) Picrate.

A solution of 2.14 g. (0.0163 mole) of 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (IX) (14) and 2.11 g. (0.0165 mole) of 3-aminopropanethiol hydrochloride (Xb) in 125 ml. of methanol was refluxed for 4 hours. Removal of the solvent yielded 3.95 g. of viscous concentrate. When a 0.380-g. portion of this concentrate in 10 ml. of ethanol was treated with excess ethanolic picric acid solution, 0.570 g. (90% yield) of solid picrate, m.p. 134-135.5°, was obtained. Recrystallization from ethanol gave yellow prismatic crystals, m.p. 134-135.5°. The picrate gave a positive test for mercaptan with nitroprusside reagent, and its infrared spectrum showed the weak mercapto band at 3.9 μ.

Anal. Calcd. for $C_{13}H_{17}N_5O_8S$: C, 38.71; H, 4.25; N, 17.36. Found: C, 38.55; H, 4.24; N, 17.12.

2,2′-[Dithiobis(trimethyleneimino)]bis[5,6-dihydro-4*H*-1,3-oxazine] (VIIb).

To a solution of 2.40 g. of the 3.95 g. of concentrate obtained above (from IX and Xb) in 30 ml. of water was added 30 ml. of 1 *N* sodium hydroxide. The resulting solution, stirred in a bath at 10-15°, was treated dropwise with 9.75 ml. of a 0.56 *M* solution of iodine in aqueous potassium iodide. The mixture was thoroughly extracted with chloroform, and treatment of the concentrate from the extracts with ethanolic picric acid solution yielded 3.41 g. (43%) of picrate that melted from 170 to 180°. Crystallization from acetone afforded 2.68 g. (34%) of small yellow needles, m.p. 181-183°.

Anal. Calcd. for $C_{26}H_{32}N_{10}O_{16}S_2$: C, 38.80; H, 4.01; N, 17.41. Found: C, 38.92; H, 4.15; N, 17.19.

When the picrate in chloroform was treated with 0.5 *N* sodium hydroxide, as for Vb above, the base was obtained as a viscous oil that did not solidify. On tlc (4:1 95% ethanol-29% ammonium hydroxide) the oil gave a single spot; ir 2.9 (NH), 5.97 (N=C–N) (15), 8.75 μ (C–O–C); nmr δ 4.17 (t, CH_2O), 3.34 (t, CH_2N=) (16), 3.18 (t, CH_2N), 2.73 (t, CH_2S), 1.90 (m, C–CH_2–C in ring and in side chain).

Rearrangement of the Aminopropylation Product of Tetrahydro-2*H*-1,3-oxazine-2-thione (I).

1. Isolation of 2-(3-Hydroxypropylamino)-5,6-dihydro-4*H*-1,3-thiazine (Vb).

To a solution prepared from 0.710 g. (0.0309 g.-atom) of sodium and 80 ml. of absolute ethanol were added 1.81 g. (0.0154 mole) of I (17) and 3.38 g. (0.0154 mole) of 3-bromopropylamine hydrobromide. After the reaction mixture had been refluxed for 3 hours, the white precipitate was filtered off, and removal of the solvent from the filtrate gave 5.31 g. of viscous concentrate. Thin-layer chromatograms (10:1 and 4:1 95% ethanol-29% ammonium hydroxide) of the concentrate contained spots corresponding to Vb and VIIb. The thin-layer chromatograms indicated in addition that several other substances were present in small quantity and that considerable unreacted thione remained in the concentrate.

A 0.877-g. portion of the concentrate was dissolved in 18 ml. of water and 7 ml. of 1 *N* sodium hydroxide, and the solution was extracted 10 times with 25-ml. portions of chloroform. The concentrate (0.565 g.) from the dried chloroform extracts was dissolved in 3 ml. of methanol and placed on a column of 60 g. of silica gel (Merck-Darmstadt). The column was eluted with 10:1 95% ethanol-29% ammonium hydroxide, and the fractions containing Vb, which moved much more rapidly than VIIb, were combined and concentrated. Treatment of the concentrate with ethanolic picric acid yielded 0.190 g. (22.3% yield, corrected for recovered I) of Vb picrate, m.p. 131.5-134°. On recrystallization from ethyl acetate 0.145 g. of yellow needles, m.p. 135.5-137°, was obtained.

2. Isolation of 2,2′-[Dithiobis(trimethyleneimino)]bis[5,6-dihydro-4*H*-1,3-oxazine] (VIIb).

From a run with 0.719 g. of sodium, 1.83 g. of I, and 3.42 g. of 3-bromopropylamine hydrobromide, carried out as above, there was obtained 5.29 g. of viscous concentrate. A 1.23-g. portion of this concentrate was treated dropwise with 3.0 ml. of 0.56 *M* iodine solution. The resulting aqueous solution was extracted with three 30-ml. portions of chloroform, and treatment of the concentrate from the extracts with ethanolic picric acid afforded a crude picrate. Crystallization of the picrate from acetone yielded 0.113 g. (9.4% yield, corrected for recovered I) of VIIb picrate that melted from 163 to 168°. Recrystallization gave 76 mg. of small yellow needles, m.p. 174-177°, and a sample of VIIb picrate melting at 180-182° was obtained on further recrystallization.

An aqueous solution of a portion of the 5.29 g. of viscous concentrate from the reaction was thoroughly extracted with chloroform. When the concentrate from the chloroform extracts was crystallized from benzene-hexane, a 17.4% recovery of thione I was obtained.

2-(3-Hydroxypropylamino)-2-thiazoline (Va).

A solution of 5.22 g. (0.020 mole) of 2-methylthio-2-thiazoline hydroiodide (VIIIa) (12) and 1.50 g. (0.020 mole) of 3-amino-1-propanol in 100 ml. of 95% ethanol was refluxed for 21 hours. After concentration of the solution, 50 ml. of water was added, and some undissolved oil was removed by extraction with ether. The aqueous solution was concentrated, and crystallization of the residue from ethanol afforded 2.50 g. (43%) of Va hydroiodide as colorless crystals, m.p. 113-115°. On recrystallization from absolute ethanol there was obtained 1.98 g. of prismatic crystals, m.p. 116-118°.

Anal. Calcd. for $C_6H_{13}IN_2OS$: C, 25.01; H, 4.55; S, 11.13. Found: C, 25.03; H, 4.70; S, 11.06.

The hydroiodide was converted to the base by treatment with 1 *N* sodium hydroxide, extraction into chloroform, and concentration of the extracts. The base (Va) crystallized from hexane-ethyl acetate as colorless glistening plates, m.p. 74-75.5°.

Anal. Calcd. for $C_6H_{12}N_2OS$: C, 44.97; H, 7.55; N, 17.49. Found: C, 45.21; H, 7.54; N, 17.30.

The infrared spectrum of Va contained the peak at 6.14 μ for N=C–N and the nmr spectrum the triplet at δ 3.93 for CH_2N= that are characteristic of thiazolines of this type (3). The picrate of Va crystallized from ethyl acetate as yellow prismatic crystals, m.p. 165.5-167°.

Anal. Calcd. for $C_{12}H_{15}N_5O_8S$: C, 37.02; H, 3.88; N, 17.99. Found: C, 37.00; H, 4.04; N, 17.72.

2-(2-Mercaptoethylamino)-5,6-dihydro-4*H*-1,3-oxazine (VIa) Picrate

A solution of 1.72 g. (0.013 mole) of 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine (IX) and 1.48 g. (0.013 mole) of 2-aminoethanethiol hydrochloride (Xa) in 40 ml. of methanol was refluxed for 4 hours. The solvent was removed, and treatment of a 2.43-g. portion of the 3.18 g. of oily concentrate with ethanolic picric acid yielded 3.58 g. (92%) of picrate, m.p. 169-171°. Crystallization from ethyl acetate afforded yellow prismatic crystals, m.p. 170-171.5°, that gave a positive nitroprusside test for mercaptan; ir 3.9 (SH), 5.93, 6.08 μ.

Anal. Calcd. for $C_{12}H_{15}N_5O_8S$: C, 37.02; H, 3.88; N, 17.99. Found: C, 36.80; H, 4.17; N, 17.75.

2,2'-[Dithiobis(dimethyleneimino)]bis[5,6-dihydro-4*H*-1,3-oxazine] (VIIa).

After a solution of 1.20 g. (9.15 mmole) of IX and 1.05 g. (9.25 mmole) of Xa in 80 ml. of methanol had been refluxed for 4 hours, the solution was concentrated, and the oily residue was dissolved in 56 ml. of 0.5 *N* sodium hydroxide. To this solution was added dropwise 9.0 ml. of 0.56 *M* iodine solution. The resulting solution was extracted with portions of 10-15 ml. of chloroform until the extracts, examined by tlc, no longer contained VIIa. The combined extracts were concentrated, and treatment of the viscous oil obtained with ethanolic picric acid gave 1.76 g. (50%) of picrate, m.p. 188-192°. Crystallization from acetone afforded 1.35 g. of yellow needles, m.p. 195.5-197°; ir 5.95, 6.10 μ.

Anal. Calcd. for $C_{24}H_{28}N_{10}O_{16}S_2$: C, 37.11; H, 3.63; N, 18.04. Found: C, 37.00; H, 3.68; N, 17.80.

The picrate was converted to the base by treating a chloroform solution with 1 *N* sodium hydroxide in the usual way. The base (VIIa) separated from hexane-ethyl acetate as colorless crystals, m.p. 72.5-74°; ir 2.9 (NH), 5.97 (N=C–N) (15), 8.75 μ (C–O–C); nmr δ 4.17 (t, CH_2O), 3.39 (m, CH_2N= and CH_2N), 2.84 (t, CH_2S–S), 1.85 (quintet, C–CH_2–C).

Anal. Calcd. for $C_{12}H_{22}N_4O_2S_2$: C, 45.26; H, 6.96; N, 17.59. Found: C, 45.38; H, 7.08; N, 17.29.

Disulfide VIIa was also obtained from two equivalents of IX and cystamine dihydrochloride in 28% yield after 21 hours of refluxing in methanol.

Rearrangement of the Aminoethylation Product of Tetrahydro-2*H*-1,3-oxazine-2-thione (I).

1. Isolation of 2-(3-Hydroxypropylamino)-2-thiazoline (Va).

To a solution prepared from 0.530 g. (0.0230 g.-atom) of sodium and 50 ml. of absolute ethanol were added 1.35 g. (0.0115 mole) of I and 2.36 g. (0.0115 mole) of 2-bromoethylamine hydrobromide, and the solution was refluxed for 3 hours. A thin-layer chromatogram (10:1 95% ethanol-29% ammonium hydroxide) of the solution contained a fast-moving spot corresponding to Va. It also showed a strong spot corresponding to I, several weak spots, and spots for slow-moving components similar to VIIa. A thin-layer chromatogram of a similar run was essentially the same after 6 hours of refluxing; no 2-bromoethylamine appeared to be present after the first 3 hours. Removal of the solvent from the filtered solution afforded 3.36 g. of viscous concentrate. A 0.736-g. portion of this concentrate was dissolved in 15 ml. of water and 6 ml. of 1 *N* sodium hydroxide. After thorough extraction of the aqueous solution with chloroform, the concentrate (0.434 g.) from the extracts was chromatographed on a column of 60 g. of silica gel with 10:1 95% ethanol-29% ammonium hydroxide. Treatment of the concentrate from the fractions containing Va with ethanolic picric acid yielded 0.168 g. (26.6%, corrected for recovered I) of Va picrate, m.p. 165.5-167°.

2. Isolation of 2,2'-[Thiobis(dimethyleneimino)]bis[5,6-dihydro-4*H*-1,3-oxazine] (XII).

A similar run, in which 1.09 g. of sodium, 2.79 g. of I, and 4.87 g. of 2-bromoethylamine hydrobromide were used, yielded 6.41 g. of concentrate. A 2.36-g. portion of the concentrate, dissolved in 35 ml. of 0.6 *N* sodium hydroxide, was treated with 7.8 ml. of 0.56 *M* iodine solution. The resulting solution was extracted with two 30-ml. portions of chloroform, and treatment of the concentrate from the extracts with picric acid afforded 0.245 g. (11.6% crude yield, corrected for recovered I) of picrate that melted from 168 to 175°. Crystallization from acetone gave 0.103 g. (4.9%) of XII picrate as clumps of small needles, m.p. 175-178°. On recrystallization there was obtained 78 mg., m.p. 178-180°; ir 5.93, 6.10 μ.

Anal. Calcd. for $C_{24}H_{28}N_{10}O_{16}S$: C, 38.71; H, 3.79; N, 18.81; S, 4.31. Found: C, 38.73; H, 3.90; N, 18.98; S, 4.30.

Trials in which the iodine oxidation of the concentrate from the reaction was omitted gave a similar result.

Conversion of the picrate to the base in the usual manner yielded a viscous oil that did not solidify; ir 2.9 (NH), 5.96 (N=C–N), 8.75 μ (C–O–C); nmr δ 4.18 (t, CH_2O), 3.32 (m, CH_2N= and CH_2N), 2.69 (t, CH_2S), 1.86 (quintet, C–CH_2–C). This base did not give a positive test for disulfide, which was shown by VIIa, on treatment with potassium cyanide and nitroprusside. On tlc (4:1 95% ethanol-29% ammonium hydroxide), it gave a single spot that moved somewhat slower than VIIa.

A portion of the concentrate from the reaction was extracted with chloroform. Removal of the chloroform and crystallization of the residue from benzene afforded a 35.5% recovery of crystalline I.

Acknowledgment.

We are indebted to Frank H. Bissett and Dr. Ronald C. Chalk

of these laboratories for the nmr spectra and to Dr. Martin G. Ettlinger for some helpful discussions.

REFERENCES

(1) R. C. Clapp, L. Long, Jr. and T. Hasselstrom, *J. Org. Chem.*, **28**, 1308 (1963).

(2) R. C. Clapp, L. Long, Jr. and T. Hasselstrom, *ibid.*, **26**, 1666 (1961).

(3) R. C. Clapp, F. H. Bissett and L. Long, Jr., *ibid.*, **32**, 3174 (1967).

(4) L. V. Pavlova and F. Yu. Rachinskii, *Biol. Aktivn. Soedin., Akad. Nauk SSSR*, 186 (1965).

(5) J. X. Khym, D. G. Doherty and R. Shapira, *J. Am. Chem. Soc.*, **80**, 3342 (1958).

(6) T. Hino, K. Tana-ami, K. Yamada and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1201 (1966).

(7) D. G. Doherty, R. Shapira and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957).

(8) J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1094, 1099 (1961).

(9) F. H. Bissett and M. H. Halford, unpublished results.

(10) R. C. Clapp, L. Long, Jr. and T. Hasselstrom, *J. Org. Chem.*, **29**, 2172 (1964).

(11) For a discussion see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p. 198.

(12) A. F. McKay, D. J. Whittingham and M.-E. Kreling, *J. Am. Chem. Soc.*, **80**, 3339 (1958).

(13) In the spectrum of 2-methylamino-5,6-dihydro-4*H*-1,3-thiazine this strong absorption is similarly at 6.10 μ (3).

(14) R. C. Clapp, F. H. Bissett and L. Long, Jr., *J. Heterocyclic Chem.*, **5**, 107 (1968).

(15) In the spectrum of 2-benzylamino-5,6-dihydro-4*H*-1,3-oxazine (14) this band is at 6.0 μ.

(16) In the nmr spectrum of 2-methylthio-5,6-dihydro-4*H*-1,3-oxazine in reference 14 the triplet at δ 4.25 should be assigned to CH_2O and the triplet at δ 3.45 to $CH_2N{=}$.

(17) A. Kjaer and R. B. Jensen, *Acta Chem. Scand.*, **12**, 1746 (1958).

Received August 17, 1970 Natick, Mass. 01760