[CONTRIBUTION FROM THE DEFENCE RESEARCH CHEMICAL LABORATORIES, CANADA]

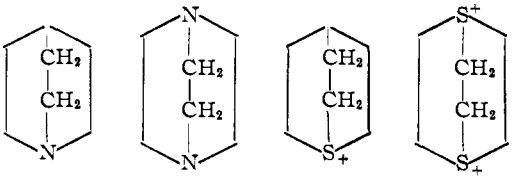
4-Azabicyclo[2,2,2]octane-1-thionium Halides: A New Ring System[1]

BY W. F. COCKBURN AND A. F. MCKAY

RECEIVED FEBRUARY 17, 1954

This paper describes the synthesis and properties of a new bicyclic system, in which one of the bridgehead atoms is sulfur and the other is nitrogen.

Several types of bicyclic compound are known, in which one or both of the bridgehead positions are occupied by a hetero atom. Examples of such molecules are the well known quinuclidine (I), triethylenediamine (II),[2] the bicyclic sulfonium salts III described by Prelog[3,4] and the bicyclic disulfonium salt IV prepared from thiodiglycol and

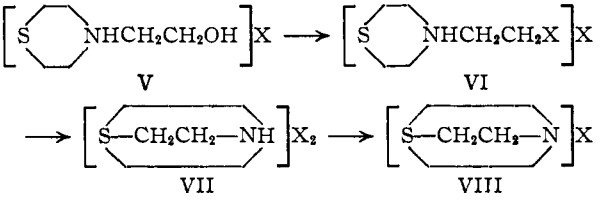


I II III IV

concentrated hydrochloric acid.[5] No account has appeared in the literature, however, of the corresponding bicyclic compound in which one of the bridgehead atoms is sulfur, and the other nitrogen. The synthesis of such a molecule therefore was undertaken, with a view to investigating its properties.

Preliminary experiments with tris-(2-chloroethyl)-amine and potassium sulfide were unsuccessful, probably due to the difficulty of closing both rings of a bicyclic molecule simultaneously. A more promising approach was the ring closure of 4-(2-haloethyl)-thiamorpholines (VI).

An attempt to synthesize the desired compound was made by heating 4-(2-hydroxyethyl)-thiamorpholine with concentrated hydrobromic acid in a sealed tube. The main product of this reaction was the hydrobromide salt (V, X = Br) of the starting material, though traces of another, high-melting substance were obtained. Since replacement of the hydroxyl group by halogen was not taking place to any extent, 4-(2-chloroethyl)-thiamorpholine hydrochloride (VI, X = Cl) was prepared by the action of thionyl chloride on 4-(2-hydroxyethyl)-thiamorpholine hydrochloride (V, X = Cl). When this chloroethyl derivative was heated in a sealed tube with water, hydrolysis took place, yielding back 4-(2-hydroxyethyl)-thiamorpholine hydrochloride. On the other hand, heating with concentrated hydrochloric acid yielded a crystalline salt which gave no depression in melting point with the starting chloroethyl compound, but which was very much less soluble in ethanol than the latter. The two substances were found by elementary analysis to be isomeric, but yielded dissimilar X-ray powder photographs. An analysis for ionic chlorine therefore was carried out, the results of which showed that the product of the above reaction contained only ionic chlorine, while in the case of the starting material, 4-(2-chloroethyl)-thiamorpholine hydrochloride, only half of the total chlorine existed as chloride ion. Similar



V VI VII VIII

results were obtained using 4-(2-bromoethyl)-thiamorpholine hydrobromide (VI, X = Br) as starting material. The product had an apparent molecular weight in aqueous solution of 91–93. Allowing for the fact that three ions are formed, the expected value is 97.

If ring closure has taken place, the products of these two reactions should be 4-azabicyclo(2,2,2)-octane-1-thionium chloride hydrochloride (VII, X = Cl) and 4-azabicyclo(2,2,2)octane-1-thionium bromide hydrobromide (VII, X = Br), respectively. The fact that no depression in melting point was observed on mixing VI and VII (X = Cl) suggests that the former ring closes during melting. In order to obtain the free amine, a sample of the hydrobromide was shaken with slightly more than one molecular equivalent of freshly prepared silver oxide in the dark. The product was filtered from silver salts, and freed from solvents *in vacuo*, yielding a feebly basic crystalline solid which analyzed correctly for 4-azabicyclo(2,2,2)octane-1-thionium bromide (VIII, X = Br).

If, as suggested by Hromatka,[6] the nitrogen atom must be in the tetracovalent state for ring-closure to occur, this effect should be even more pronounced when quaternary ammonium salts are employed as starting material. On the other hand, the presence of a strong positive charge on the nitrogen atom might be expected to inhibit both the ionization of the bromine atom, and the formation of a positively charged sulfonium atom in the same molecule, accordingly, 4-(2-bromoethyl)-thiamorpholine N-methobromide (X) was prepared, and heated in a sealed tube with concentrated hydrobromic acid. This process yielded a crystalline

(1) Issued as DRCL Report No. 146.

(2) (a) O. Hromatka, *Ber.*, **75B**, 1302 (1942); (b) **76B**, 712 (1943).

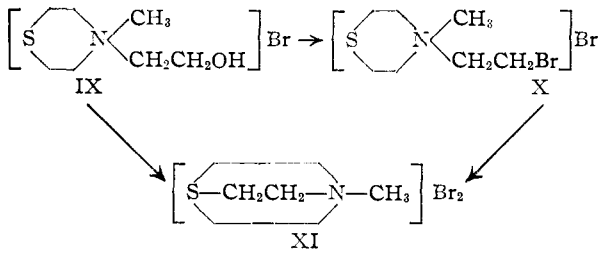
(3) V. Prelog and E. Cerkovnikov, *Ann.*, **537**, 214 (1939).

(4) V. Prelog and D. Kohlbach, *Ber.*, **72B**, 672 (1939).

(5) M. A. Stahmann, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 704 (1946).

(6) V. Prelog, E. Cerkovnikov and C. Ustricev, *Ann.*, **535**, 37 (1938), made unsuccessful attempts to prepare triethylenediamine (II) by the ring closure of 1-(2-bromoethyl)-piperazine. Prelog attributed this failure to the rapid oscillation of the nitrogen atom about its mean position. The suggestion was made by Hromatka[2b] that this oscillation would be absent if the nitrogen atom were in the tetracovalent state, and he was able to carry out the synthesis of triethylenediamine by heating 1-(2-bromoethyl)-piperazine hydrobromide in both open and sealed tubes.[2b]

product of high decomposition point, which was isomeric with the starting compound, but yielded a different X-ray powder photograph, and contained

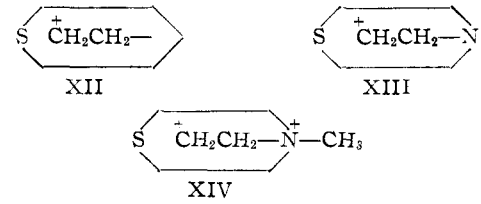


only ionic bromine. The yield of this methobromide XI was 92%, as compared with 78% for the hydrobromide described above. Furthermore, when 4-(2-hydroxyethyl)-thiamorpholine N-methobromide (IX) was heated with hydrobromic acid under similar conditions, a 26% yield of XI was obtained, in spite of the fact that the corresponding reaction with 4-(2-hydroxyethyl)-thiamorpholine hydrobromide (V, X = Br) had failed to yield any appreciable quantity of the desired bicyclic compound. In order to find out if heating under pressure were necessary, a sample of X was allowed to stand in concentrated hydrobromic acid for several months. This procedure resulted in a 96% yield of XI. These results seem to show that the steric stability conferred by the quaternary nitrogen atom outweighs the increased inhibiting effect on the ionization of the bromine atom.

A similar experiment with 4-(2-hydroxyethyl)-thiamorpholine N-methiodide (IX, I in place of Br) and hydriodic acid gave only recovered starting material, largely owing to the decomposition of the acid. It is of interest that even prolonged treatment of 4-(2-hydroxyethyl)-thiamorpholine N-methiodide with methyl iodide failed to produce the corresponding methyl sulfonium iodide. This must be ascribed to the well-known ready dissociation of sulfonium salts, along with an unfavorable equilibrium position due to the close proximity of the positively charged nitrogen atom. Similar results have been reported in the case of 2-methylthiazoline and 2-methyldihydro-1,3-thiazine, both of which form only monomethiodides.[7-9]

In view of the fact that the bicyclic sulfonium salt III described by Prelog is biologically active the above compounds were tested for toxicity by intraperitoneal injection into white mice, and approximate LD_{50} values obtained. The results indicated a figure of 80–100 mg./kg. for 4-azabicyclo(2,2,2)octane-1-thionium bromide hydrobromide (VII) which had been neutralized by addition of one molecular equivalent of sodium carbonate, and a slightly higher figure (*ca.* 150 mg./kg.) for the hydrobromide alone. Compound VI thus possesses about a tenth of the toxicity of III. The quaternary ammonium bromide XI, on the other hand, elicited no toxic effects at a dosage level of 100 mg./kg.

These results are in agreement with the theory that the toxic action of Prelog's bicyclic sufonium salt III is due to dissociation of the sulfur atom, with the formation of an active alkylating agent.[10] Such dissociations of III, VIII and XI would give rise to XII, XIII and XIV, respectively. In this



dissociation, the bonding electrons between the sulfur and carbon atoms are retained by sulfur. Since the tertiary amino group in VIII is weakly electronegative, it will attract the bonding electron pair away from the sulfur atom, and thus oppose the formation of the active intermediate XIII. In the case of the quaternary ammonium salt XI, the electron attracting force of the positively charged nitrogen atom is much stronger than in VIII. In addition, its action is reinforced by the fact that dissociation would bring the two unit positive charges in the molecule closer together. Hence the dissociation is very strongly inhibited, and the compound is inactive.

Acknowledgments.—The authors are indebted to Dr. M. Chaput and Mr. L. G. Wilson of these laboratories for the reported toxicities and the X-ray powder photographs, respectively.

Experimental[11]

4-(2-Hydroxyethyl)-thiamorpholine.[12]—This amine was prepared from bis-(2-bromoethyl) sulfide and ethanolamine, in 50% yield, being isolated as the hydrochloride, m.p. 162–164° (cor.); free base m.p. 34.5–35.5° (cor.). The hydrobromide was found to exist in two crystalline forms, both of which usually were obtained simultaneously by crystallization from acetone or ethanol. The low melting isomer was obtained by slow crystallization from ethanol, m.p. 124–126° (cor.), while the pure high melting isomer was obtained, on one occasion only, from hot acetone, m.p. 143–144° (cor.). Recrystallization of both forms again gave a mixture of the two, however, and no reproducible method was found of obtaining either form pure.

Anal. Calcd. for $C_6H_{14}BrNOS$: C, 31.59; H, 6.18; N, 6.14. Found: C, 31.68, 31.99; H, 6.12, 6.47; N, 5.86.

4-(2-Chloroethyl)-thiamorpholine Hydrochloride.[13]—To a suspension of 3.67 g. (0.02 mole) of finely ground 4-(2-hydroxyethyl)-thiamorpholine hydrochloride in 25 ml. of dry chloroform, was added 3.3 g. (0.0275 mole) of thionyl chloride, and the mixture heated to reflux for 2 min. The chloroform was removed by evaporation under reduced pressure, and the solid residue recrystallized from ethanol, yield 3.45 g. (85%), m.p. 209–212° dec.

Anal. Calcd. for $C_6H_{13}Cl_2NS$: C, 35.65; H, 6.48; S, 15.86; Cl, 35.08, ionic Cl, 17.54. Found: C, 36.09; H, 6.70; S, 16.18; Cl, 35.25; ionic Cl, 17.33.

4-(2-Bromoethyl)-thiamorpholine Hydrobromide.—Treatment of 4-(2-hydroxyethyl)-thiamorpholine hydrobromide

(7) L. G. S. Brooker, THIS JOURNAL, **58**, 664 (1936).

(8) F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.*, 243 (1943).

(9) B. Beilenson, F. M. Hamer and R. J. Rathbone, *ibid.*, 222 (1945).

(10) *Cf.* ref. 5.

(11) All melting points are uncorrected, unless otherwise stated. Melting point capillaries, in most cases, were inserted in the apparatus about 15° below the expected melting point, to reduce prior decomposition. Microanalyses are by C. W. Beazley, Skokie, Ill. The molecular weight of 4-azabicyclo(2,2,2)octane-1-thionium bromide hydrobromide was determined by the Huffman Microanalytical Laboratories, Wheatridge, Col.

(12) L. A. Burrows and E. E. Reid, THIS JOURNAL, **56**, 1720 (1934).

(13) This compound was reported by H. Gilman and L. A. Woods, *ibid.*, **67**, 1843 (1945), but no experimental details or analysis figures were given.

with thionyl bromide, according to the above procedure, gave a 24% yield of the desired compound. The product was obtained by crystallization from ethanol in long needles which decomposed at 215–225° on rapid heating.

Anal. Calcd. for $C_6H_{13}Br_2NS$: C, 24.76; H, 4.50; Br, 54.92; ionic Br, 27.46. Found: C, 25.13; H, 4.14; Br, 54.81; ionic Br, 28.50.

4-(2-Hydroxyethyl)-thiamorpholine N-Methiodide.—To 1.2 g. (0.0082 mole) of 4-(2-hydroxyethyl)-thiamorpholine was added 5 g. (0 035 mole) of methyl iodide, and the mixture swirled at room temperature Within one minute a clear solution was obtained, which soon started to deposit fine crystals. After standing overnight, the solid mixture was warmed on the hot-plate with 2 ml. of methanol, and the clear solution so obtained induced to crystallize by scratching with a spatula. The product was filtered off and washed with 1 ml. of cold methanol, giving 2.0 g. of colorless fine crystals, m.p. 218–220° dec. Evaporation of the mother liquors gave a further 0.27 g. of material, making a total of 2.27 g. of solid products, which proves that only one molecule of methyl iodide had taken part in the reaction. Since the *p*H of a 1% aqueous solution of the product was found to be 5, as compared with *p*H 8 for a solution of the starting material, it is apparent that the nitrogen atom is involved in salt formation, rather than the sulfur atom. Two recrystallizations from ethanol gave long flat needles, m.p. 220–221° dec.

Anal. Calcd. for $C_7H_{16}INOS$: C, 29.07; H, 5.58; I, 43.88. Found: C, 29.40; H, 5.53; I, 43.78.

4-(2-Hydroxyethyl)-thiamorpholine N-Methobromide.—4-(2-Hydroxyethyl)-thiamorpholine N-methiodide was converted to the quaternary hydroxide by shaking with excess, freshly prepared silver oxide in methanol. After filtration from silver compounds, the alkaline filtrate was acidified with concentrated hydrobromic acid, and the solution evaporated to dryness under reduced pressure. The solid residue was recrystallized twice from ethanol, being obtained in colorless platelets, which melted with decomposition at 255° after darkening at 248°, when inserted in the bath at 230°, yield 78%.

Anal. Calcd. for $C_7H_{16}BrNOS$: C, 34.70; H, 6.66; Br, 33.00. Found: C, 35.09; H, 6.80; Br, 33.38.

4-(2-Bromoethyl)-thiamorpholine N-Methobromide.[14]—4-(2-Hydroxyethyl)-thiamorpholine N-methobromide was treated with a threefold excess of freshly distilled thionyl bromide in chloroform, and the mixture heated on the hot-plate until the heavy brown oil formed initially had solidified to a reddish cake. After standing at room temperature for two hours, the volatile parts were removed under reduced pressure, the solid residue dissolved in ethanol and filtered hot. On cooling and scratching with a spatula, the solution deposited fine white needles, which were recrystallized from ethanol. The product melted with decomposition at 278° if inserted in the heating block at 260° and heated rapidly but, on slow heating, it blackened and decomposed without melting. It gave a strong melting point depression on admixture with the starting material, yield 65%.

Anal. Calcd. for $C_7H_{15}Br_2NS$: C, 27.55; H, 4.96; Br, 52.40; ionic Br, 26.20. Found: C, 27.65; H, 4.80; Br, 52.73; ionic Br, 27.11.

Attempted Ring Closure of 4-(2-Chloroethyl)-thiamorpholine Hydrochloride.—A solution of 1 g. of 4-(2-chloroethyl)-thiamorpholine hydrochloride in 10 ml. of water was heated in a sealed tube at 100° for 23 days. After cooling, the tube contents were evaporated to dryness under reduced pressure, leaving a yellowish crystalline solid. Recrystallization of this material from ethanol gave 780 mg. of colorless crystals m.p. 160–161°. Admixture with 4-(2-hydroxyethyl)-thiamorpholine hydrochloride (m.p. 160–163°) caused no depression in melting point.

4-Azabicyclo(2,2,2)octane-1-thionium Chloride Hydrochloride.—A solution of 0.4 g. of 4-(2-chloroethyl)-thiamorpholine hydrochloride in 4 ml. of concentrated hydrochloric acid was heated in a sealed tube at 100° for 7 days. After evaporation to dryness under reduced pressure, the reaction product was boiled with 30 ml. of ethanol, and filtered hot. The residue from this filtration consisted of 150 mg. of fine crystals, m.p. 210–212°, while the filtrate, on cooling, deposited 170 mg. of crystalline material, m.p. 207–212°. Neither substance depressed the melting point of the starting material (m.p. 209–212°). The difference in their solubilities in ethanol suggested that they were not identical, however. The insoluble residue described above therefore was recrystallized from methanol, being obtained in needles, m.p. 208–210°.

Anal. Calcd. for $C_6H_{13}Cl_2NS$: C, 35.65; H, 6.48; N, 6.93; S, 15.86; ionic Cl, 35.08. Found: C, 35.38; H, 6.57; N, 6.87; S, 15.27; ionic Cl, 34.55.

This substance was found to yield an X-ray powder photograph which was different from that given by the starting material. On account of the difficulty of completely separating the bicyclic compound from starting material, the yield could not be determined exactly. At least 40% of bicyclic product was obtained, however.

4-Azabicyclo(2,2,2)octane-1-thionium Bromide Hydrobromide.—A solution of 465 mg. of 4-(2-bromoethyl)-thiamorpholine hydrobromide in 10 ml. of 42% hydrobromic acid was heated at 100° in a sealed tube for 72 hours. The tube contents were evaporated to dryness under reduced pressure, and the residue boiled out twice with 30 ml. of ethanol. The first washing, on cooling in the ice-box, deposited 68 mg. of starting material. The insoluble residue could be recrystallized by the procedure described below for 4-azabicyclo(2,2,2)octane-1-thionium bromide methobromide, being obtained as a white, micro-crystalline powder, which melted with decomposition at 241–242° with rapid heating from 225°. A different crystalline form was obtained by simply boiling the reaction product with ethanol, in place of recrystallization. The two forms had the same m.p., but gave X-ray powder photographs which differed from each other and from that given by 4-(2-bromoethyl)-thiamorpholine hydrobromide, yield 78%. The virtual insolubility of both this compound and 4-azabicyclo-(2,2,2)octane-1-thionium bromide methobromide in ethanol made an accurate determination of yield much easier than was the case with 4-azabicyclo(2,2,2)octane-1-thionium chloride hydrochloride.

Anal. Calcd. for $C_6H_{13}Br_2NS$: C, 24.76; H, 4.50; N, 4.81; S, 11.02; ionic Br, 54.92. Found: C, 25.01; H, 4.58; N, 4.60; S, 11.10; ionic Br, 54.28.

The molecular weight in aqueous solution was measured by the isopiestic method, the observed values being 91 and 93. The formula weight is 291 but, since the molecule gives rise to three ions in solution, the apparent molecular weight should be 97.

4-Azabicyclo(2,2,2)octane-1-thionium Bromide.—A solution of 100 mg. (0.00035 mole) of 4-azabicyclo(2,2,2)octane-1-thionium bromide hydrobromide was shaken with silver oxide for one hour, the reaction being protected from the light. The silver oxide was freshly prepared from 65 mg. (0.00038 mole) of silver nitrate. The solution was filtered to remove silver bromide, and the filtrate evaporated to dryness under reduced pressure. The residue was recrystallized from 2 ml. of ethanol, being obtained in colorless needles, which melted with decomposition at about 250°, if inserted in the melting-point block at that temperature, but gradually charred on slow heating, yield 56 mg. (78%). Addition of this compound to distilled water raised the *p*H value from 5 to 7, indicating weakly basic properties.

Anal. Calcd. for $C_6H_{12}BrNS$: C, 34.30; H, 5.76; N, 6.67; S, 15.26; Br, 38.04. Found: C, 34.60; H, 5.74; N, 6.60; S, 14.91; Br, 37.51.

The dipicrate was formed by addition of methanolic picric acid to a methanolic solution of 4-azabicyclo(2,2,2)octane-1-thionium bromide. It was obtained by recrystallization from acetone–methanol in small prisms, m.p. 210–215° dec.

Anal. Calcd. for $C_{18}H_{18}N_7O_{14}S$: C, 36.74; H, 3.08. Found: C, 36.73; H, 3.32.

The free base was also reconverted to the hydrobromide by treatment with HBr, and the product found to be identical with the original 4-azabicyclo(2,2,2)octane-1-thionium bromide hydrobromide by m.p. and mixed m.p., and by X-ray powder photograph.

4-Azabicyclo(2,2,2)octane-1-thionium Bromide Methobromide. (1) From **4-(2-Bromoethyl)-thiamorpholine N-Methobromide.**—A solution of 60 mg. of 4-(2-bromoethyl)-thiamorpholine N-methobromide in 5 ml. of 42% hydrobromic acid was heated at 100° in a sealed tube for 72 hours.

(14) 4-(2-Chloroethyl)-thiamorpholine N-methochloride was reported by A. H. Ford-Moore and H. R. Ing, *J. Chem. Soc.*, 55 (1947).

After cooling, the contents of the tube were evaporated to dryness under reduced pressure, and the solid residue boiled with 20 ml. of ethanol, which failed to dissolve all the material. This very low solubility in ethanol is in contrast with the properties of the starting methobromide. The flask was cooled overnight in the ice-box, and the solid filtered off, giving 55 mg. of crystals of high decomposition point. These could be recrystallized in long needles, by dissolving in 30 ml. of ethanol containing 2 ml. of water, and removing most of the water by repeated boiling with benzene. The product melted at 270° with rapid heating, if inserted in the melting-point block at 250°. It gave an X-ray powder photograph which was quite distinct from that of the starting material, yield 92%.

Anal. Calcd. for $C_7H_{16}Br_2NS$: C, 27.55; H, 4.96; N, 4.59; S, 10.51; ionic Br, 52.40. Found: C, 28.05; H, 5.10; N, 4.60; S, 10.91; ionic Br, 52.58.

This reaction was carried out also at room temperature, by allowing 70 mg. of 4-(2-bromoethyl)-thiamorpholine N-methobromide in 5 ml. of 40% hydrobromic acid to stand for 172 days. The reaction mixture was worked up as before, yielding 67 mg. (96%) of 4-azabicyclo(2,2,2)octane-1-thionium bromide methobromide, which was identified by its X-ray powder photograph.

(2) From 4-(2-Hydroxyethyl)-thiamorpholine N-Methobromide.—A solution of 150 mg. of 4-(2-hydroxyethyl)-thiamorpholine N-methobromide in 3 ml. of 42% hydrobromic acid was heated at 100° in a sealed tube for 285 hours. The product was worked up as in the previous preparation yielding 40 mg. of small prismatic crystals of high decomposition point. The X-ray powder photograph of this substance was identical to that given by the product of the previous run; yield 26%.

Anal. Calcd. for $C_7H_{15}Br_2NS$: C, 27.55; H, 4.96; Br, 52.40. Found: C, 27.77; H, 5.22; Br, 52.32.

Concentration of the alcoholic mother liquors yielded 95 mg. of starting material.

OTTAWA, ONTARIO

[CONTRIBUTION FROM THE CHEMOTHERAPY DEPARTMENT, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

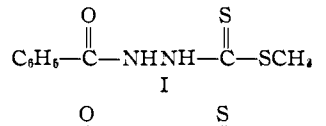
The Cyclization of 3-Acyldithiocarbazate Esters[1]

BY RICHARD W. YOUNG AND KATHRYN H. WOOD

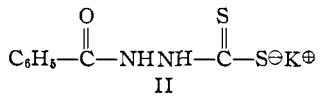
RECEIVED JULY 7, 1954

Acid-catalyzed cyclodehydration of 3-acyldithiocarbazic acid esters has been shown to produce 2-substituted 5-sulfido-1,3,4-thiadiazoles. The mechanism for this reaction as well as for the formation of 1,3,4-oxadiazoles in alkaline cyclizations is discussed. A series of 2-substituted-5-mercapto-1,3,4-oxadiazoles and 2-substituted-5-benzylmercapto-1,3,4-thiadiazoles has been prepared.

In the course of an investigation of the stereochemistry of hydrazones, Busch and Starke[2] prepared methyl-3-benzoyldithiocarbazate (I) by methylation of the salt formed from benzoic acid hydrazide and carbon disulfide in alcoholic potassium hydroxide. Although no evidence was put forth, the salt was assigned the structure II.



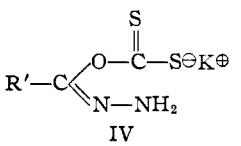
I



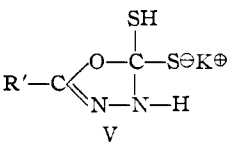
II

Recently Hoggarth[3] discovered that both the salt and the ester could be converted to 2-phenyl-5-mercapto-1,3,4-oxadiazole (III) by boiling in pyridine solution. In our own work, we found that the salt need not be isolated; merely refluxing of the alcoholic alkaline solution containing the hydrazide and carbon disulfide results in evolution of hydrogen sulfide and an excellent yield of III is obtained. (The same oxadiazole was obtained by refluxing the ester (I) with sodium ethylate in ethanol.) Other 2-substituted oxadiazoles were prepared from the corresponding hydrazides in the same manner (Table I).

The mechanism of the formation of oxadiazoles under these conditions is interesting, in view of the structures proposed for I and II. Instead of the formation of II as the initial product of the reaction, the first logical intermediate should be formed by a nucleophilic attack of the enolate ion of the hydrazide on carbon disulfide forming a "xanthate-type" salt IV.[4] By intramolecular acylation of the neighboring amino function the oxadiazole would be produced with concomitant loss of hydrogen sulfide or, alternatively, IV might rearrange to II *via* an intermediate oxadiazoline V



IV



V

analogous to the intermediate suggested[5] for the N → O and O → N acyl migrations of amino alcohols. Furthermore, V would be involved in formation of the oxadiazoles under these conditions whether derived from II or IV. The fact that alkylation of the salt produced I does not constitute structural evidence for the salt in view of the possibility for rearrangement after alkylation.[6]

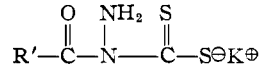
By analogy with the amino alcohol systems, an attempt was made to effect the N → O migration of I to the ester corresponding to IV, by dissolving I in concentrated sulfuric acid for a few minutes.

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society, New York, N. Y., September, 1954.

(2) M. Busch and M. Starke, *J. prakt. Chem.*, [2] **93**, 49 (1916).

(3) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(4) The possibility for the formation of the other carbazate salt is recognized but is not considered, in view of the necessity for prior rearrangement to either II or IV in order to produce the observed products.



(5) (a) M. Bergmann, E. Brand and F. Weinmann, *Z. physiol. Chem.*, **131**, 1 (1923); (b) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).

(6) The infrared spectrum of the dry salt in Nujol mull did not permit a decision between the alternative structures, although the low amide absorption (1615 cm.$^{-1}$) tends to favor IV.