bis(2-thiopseudourea)dipicrate, prepared from 1,4-diiodobutane made by a modification of the method of Stone and Schechter.[17] To 5 g. of potassium iodide was added 5 ml. of sirupy phosphoric acid (85%) and 1 ml. of rearrangement product. The mixture was refluxed gently for 1.5 hr., then 10 ml. of water was added, and the whole was extracted with 15 ml. of ether. The ether solution was washed with water, sodium thiosulfate solution and again with water; then the ether was removed and replaced by 10 ml. of ethanol. A 1-g. sample of thiourea was added, and after 10 min. refluxing, 0.5 g. of picric acid. The precipitated tetramethylene bis(2-thiopseudourea)dipicrate was filtered, washed with ethanol, and dried, m.p. 240° dec. (lit.[18] 240–242° dec.). A specimen prepared in the same way from authentic tetrahydrofuran also had m.p. 240° dec., and the mixed melting point of the two was the same.

Trimethylene sulfite gave a product which showed five peaks on the gas chromatograph, at q = 0.17 (26), 0.32 (100), 0.42 (48), 0.86 (48), 2.22 (7). The second peak was an unresolved mixture of acrolein (q = 0.29) and propionaldehyde (q = 0.32). In check experiments, these were not resolved on a squalane column at 100° or 64°. Three aldehydes were detected by paper chromatography, acrolein (R_f = 0.21), propionaldehyde (R_f = 0.26) and a third (R_f = 0.35) which is thought to be an aldol condensation product. Infrared spectroscopy of the mixture confirmed the presence of acrolein and propionaldehyde by the C=C and C=O stretching bands in the 6μ region. There were no indications at any time of the presence of acetone.

Ethylene sulfite gave a product which showed seven peaks on the gas chromatograph at q = 0.14 (100), 0.54 (6), 0.60 (6), 0.90 (35), 1.14 (12), 1.64 (94), and 3.18 (6). Two of these were identified as acetaldehyde (q = 0.16) and paraldehyde (q = 0.56). Paper chromatography of the dinitrophenylhydrazone from the product showed only one spot due to acetaldehyde (R_f = 0.12), and the 6μ region of the infrared spectrum confirmed this.

Acknowledgments. The author is indebted to Mr. G. J. Long for experimental assistance and to the Chief Scientist, Australian Defence Scientific Service, Department of Supply, Melbourne, Australia, for permission to publish.

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(17) H. Stone and H. Schechter, *Org. Syntheses*, **30**, 33 (1950).

(18) A. W. Nineham, *J. Chem. Soc.*, 2601 (1953).

Synthesis of Certain Sulfonium Analogs of Meperidine and of the Methadone Class of Analgesics

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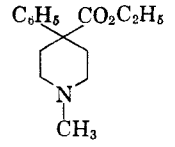
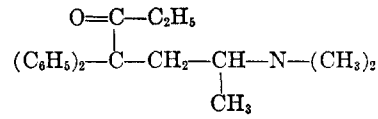
Received October 12, 1959

In continuation of our investigations[1] dealing with the preparation of sulfonium analogs of pharmacologically active tertiary and quaternary amines, we wish to report the synthesis of sulfonium analogs of meperidine[3] and also of the methadone class. Both meperidine and methadone are important analgesic agents.



Meperidine



Methadone

The meperidine sulfonium analog VI was prepared from the known 4-cyano-4-phenyltetrahydrothiapyran (III).[7] This nitrile (III) was converted to the 4-carbethoxy intermediate (V) by direct ethanolysis in the presence of sulfuric acid or, more satisfactorily, in two steps by hydrolysis with 70% aqueous sulfuric acid to the corresponding acid[7] (IV) followed by esterification with ethanolic hydrogen chloride. Treatment of V with excess methyl iodide then gave the desired analog (VI); reaction of V with excess ethyl iodide afforded the corresponding ethiodide.

The intermediate nitrile (III) was obtained directly by the sodium amide-catalyzed condensation of phenylacetonitrile (I) with bis(2-chloroethyl) sulfide, a synthesis originally described by Eisleb[7] and which in our hands afforded a 40% yield of III. This nitrile (III) was also prepared from 1,5-dichloro-3-cyano-3-phenylpentane (II)[8] on treatment with sodium sulfide. Although the latter procedure avoids the use of the dangerous mustard gas, the preparation of the 1,5-dichloride (II) requires three steps, and in our experience proceeded in relatively poor over-all yield (11%).[9] It was also possible to prepare the more advanced intermediate, 4-carbethoxy-4-phenyltetrahydrothiapyran (V), by direct condensation of bis(2-chloro-

(1) M. J. Weiss and M. B. O'Donoghue, *J. Am. Chem. Soc.*, **79**, 4771 (1957). This paper contains a review of sulfonium analog work in the pharmaceutical field. The preparation of sulfonium derivatives in the phenazine series has been reported recently.[2]

(2) S. O. Winthrop and M. A. Davis, *J. Am. Chem. Soc.*, **80**, 4331 (1958).

(3) There are two reports in the literature concerning unsuccessful attempts to prepare sulfonium analogs of the 1-methyl-4-acyloxy-4-phenylpiperidine class.[4,5] These piperidines are closely related to meperidine and are active analgesics.[6]

(4) H. M. E. Cardwell, *J. Chem. Soc.*, 1059 (1950).

(5) V. Mychajlyszn and J. O. Jilek, *Chem. Listy*, **50**, 1479 (1956); *Chem. Abstr.*, **51**, 2666 (1957).

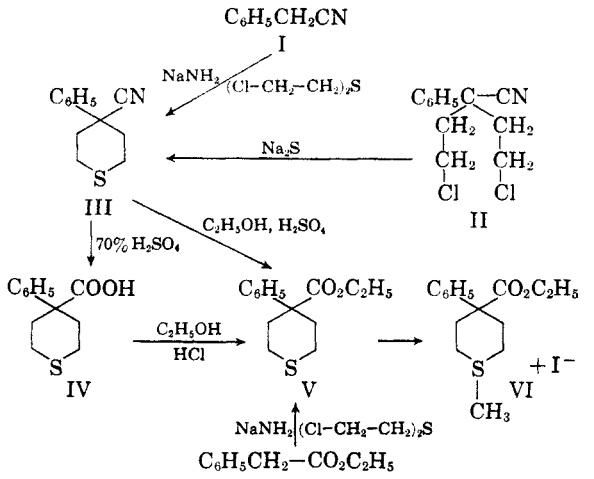
(6) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(7) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

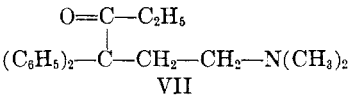
(8) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 265 (1944).

(9) Dichloride II was obtained by condensation (sodium amide) of phenylacetonitrile (I) with 2-vinyloxyethyl chloride, acid hydrolysis of the vinyloxy groups and treatment of the resulting 1,5-diol with thionyl chloride.[8]

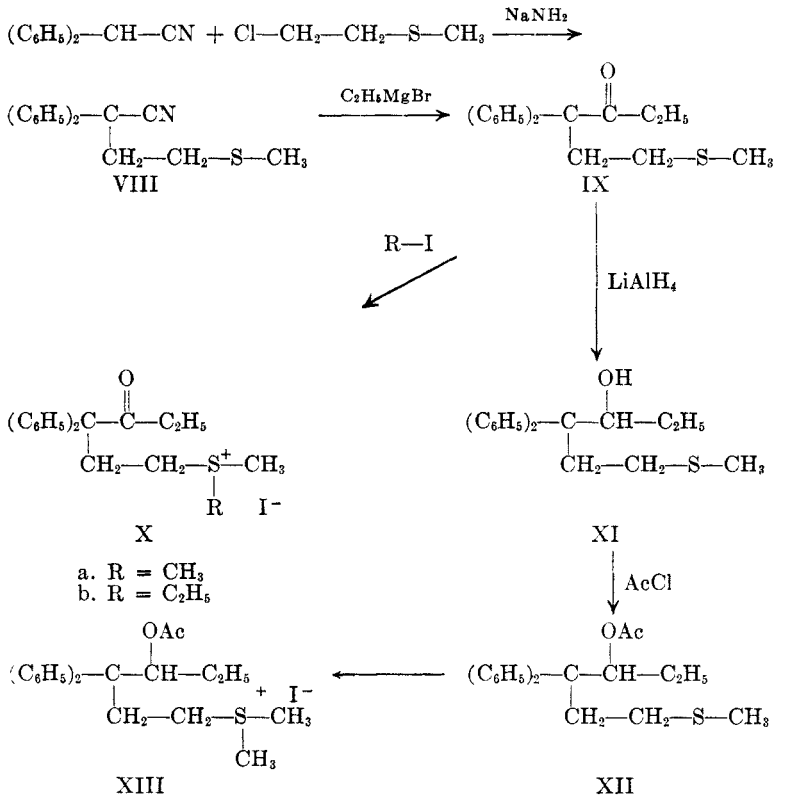
ethyl) sulfide with ethyl phenylacetate in the presence of sodium amide. However, the yield for this reaction was very poor (12% crude).



A sulfonium analog of methadone itself was not prepared because of the potential synthetic difficulties involved in the development of the isopropyl side chain.[10] Instead, analogs of the closely related VII were prepared. This compound has a β-dimethylaminoethyl side-chain instead of the β-dimethylaminoisopropyl side-chain found in methadone, and it is reported to be an effective analgesic agent in experimental animals and man although it is not as active as methadone.[11] Since the completion of our work, the synthesis of one sulfonium analog of VII has been reported.[5] We have also prepared this compound (Xa) although by a somewhat different route, and have in addition prepared several other methadone-type sulfonium analogs.



Condensation of diphenylacetonitrile with (2-chloroethyl)methyl sulfide in the presence of sodium amide afforded the alkylated diphenylacetonitrile-(VIII) in 42% yield. This compound was prepared by the Czechoslovak workers[5] from 3,3-diphenyl-3-cyanopropyl bromide and sodium methyl mercaptide. Conversion of VIII to the dimethyl sulfonium analog (Xa) was carried out in the same manner as reported by these workers;[5] that is, by methyl iodide treatment of the sulfide (IX), prepared by reaction of ethyl magnesium bromide with nitrile (VIII). Reaction of IX with ethyl iodide afforded the ethyl sulfonium analog (Xb).



Although reduction of the carbonyl group in methadone to give methadol generally causes a decrease in analgesic activity, acetylation of meth-

(10) A. Berger, *Medicinal Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1951, p. 182.

(11) C. C. Scott, E. B. Robbins, and K. K. Chen, *Science*, **104**, 587 (1946); E. C. Kleiderer, J. B. Rice, V. Conquest, and J. H. Williams, Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D. C.

adol results in a restoration of this activity.[12] Therefore, it was of interest to prepare a sulfonium analog of the acetyl methadol type structure. Lithium aluminum hydride reduction of ketone IX gave the corresponding carbinol (XI) in 65% yield. Treatment of this carbinol with acetyl chloride produced a 59% yield of the acetate (XII), which on reaction with methyl iodide afforded the desired sulfonium analog (XIII).

None of the sulfonium analogs reported in this paper showed significant analgesic activity.

EXPERIMENTAL[13]

1,5-Dichloro-3-cyano-3-phenylpentane (II). This compound was prepared by the three-step synthesis described by Bergel and coworkers[8] in an over-all yield of 11.4%, m.p. 51–52°.

4-Cyano-4-phenyltetrahydrothiapyran (III). To a solution of 25.3 g. (0.105 mole) of 1,5-dichloro-3-cyano-3-phenylpentane (II) in 125 ml. of ethanol was added a solution of 25.2 g. (0.105 mole) of sodium sulfide nonahydrate in 75 ml. of water. A clear solution did not form. The mixture was refluxed on a steam bath for 27 hr., then cooled and poured into ice water. The milky solution was extracted several times with ether. The combined ether extracts were dried, filtered, and evaporated. The residue consisted of two oily layers. The lower layer was distilled; the main fraction, 7.8 g. (37%), boiled at 137–142° at 1 mm., n_D^{26} 1.5729. Eisleb[7] reports a boiling point of 175° at 6 mm.

4-Carbethoxy-4-phenyltetrahydrothiapyran (V). (A) *By ethanolysis of nitrile* III. A mixture of 20.3 g. (0.1 mole) of 4-cyano-4-phenyltetrahydrothiapyran (III), 30 g. of 98% sulfuric acid, 0.26 g. of water, 46 g. of ethanol, and 5.36 g. of ammonium chloride was heated in a glass-lined autoclave at 160° for 7 hr. The contents of the autoclave were treated with ice water and the mixture was extracted with ether. The ether extracts were dried, filtered, and evaporated to give 5.5 g. (22%) of the ester as an oil.

(B) *By esterification of acid* IV. A mixture of 5.5 g. (0.025 mole) of 4-carboxy-4-phenyltetrahydrothiapyran (IV)[7] and 35 ml. of ethanol, which had been saturated with hydrogen chloride, was placed in a pressure bottle, and warmed on a steam bath for about 14 hr. After cooling, the solvent was removed and the residue was dissolved in ether. The ether solution was washed with a dilute sodium carbonate solution, dried, and evaporated. This gave the ester V as a light brown oil, which was used as such for the preparation of the sulfonium salts VI.

(C) *From ethyl phenylacetate and bis(2-chloroethyl)sulfide.* To a solution of sodium amide,[14] prepared from 16.6 g. (0.72 mole) of sodium and 500 ml. of liquid ammonia, was added 59 g. (0.36 mole) of ethyl phenylacetate in 100 ml. of dry ether. The mixture was stirred and warmed gently to remove the ammonia which was replaced with 300 ml. of ether. A solution of 30 ml. (0.284 mole) of bis(2-chloroethyl)sulfide was then added dropwise during 5 min. The mixture was refluxed on a steam bath for 1 hr., 200 ml. of toluene was added and refluxing was continued for 90 min. (reflux temperature was 95–100°).

After cooling to 10°, water was added cautiously to decompose any unreacted sodium amide, and when the reaction was no longer exothermic, a large amount of ice water was added. The toluene layer was dried over calcium sulfate (Drierite), filtered and distilled. A 10-g. forerun boiling at 82–83° at 1 mm. was followed by the product (8.4 g., 29%) boiling at 160–162° at 1 mm. A small amount of solid which codistilled with the product proved to be phenylacetamide, m.p. 155.5–156.5°, admixture of which with an authentic sample showed no depression in melting point.

4-Carbethoxy-1-methyl-4-phenylhexahydrothiapyrylium iodide (VI). A solution of 4-carbethoxy-4-phenyltetrahydrothiapyran (V), obtained *via* procedure B from 5.5 g. of IV, in 45 ml. of methyl iodide, was allowed to stand at room temperature for 24 hr. The sulfonium salt separated as a crystalline solid (3.5 g., 36%), m.p. 139–140° dec.

In a pilot run, the product was recrystallized from ethanol to give white crystals melting at 135–136° dec.

Anal. Calcd. for $C_{15}H_{21}IO_2S$: C, 45.9; H, 5.40; I, 32.4; S, 8.17. Found: C, 45.9; H, 5.65; I, 32.4; S, 8.00.

4-Carbethoxy-1-ethyl-4-phenylhexahydrothiapyrylium iodide. This compound was prepared in a manner similar to that described above for the methiodide salt except that the ester was dissolved in acetone and then treated with a large excess of ethyl iodide. The ethiodide salt was obtained after drowning the reaction solution in ether. The product melted at 117.5–118°.

Anal. Calcd. for $C_{16}H_{23}IO_2S$: C, 47.3; H, 5.70; I, 31.2; S, 7.89. Found: C, 47.1; H, 5.68; I, 30.5; S, 8.23.

2,2-Diphenyl-4-methylthiobutyronitrile (VIII). A solution of 386.5 g. (2 moles) of diphenylacetonitrile in 1530 ml. of dry benzene was added dropwise with stirring, over a period of 1 hr., to a mixture of 100 g. (2.5 moles) of sodium amide[14] in 1000 ml. of dry benzene. The reaction was not exothermic. The mixture was stirred at 40° for 1 hr., then 221 g. (2 moles) of 2-chloroethyl methyl sulfide[15] was added dropwise at 32–34° during 2.5 hr. The mixture was then stirred at 50–70° for 15 hr. The liquid was decanted from the precipitated solids into a separatory funnel and water was added. The benzene layer was separated and washed three times with small portions of water. The solvent was removed and the residual oil was distilled. After an initial fraction (b.p. 124–170° at 2 mm.) which consisted largely of diphenylacetonitrile (187 g., 49% recovery) and a small intermediate fraction, the product VIII was obtained boiling at 182–185° at 2 mm. (227 g., 42%; n_D^{26} 1.5880).

Anal. Calcd. for $C_{17}H_{17}NS$: C, 76.4; H, 6.41; N, 5.24; S, 12.0. Found: C, 76.3; H, 6.38; N, 5.33; S, 11.2.

Mychajlyszn and Jilek[5] prepared this compound in 71% yield, b.p. 160–165° at 1 mm., by the reaction of sodium methylmercaptide with 2,2-diphenyl-4-bromobutyronitrile.

4,4-Diphenyl-6-methylthiohexanone-3 (IX). Ethyl magnesium bromide was prepared from 36 g. (0.33 mole) of ethyl bromide, 8 g. (0.33 mole) of magnesium and 160 ml. of ether. A solution of 53.5 g. (0.2 mole) of 2,2-diphenyl-4-methylthiobutyronitrile (VIII) in 120 ml. of toluene was added. The solvent was distilled until the internal temperature rose to 102°. The mixture was stirred, warmed at 102–110° for 4.5 hr., and then allowed to stand at room temperature overnight. Ice was cautiously added to decompose the Grignard complex. The reaction was exothermic and the temperature rose to 50–60°. When the heat evolution had subsided, 100 ml. of dilute hydrochloric acid was added and the mixture was warmed on the steam bath for 2 hr. The two layers were separated, and the aqueous layer was extracted three times with small portions of benzene. The benzene extracts were combined with the toluene layer and distilled at reduced pressure. After a small forerun (8.8 g.), the product (IX) boiled at 165–178° at 1 mm., and weighed 39.9 g. (67%), n_D^{30} 1.5823. Mychajlyszn and Jilek[5] report a b.p. of 170–173° at 0.5 mm.

A sample of material boiling at 176–177° at 1 mm., n_D^{29} 1.5828, was analyzed.

Anal. Calcd. for $C_{19}H_{22}OS$: C, 76.5; H, 7.43; S, 10.7. Found: C, 76.5; H, 7.43; S, 10.8.

(12) Ref. 10, p. 184.

(13) Melting points are uncorrected.

(14) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

(15) *Org. Syntheses*, Coll. Vol. II, p. 136, John Wiley and Sons, New York, N. Y., 1943.

Dimethyl-(3,3-diphenyl-4-oxohexyl)sulfonium iodide (Xa). A solution of 5.8 g. of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 20 ml. of methyl iodide was allowed to stand for 4 days. The product (Xa) separated as a white crystalline material, which after 2 recrystallizations from 95% ethanol, weighed 5.3 g., m.p. 125.5° (gas evolution). Mychajlyszn and Jilek[5] report a m.p. of 122°.

(3,3-Diphenyl-4-oxohexyl)-ethylmethylsulfonium iodide (Xb). A solution of 25.3 g. (0.085 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 75 ml. acetone was treated with 46.8 g. (0.3 mole) of ethyl iodide. The solution was allowed to stand at room temperature for several days. The sulfonium salt separated out during this time as a crystalline solid. The mixture was filtered and the light yellow solid weighed 5.4 g., m.p. 114–115.5°. After recrystallization from 15 ml. of 95% ethanol there was obtained 4.3 g. of a white solid, m.p. 118.5–119°.

Anal. Calcd. for $C_{21}H_{27}IOS$: C, 55.5; H, 5.99; I, 27.9; S, 7.06. Found: C, 55.4; H, 5.61; I, 27.8; S, 7.47.

4,4-Diphenyl-6-methylthiohexanol-3 (XI). A mixture of 4.6 g. (0.12 mole) of lithium aluminum hydride in 200 ml. of ether was refluxed on a steam bath in an atmosphere of nitrogen for 4.5 hr. A solution of 119.3 g. (0.4 mole) of 4,4-diphenyl-6-methylthiohexanone-3 (IX) in 200 ml. of ether then was added dropwise over a period of 40 min. The mixture was refluxed for 2.5 hr. Wet ethyl acetate (40 ml.) was added cautiously to decompose the complex and any unreacted lithium aluminum hydride. After the decomposition was complete, 300 ml. of ice water was added. This gave a milky solution, which separated into 2 layers after standing overnight. The aqueous layer was acidified with dilute sulfuric acid, and then extracted several times with ether. The ether extracts were combined, dried over sodium sulfate, filtered, and evaporated. The residue, a thick viscous oil, was distilled at reduced pressure. The product boiled at 182–184° at 1–2 mm. and weighed 77.4 g. (64.5%). This oil solidified to a white solid, m.p. 66–69°. Recrystallization from a mixture of hexane and petroleum ether gave 75.2 g. of the product XI, m.p. 70–71.5°.

Anal. Calcd. for $C_{19}H_{24}OS$: C, 75.9; H, 8.05; S, 10.7. Found: C, 76.1; H, 8.22; S, 10.6.

4,4-Diphenyl-6-methylthio-3-hexyl acetate (XII). A mixture of 90 g. (0.3 mole) of 4,4-diphenyl-6-methylthiohexanol-3 (XI) in 400 ml. of dry pyridine was stirred and cooled in an ice bath while 27 g. (0.35 mole) of acetyl chloride was added over a period of 30 min. at 10–12°. The ice bath was removed and the temperature raised slowly until a clear solution formed (about 2 hr.). The solution was stirred at room temperature for 3 hr., and then poured onto ice water which had been made slightly acid with dilute hydrochloric acid. The mixture was extracted three times with portions of ether, and the ether extracts were combined, dried, filtered, and evaporated. The residue, a thick viscous amber oil, was distilled at reduced pressure. The product (XII) boiled at 180–188° at 1 mm. and weighed 60.5 g. (59%).

(4-Acetoxy-3,3-diphenylhexyl)-dimethylsulfonium iodide (XIII). This compound was prepared from XII and methyl iodide by the procedure described above for the preparation of Xa. It was obtained in 38% yield after crystallization from 95% ethanol, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{22}H_{29}IO_2S$: C, 54.5; H, 6.03; I, 26.2; S, 6.62. Found: C, 54.2; H, 6.44; I, 26.2; S, 6.21.

Acknowledgment. We wish to thank Mr. O. Sundberg and staff for microanalyses. We are indebted to Dr. A. Osterberg and staff of the Experimental Therapeutics Section of these laboratories for the pharmacological evaluation of these compounds.

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Preparation of 2-Thioöxazolidones from Substituted Dithiocarbamylacetic Acids

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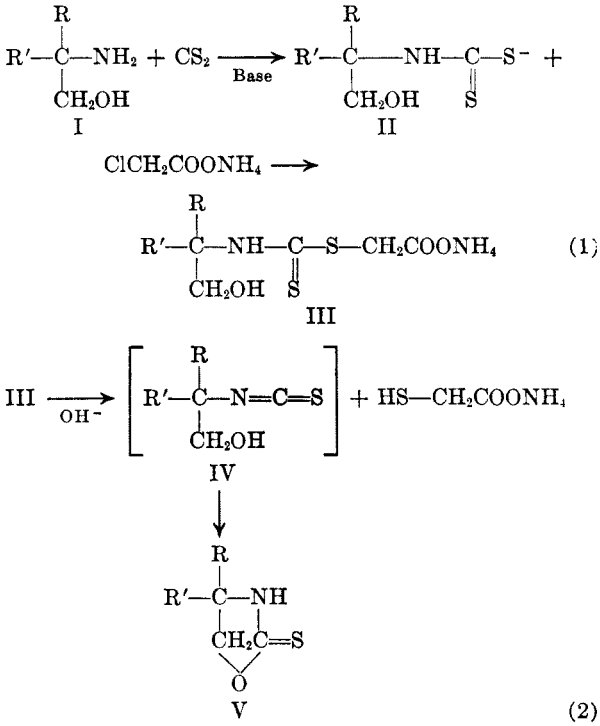
2-Thioöxazolidones[1] substituted in the 4- and 5- positions have been prepared from aminoalcohols by reaction with carbon disulfide and potassium hydroxide[2,3] and by the decomposition of thiuram disulfides derived from 2-aminoalcohols.[3]

We have now found that *N*-substituted dithiocarbamylacetic acid derivatives produced from 2-aminoalcohols, carbon disulfide, and monochloracetic acid (Equation 1) may be decomposed by alkali to form a substituted 2-thioöxazolidone and thioglycolic acid (Equation 2).



The expected product of the scission of the substituted dithiocarbamylacetic acid would be a hydroxyalkyl isothiocyanate (IV), but this apparently cyclizes to the corresponding 2-thioöxazolidone (V).[4]

In the above manner, 2-methyl-2-aminopropanol-1, I R=R′=CH_3, yields 4,4-dimethyl-2-

(1) We have confirmed the work of M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950), who has shown by infrared spectra that these materials are thioketones and do not contain SH groups. Therefore, they are more properly termed 2-thioöxazolidones rather than oxazoline-2-thiols.

(2) H. A. Bruson and J. W. Eastes, *J. Am. Chem. Soc.*, **59**, 2011 (1937).

(3) A. A. Rosen, *J. Am. Chem. Soc.*, **74**, 2994 (1952).

(4) B. Holmberg, *J. Prakt. Chem.*, **79**, 263 (1909) observed that dithiocarbamylacetic acid in alkali solution produced thioglycolic acid and thiocyanic acid.