[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY, SCHOOLS OF MEDICINE, WESTERN RESERVE AND YALE UNIVERSITIES]

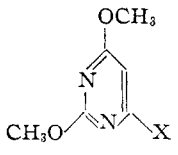
6-Uracilsulfonic Acid, a Sulfonic Acid Analog of Orotic Acid[1]

BY SHELDON B. GREENBAUM[2] AND WILLIAM L. HOLMES[2]

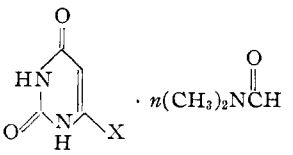
RECEIVED DECEMBER 4, 1953

6-Uracilsulfonic acid (the sulfonic acid analog of orotic acid) was prepared by a series of reactions starting from 2,4-dimethoxy-6-chloropyrimidine. The latter was converted to 2,4-dimethoxy-6-pyrimidinethiol by treatment with sodium hydrosulfide. Mild oxidation of the thiol produced the disulfide and further oxidation gave 2,4-dimethoxy-6-pyrimidine sulfonic acid. Demethylation was accomplished by heating with very dilute acid. Some barbituric acid was formed during the demethylation under these conditions; it was the major product when strong acid was used.

Orotic acid (VII) has been shown to be a precursor of nucleic acid pyrimidines in rats (both *in vivo*[3] and *in vitro*[4]) and in human tumors (*in vitro*[4]). It is also an essential metabolite of *Lactobacillus bulgaricus* 09.[5] It was desirable, therefore, to synthesize a series of compounds which might serve as metabolic antagonists of this substance. In view of the well-established antimetabolic activity of both sulfonic acid and sulfonamido analogs of naturally occurring compounds (*e.g.*, pantoyltaurine *vs.* pantothenic acid[6,7] and the *p*-aminobenzenesulfonamido derivatives *vs.* *p*-aminobenzoic acid[8]), the synthesis of 6-uracilsulfonic acid and certain of its amido derivatives was undertaken. The preparation of the sulfonic acid is described in this report.



I, X = Cl
II, X = SH
III, X = SO_2
IV, X = SO_3H



V, X = SO_3H, n = 0
Va, X = SO_3H, n = 2
Vb, X = SO_3H, n = 1
VI, X = OH, n = 0
VII, X = COOH, n = 0

2,4-Dimethoxy-6-chloropyrimidine (I) was chosen as the starting material for the synthesis of the sulfonic acid since it was readily available by the improved method of Fisher and Johnson[9] and could lead to the desired compound by a sequence involving a replacement of the chloro by sulfhydryl, an oxidation, and a final demethylation. 2,4-Dimethoxy-6-pyrimidinethiol (II) was prepared from I by the action of ethanolic sodium hydrosulfide. The thiol was easily converted to the disulfide III by hydrogen peroxide in dioxane. Toennies and Homiller have found that the oxidation of cystine to cysteic acid by performic acid required only a short standing period at room temperature.[10] Compound III was readily soluble in this reagent and was converted to the dimethoxysulfonic acid (IV) under these same mild conditions. Compound IV was obtained as a crystalline solid (m.p. 208–209°). It demonstrated the same ultraviolet absorption maximum, λ 267 mμ, in either acid or basic solution.

The demethylation of IV with strong acid led to a replacement of the sulfonic group by hydroxyl and the formation of barbituric acid (VI) as the major product. This type of hydrolysis of a sulfonic group bears little relation to the acid hydrolysis of a typical aromatic sulfonic acid and is more likely related to the acid-catalyzed replacement by hydroxyl or amine of various other groups situated at the 2-, 4- or 6-position of the pyrimidine nucleus.[11] The desired 6-uracilsulfonic acid was obtained in reasonably good yield together with a smaller quantity of barbituric acid by heating IV in very dilute acid for a limited period of time. The progress of the hydrolysis was followed by comparing the intensities of the typical ultraviolet bands of IV, V and VI in alkalized aliquots of the hydrolysate (Fig. 1). In practice, the hydrolysis was stopped after one hour and the uracilsulfonic acid was separated from the barbituric acid by ion-exchange column technique.

Recrystallization of V from a dimethylformamide–ether system apparently led to its recovery in the form of a complex with two moles of dimethylformamide (Va). Recrystallization of this substance from nitromethane–ether apparently generated the more stable monocomplex Vb. The free acid could be produced from either substance by

(1) This work was supported by a grant from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council. Presented in part before the Divison of Organic Chemistry, 125th Meeting of the American Chemical Society, Kansas City, Mo., March 26, 1954; abstracts of Papers, p. 31N.

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(3) H. Arvidson, N. A. Eliasson, E. Hammersten, P. Reichard, H. V. Ubisch and S. Bergstrom, *J. Biol. Chem.*, **179**, 169 (1949).

(4) L. L. Weed, *Cancer Research*, **11**, 470 (1951).

(5) L. D. Wright, K. A. Valentic, D. S. Spicer, J. W. Huff and H. R. Skeggs, *Proc. Soc. Exp. Biol. Med.*, **75**, 293 (1950).

(6) H. McIlwain, *Biochem. J.*, **36**, 417 (1942).

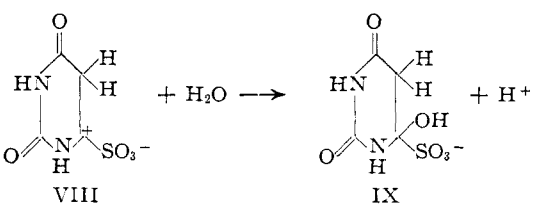
(7) H. McIlwain and F. Hawking, *Lancet*, I, 449 (1943).

(8) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publ. Corp., New York, N. Y., 1948.

(9) H. J. Fisher and T. B. Johnson, THIS JOURNAL, **54**, 727 (1932).

(10) G. Toennies and R. P. Homiller, *ibid.*, **64**, 3054 (1942).

(11) These acid-catalyzed nucleophilic displacements on the pyrimidine nucleus have been explained by assuming that the initial addition of a proton to one of the nitrogens stabilizes a positive charge at the carbon involved (C. K. Banks, THIS JOURNAL, **66**, 1127 (1944)) and that an appropriate "neutral transition state" is subsequently formed (B. Lythgoe, *Quart. Rev.*, **3**, 198 (1949)). It is likewise possible that a proton-adduct VIII of the sulfonic acid passes through a related transition stage IX, and that this is unstable by virtue of its similarity to a carbonyl–bisulfite addition complex. The proton is initially added to the 5-carbon in this sequence to preserve the diketo form suggested for acid solutions of uracil and related compounds (*e.g.*, ref. 14). The loss of bisulfite from IX would leave an oxygen function at position 6.



VIII IX

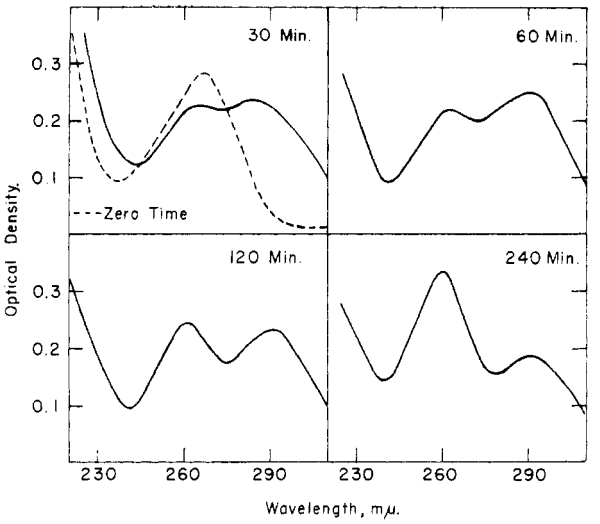


Fig. 1.—Ultraviolet absorption spectra taken during the hydrolysis of 2,4-dimethoxy-6-pyrimidinesulfonic acid (IV) in very dilute acid (*p*H adjusted to 12). The new bands appearing at 260 and 293 mμ represent the formation of barbituric acid and 6-uracilsulfonic acid (V), resp.

passing dry hydrogen chloride into a nitromethane solution.[12] The final product, 6-uracilsulfonic acid (m.p. 248–250°) behaved as a typical diprotic acid at *p*H ranges up to 11 (pK_{a_2} 7.2). The value of this second dissociation represents a hundredfold increase over the value of the primary dissociation of uracil (pK_{a_1} 9.45)[13] or the value of the secondary dissociation of orotic acid (pK_{a_2} 9.45).[14]

The ultraviolet absorption spectrum of V undergoes a pronounced bathochromic shift upon changing from acid to alkaline solvent (λ_{max} 264, 293 mμ, resp.). This shift is typically found in the spectra of uracil-like pyrimidines.[14] A large hypsochromic shift was found in the spectrum of the dimethoxythiol (II) under these same conditions (Fig. 2). The shift observed in the spectrum of the disulfide III (Fig. 2) was probably caused by decomposition in the alkaline solvent as a considerable quantity of II was isolated from the alkaline solution after a short period at room temperature.[15]

Acknowledgments.—The authors wish to express their appreciation to Professor Arnold D. Welch for his initiation of this investigation and for his aid and encouragement in its development. We are grateful also to Dr. Bernard W. Langley for his many helpful suggestions.

(12) The ability of dimethylformamide to form stable complexes with acidic substances has been established; crystalline monocomplexes with boron trifluoride, sulfur trioxide and hydrogen chloride have been isolated and characterized (E. I. du Pont de Nemours and Co., Wilmington, Del., "DMF Products Bulletin," p. 18).

(13) P. A. Levine, L. W. Bass and H. S. Simms, *J. Biol. Chem.*, **70**, 229 (1926).

(14) D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952).

(15) Compounds such as diphenyl disulfide have been reported to decompose upon heating with alcoholic alkali according to the equations (R. Schiller and R. Otto, *Ber.*, **9**, 1637 (1876); E. Fromm, *ibid.*, **41**, 3403 (1908)). A number of other examples are cited in N. Kharasch, S. J. Potempka and H. L. Wehrmeister, *Chem. Revs.*, **39**, 275 (1946), and in D. S. Tarbell and D. P. Harnish, *ibid.*, **49**, 10ff (1951).

$$KOH + C_6H_5—S—S—C_6H_5 \longrightarrow C_6H_5SK + C_6H_5SOH \quad (1)$$

$$2\ C_6H_5SOH \longrightarrow C_6H_5SH + C_6H_5SO_2H \quad (2)$$

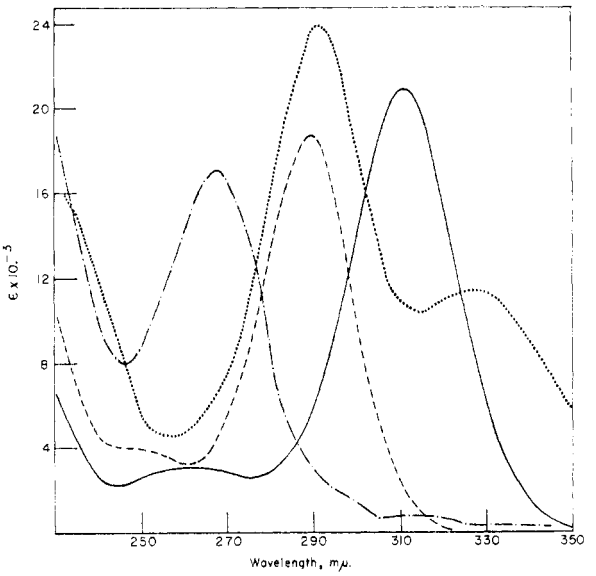


Fig. 2.—Ultraviolet absorption spectra of 2,4-dimethoxy-6-pyrimidinethiol: ———, in 0.1 *N* HCl; – – –, in 0.1 *N* NaOH; bis-(2,4-dimethoxy-6-pyrimidine) disulfide: –·–·–, in 0.1 *N* HCl (95% alcoholic); . . . ., in 0.1 *N* NaOH (95% alcoholic).

Experimental

The absorption spectra were determined with a Beckman model DU quartz spectrophotometer using matched silica cells. The melting points were taken with a calibrated thermometer but are otherwise uncorrected. Microanalyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado.

2,4-Dimethoxy-6-chloropyrimidine (I).—This compound was prepared from 2,4,6-trichloropyrimidine[16] by a modification of the method of Fisher and Johnson[9] in that a 30% excess of sodium methoxide was employed.

2,4-Dimethoxy-6-pyrimidinethiol (II).—A solution made by dissolving 55 g. of sodium in 1000 ml. of commercial absolute ethanol was cooled in ice and saturated with hydrogen sulfide (*ca.* 104 g.). After the addition of 198 g. of 2,4-dimethoxy-6-chloropyrimidine the mixture was heated under reflux for five hours. The mixture was cooled, diluted with sufficient distilled water (*ca.* 600 ml.) to dissolve the precipitate and acidified in the cold by the dropwise addition of concentrated hydrochloric acid. The crude thiol was freed from the salt by thorough washing with cold water (dry weight 148 g.). Small portions (15 g.) were recrystallized from several liters of 0.1% sodium bisulfite solution to which a few drops of phosphoric acid were added; total yield 91 g. (46.5%). The pale yellow needles softened at 170° (with the evolution of hydrogen sulfide) and melted at 282–285°. The compound gave white insoluble lead or silver salts and a cherry-red color with a modified ferric chloride reagent.[17]

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.89; H, 4.72; N, 16.21; S, 18.52.

Warming II with an alcoholic solution of 2,4-dinitrochlorobenzene in the presence of alkali produced **2,4-dimethoxy-6-(2,4-dinitrophenylmercapto)-pyrimidine**; flat yellow plates (*n*-propyl alcohol), m.p. 199°.

Anal. Calcd. for $C_{12}H_{10}N_4O_6S$: C, 42.60; H, 2.98; N, 16.56; S, 9.48. Found: C, 42.52; H, 3.20; N, 16.49; S, 9.43.

(16) J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944).

(17) A solution of 0.5 g. of ferric chloride hexahydrate in 1 ml. of water was diluted with 20 ml. of glacial acetic acid. A few crystals of the compound was added to a few drops of the reagent. No color was obtained with uracil, 2-thiouracil or the dilsulfide III.

Bis-(2,4-dimethoxy-6-pyrimidine) Disulfide (III).—A suspension of 11.5 g. of the above thiol in 220 ml. of dioxane was treated with 50 ml. of 3% hydrogen peroxide.[18] The thiol dissolved in 30 minutes with the aid of occasional shaking. The disulfide was precipitated by gradually diluting the solvent with two volumes of water along with cooling and scratching. The precipitate was washed with water and dried; yield 8.3 g. (73%), m.p. 113–115°. Recrystallization from dilute alcohol afforded white needles, m.p. 115–116°. In contrast to the mercaptan, the disulfide was readily soluble in the common organic solvents.

Anal. Calcd. for $C_{12}H_{14}N_4O_4S_2$: C, 42.09; H, 4.12; N, 16.37; S, 18.73. Found: C, 42.12; H, 4.12; N, 16.26; S, 18.70.

Reduction of III with $LiAlH_4$.—A solution of 0.68 g. of the disulfide (above) in 60 ml. of absolute ether was added to 20 ml. of the supernatant liquid produced by the treatment of 1.6 g. of lithium aluminum hydride with 80 ml. of absolute ether. After 30 minutes the mixture was treated with 12 ml. of water and then with 24 ml. of 2 *N* sulfuric acid. Recrystallization of the precipitate from 80 ml. of water afforded 0.55 g. (76%) of the original dimethoxythiol II.

Effect of Alcoholic Acid or Alkali on III.—In connection with the spectral shift obtained with III, 0.2-g. portions were dissolved in minimum quantities of 95% alcohol solutions which were 0.1 *N* with respect to sodium hydroxide or hydrochloric acid. After one hour the solutions were diluted with two volumes of water and chilled. The acid solution regenerated 0.193 g. of the original disulfide; the alkaline solution did not regenerate any disulfide until it was acidified and then only 0.032 g. was recovered. By concentrating the second filtrate under reduced pressure, 0.094 g. of the dimethoxythiol II was also obtained.

2,4-Dimethoxy-6-pyrimidinesulfonic Acid (IV).—A clear solution of 7.9 g. of the disulfide III in 350 ml. of 88% formic acid was treated with 35 ml. of 30% hydrogen peroxide. The solution was allowed to stand for three hours after which time a small aliquot failed to regenerate the disulfide upon dilution with several volumes of water. The sulfonic acid was isolated by diluting the main solution with two volumes of distilled water and then evaporating it under reduced pressure. Recrystallization was effected by dissolving the residue in dimethylformamide (225 ml.) and then adding two volumes of absolute ether with cooling and scratching. The fine colorless crystals were washed with absolute ether and dried at 55° *in vacuo;* yield 7.9 g. (78%). Several recrystallizations from the same solvent pair afforded 5.4 g. of the pure compound, m.p. 208–209°; absorption: λ_{max} 267 mμ (ε 6,840, 0.1 *N* HCl) (ε 6,480, 0.1 *N* NaOH).

Anal. Calcd. for $C_6H_8N_2O_5S$: C, 32.72; H, 3.66; N, 12.72; S, 14.56; neut. equiv., 221. Found: C, 32.94; H, 3.63; N, 12.53; S, 14.30; neut. equiv., 222.

The S-benzylthiouronium salt of IV was prepared under slightly acid conditions. Several recrystallizations from water afforded colorless needles, m.p. 125–126°.

Anal. Calcd. for $C_{14}H_{18}N_4O_5S_2$: N, 14.50; S, 16.59. Found: N, 14.30; S, 16.41.

Hydrolysis of IV in Strong Acid.—A solution of 0.2 g. of the dimethoxysulfonic acid IV in 20 ml. of hydrochloric acid was heated under reflux for one hour. The residue (obtained by diluting the acid with water and evaporating the solution under reduced pressure) contained no sulfur and possessed acid and alkaline ultraviolet absorption spectra very similar to those of barbituric acid.[19] The benzal derivative of the residue had the same melting point as the derivative of an authentic sample of barbituric acid; admixture did not depress the melting point, 261–262° (lit.[20] 256°). Sulfur dioxide was identified as an effluate of this reaction. It was oxidized and precipitated as barium sulfate.

Dilute Acid Hydroysis of IV: Paper Chromatography.—A dilute solution of IV (0.5 mg./ml.) in 0.02 *N* hydrochloric acid was autoclaved at 250°F. (15 p.s.i.). Aliquots taken at suitable intervals were examined spectrophotometrically in 0.1 *N* sodium hydroxide. These spectra (Fig. 1) indicated that one hour was the optimal period of hydrolysis. The components of a one-hour hydrolysate were chromatographed on filter paper (Whatman #1), located with an ultraviolet lamp (2537 Å.), and eluted with water. Spectra taken under acid and alkaline conditions revealed that component A was barbituric acid, and that component B was the compound responsible for the absorption at 293 mμ in alkali. Component B was subsequently shown to be the desired 6-uracilsulfonic acid. The R_f values of these components and of related substances are listed for two developing systems:

Substance	R_f[a] (*n*-Butyl alcohol satd. with water)[21]	R_f (Isoamyl alcohol satd. with 5% Na_2HPO_4)[22]
Barbituric acid	..	0.71
Component A	0.12	.72
Component B	.04	.80
Compound IV	.22	.85

[a] Spot neutralized with ammonia prior to development.

Dilute Acid Hydrolysis of IV: Ion-exchange Chromatography.—A solution of 2.0 g. of 2,4-dimethoxy-6-pyrimidinesulfonic acid (above) in 320 ml. of 0.02 *N* hydrochloric acid was autoclaved for one hour at 250°F. (15 p.s.i.). The solution was cooled, brought to *p*H 7 (sodium hydroxide) and passed through a Dowex 1 (chloride form, 200–400 mesh) ion-exchange column (20 cm. × 7 cm.[2]). The components were eluted with the following reagents (1 ml./min.):

0.05 *N* HCl.—The passage of 3000 ml. of this reagent removed a compound having the spectral and R_f characteristics of barbituric acid (fraction 1). The course of the elution was followed by determining the optical density at 255 mμ of aliquots brought to *p*H 12.

0.5 *N* HCl.—The more concentrated acid eluted two further components, the minor component in the 375–750-ml. fraction (fraction 2), and the major component in the 800–2800-ml. fraction (fraction 3). The course of this elution was followed at 265 mμ, eluant *p*H.

6-Uracilsulfonic Acid (V).—Fraction 3 (above) was reduced to dryness at 45° under reduced pressure. The residue was taken up in 30 ml. of dimethylformamide and precipitated with two volumes of absolute ether. After a second such recrystallization, the microcrystalline substance was washed with absolute ether and dried at 55° *in vacuo*. It melted continuously between 126 and 150° and was apparently V with two molecules of dimethylformamide of crystallization (*i.e.*, Va); yield 1.56 g. This substance slowly loses weight on standing in the open air but not when it is kept *in vacuo*.[23]

Anal. Calcd. for $C_{10}H_{18}N_4O_7S$: C, 35.50; H, 5.36; N, 16.56; S, 9.48; neut. equiv., 169. Found: C, 35.25; H, 5.45; N, 16.49; S, 9.56; neut. equiv., 170.

When Va was dissolved in nitromethane and precipitated by the addition of absolute ether, a new crystalline substance (Vb) was produced, m.p. 159–161°. Vb was most likely V with one molecule of dimethylformamide of crystallization.

Anal. Calcd. for $C_7H_{11}N_3O_6S$: S, 12.09; neut. equiv., 133. Found: S, 11.92; neut. equiv., 134.

When 1.56 g. of Va was dissolved in 375 ml. of cold nitromethane and the solution saturated with dry hydrogen chloride, the crystalline free 6-uracilsulfonic acid (V) was regenerated. The product was washed with absolute ether and dried at 55° *in vacuo;* yield 0.84 g. (48% of the theoretical yield of the hydrolysis), m.p. 248–250° dec. The electrometric titration curve contained two inflections up to *p*H 11; pK_{a_1} 7.2; absorption: λ_{max} 264 mμ (ε 8,470, 0.1 *N* HCl), λ_{max} 293 mμ (ε 9,190, 0.1 *N* NaOH).

Anal. Calcd. for $C_4H_4N_2O_5S$: methoxyl, 0; neut. equiv., 96. Found: methoxyl, 0; neut. equiv., 95.

The hygroscopic sulfonic acid was conveniently handled as its **monosodium salt (monohydrate)**. The salt was pre-

(18) The hydrogen peroxide was not even required with the first sample of dioxane employed. Analysis for its peroxide content (W. Dasler and C. D. Bauer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 52 (1946)) revealed 70,750 micromoles of available oxygen per liter (0.283 *N*).

(19) (a) R. E. Stuckey, *Quart. J. Pharm. Pharmacol.*, **13**, 312 (1940); (b) J. J. Fox and D. Shugar, *Bull. soc. chim. Belg.*, **61**, 44 (1952).

(20) M. Conrad and H. Reinbach, *Ber.*, **34**, 1340 (1901).

(21) E. Vischer and E. Chargaff, *J. Biol. Chem.*, **176**, 703 (1948).

(22) C. E. Carter, THIS JOURNAL, **72**, 1467 (1950).

(23) We are indebted to Dr. Huffman for this observation and for a successful analysis of the compound. In the Dumas determination of nitrogen it was found necessary to cool the sample chamber with Dry Ice during the preliminary flush with carbon dioxide in order to obtain an acceptable value. Without this cooling, a value closer to that required by the monocomplex Vb was obtained.

pared from Va or V and one equivalent of sodium hydroxide. It was recrystallized by dissolving it in water and adding several volumes of alcohol.

Anal. Calcd. for $C_4H_5N_2O_6SNa$: C, 20.69; H, 2.17; N, 12.07; S, 13.81; neut. equiv., 232. Found (salt from V): C, 20.46; H, 2.13; N, 11.86; S, 13.80. Found (salt from Va): neut. equiv., 232.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

1,4-Thiazans. I. C-Alkyl Thiomorpholines

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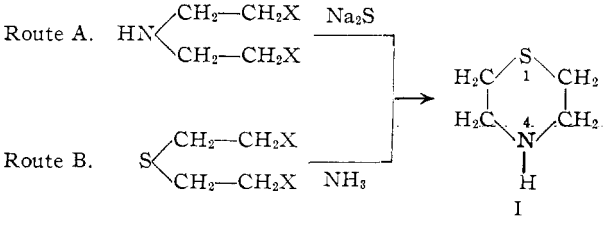
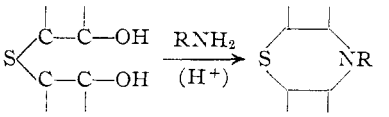
The nine possible C-monomethyl substituted thiomorpholines were prepared to study the properties of the 1,4-thiazan system. Cyclizations of either substituted bis-haloethyl sulfides or amines were the methods of choice.

Carbon substituted derivatives of the 1,4-tetrahydrothiazine ring system (1) (thiomorpholine) have rarely been studied. N-Substituted derivatives have been prepared,[2] but the only carbon-substituted compound which has been reported is 2,6-dimethylthiomorpholine.[3] This paper is concerned with the synthesis of all nine possible C-methyl-1,4-thiazans, prepared *via* the reaction of bis-2-haloethylamines with sodium sulfide (A) or bis-2-haloethyl sulfides with ammonia (B).

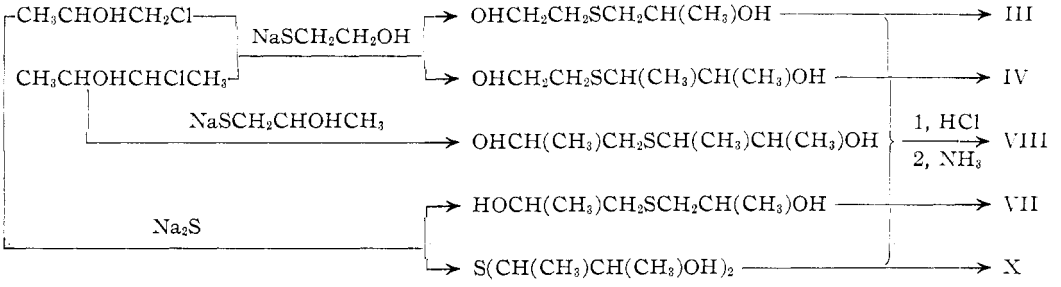


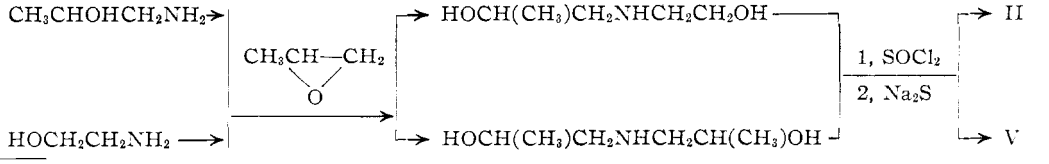
The relatively unstable nature of the nitrogen mustards usually rendered route B more desirable, unless rearrangements necessitated other methods. Rearrangements of both β-haloiospropyl sulfides[4] and 1,2-aminochloroalkanes[5] to the normal structures have been demonstrated *via* cyclic sulfonium and imonium intermediates.

The vesicant nature of the haloethyl sulfides (mustard gases) prompted an attempt to bypass them *via* the reaction of the precursor hydroxy sulfide with amines. Small yields were obtained. Syntheses with aliphatic amines were less successful than with the less basic aromatic amines.



Reaction of C-methyl-substituted bis-(2-haloethyl) sulfides with ammonia (route B) was utilized to prepare the 3-methyl-(III), 2,3-dimethyl-(IV), 3,5-dimethyl-(VII), 2,3,5-trimethyl-(VIII) and 2,3,5,6-tetramethylthiomorpholines (X). Condensation of *vic*-chlorohydrins with 1,2-hydroxymercaptans served as the starting point for III, IV and VIII, while reaction of the chlorohydrins with sodium sulfide yielded the bis-(2-hydroxyethyl) sulfides necessary to reach VII and X.





The 2-methyl (II) and 2,6-dimethyl (V) isomers resulted from route A. The required amino diols were prepared from the addition of 1,2-aminoalcohols to propylene oxide.

(1) An abstract of a portion of a thesis submitted by Bernard Idson to the Polytechnic Institute of Brooklyn, 1952, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) H. T. Clark, *J. Chem. Soc.*, **101**, 1583 (1912); O. B. Helfrich and E. E. Reid, THIS JOURNAL, **42**, 1208 (1920); R. Robinson and F. W. Kay, British Patent 133,108 (June 26, 1918); W. E. Lawson and E. E. Reid, THIS JOURNAL, **47**, 2821 (1925); E. Fromm and B. Ungar, *Ber.*, **56B**, 2286 (1923); V. V. Korshak and Yu A. Strepikheev, *J. Gen. Chem. (U.S.S.R.)*, **14**, 312 (1944); *C. A.*, **39**, 3790 (1945); A. H. Ford-Moore, A. G. Lidstone and W. A. Waters, *J. Chem. Soc.*, 819 (1946); W. F. Hart and J. B. Niederl, THIS JOURNAL, **66**, 1610 (1944); **68**, 714 (1946); *J. Org. Chem.*, **14**, 579 (1949).

(3) D. Harman and W. E. Vaughan, THIS JOURNAL, **72**, 631 (1950).

(4) R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946).

(5) J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, THIS JOURNAL, **69**, 2961 (1947).