

[CONTRIBUTION NO. 614 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. VI. Substitution Reactions of 3-Thenoic Acid

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3-Thenoic acid was brominated, chlorinated and nitrated in the 5-position. A second substituent was found to enter in the 2-position to form the 2,5-disubstituted-3-thenoic acids. However, 5-nitro-3-thenoic acid could not be further nitrated, even at high temperatures in mixed acid. Lithium aluminum hydride was found to cause reductive dehalogenation of 5-bromo- and 2,5-dichloro-3-thenoic acids to form 3-thenyl alcohol. Amides and anilides of the 5-substituted-3-thenoic acid were prepared.

Although many derivatives of 3-thenoic acid (I) have been reported, substitution reactions of this compound have not been investigated.² Rinkes³ nitrated the methyl ester of 3-thenoic acid, and hydrolyzed his product to form a nitro-3-thenoic acid, m.p. 147°. This acid differed from the acid, m.p. 155–156°, obtained by oxidation of 2-nitro-3-methylthiophene.

Monosubstitution of 3-thenoic acid would be expected to occur at the 5-position, since this is a reactive α -position which is meta to the carboxyl group. A second group would probably enter the 2-position with more difficulty, since both available positions (2- or 4-) are *ortho* to the carboxyl, but the 2-position is more reactive. A third group could probably be introduced in the 4-position only with great difficulty, if at all.

The above predictions were borne out by the experiments summarized in Chart I. Treatment of I in glacial acetic acid with the theoretical amount of bromine produced an acid, m.p. 117–118°, which differed from the known 2-bromo-3-thenoic acid (V),⁴ m.p. 178–179°, and 4-bromo-3-thenoic acid,⁵ m.p. 150–152°. This acid was proved to be 5-bromo-3-thenoic acid (II) by further bromination to produce 2,5-dibromo-3-thenoic acid (III), m.p. 179–180°, which was also formed by direct bromination of V. Treatment of I with excess bromine in glacial acetic acid converted it directly to III. II was further characterized by preparation of 5-bromo-3-thenamide (IVa) and 5-bromo-3-thenanilide (IVb).

Substituted thiophenes have been chlorinated in good yield with sulfuryl chloride,⁶ but refluxing I in carbon tetrachloride with sulfuryl chloride, with or without added stannic chloride as catalyst, did not produce any chlorinated products. Although direct chlorination of 2-thenoic acid caused extensive decomposition and gave only traces of 4,5-dichloro-2-thenoic acid,⁷ when the theoretical amount of chlorine was bubbled into a dilute solu-

(1) Taken in part from the thesis submitted by R. C. B. in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, June, 1951.

(2) The "2,5-dibromo-3-thenoic acid," m.p. 222°, (H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 381) which R. Bonz (*Ber.*, **13**, 2308 (1886)) obtained on bromination of an acid formed by the oxidation of acetylated thiophene, is obviously 4,5-dibromo-2-thenoic acid, as shown by comparison of the melting points of the acid chlorides, amides and methyl esters.

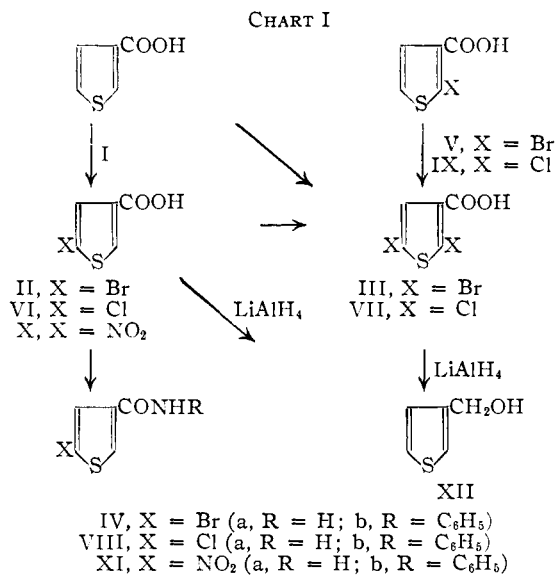
(3) I. Rinkes, *Rec. trav. chim.*, [4] **53**, 643 (1934).

(4) E. Campaigne and W. M. LeSueur, *THIS JOURNAL*, **71**, 333 (1949).

(5) W. Steinkopf, H. Jacob and H. Penz, *Ann.*, **512**, 136 (1934).

(6) E. Campaigne and W. M. LeSueur, *THIS JOURNAL*, **70**, 415 (1948).

(7) W. Steinkopf and W. Kohler, *Ann.*, **532**, 250 (1937).



tion of I in glacial acetic acid, a monochloroacid, VI, melting at 156–157°, was obtained which depressed the melting point (163°) of 2-chloro-3-thenoic acid (IX).⁴ The identity of VI as 5-chloro-3-thenoic acid was confirmed by its further chlorination to 2,5-dichloro-3-thenoic acid (VII),⁸ which is also formed from IX or by direct chlorination of I. VI was readily converted to 5-chloro-3-thenamide (VIIa) and 5-chloro-3-thenanilide (VIIIb).

Compound I was nitrated readily in cold mixed acid to a nitro-acid melting at 145–146°, which agrees well with the acid assigned the structure X by Rinkes.³ This acid was converted to its amide XIa and anilide XIb, but could not be nitrated to a dinitro acid, even at high temperatures. The acid is remarkably stable for a thiophene compound, and could be recovered after treatment in mixed acid at 140° for two hours.

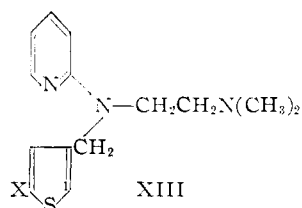
Although halogenation of the thiophene nucleus in antihistaminic compounds of the 2-thenyl series was reported to improve the therapeutic ratio,⁹ the opposite effect was observed in the 2-halo-3-thenyl series.¹⁰ Since this difference may be due to the position of the halogen atom, it was desirable to obtain samples of the N-(5-halo-3-thenyl)-ethylenediamines (XIII) (X = Cl, Br).

In an attempt to prepare the bromo compound directly, II was converted to the acid chloride and condensed with N'-(α -pyridyl)-N,N-dimethylethyl-

(8) H. Hartough and L. G. Conley, *THIS JOURNAL*, **69**, 3096 (1947).

(9) R. C. Clapp, *et al.*, *ibid.*, **69**, 1549 (1947).

(10) A. M. Lands, J. O. Hoppe, O. H. Siegmund and F. P. Luduena, *J. Pharm. Exp. Ther.*, **95**, 45 (1949).



enediamine to form an amide which was reduced with lithium aluminum hydride. The product proved to be *N'*-(3-thienyl)-*N'*-(α -pyridyl)-*N,N*-dimethylethylenediamine¹¹ (XIII) (X = H), showing that a nuclear debromination had occurred. Since the chlorobenzoic acids have been successfully reduced by lithium aluminum hydride to the chlorobenzyl alcohols without dehalogenation,¹¹ this reaction was investigated further by reduction of the bromo-acid II and the dichloro-acid VII with lithium aluminum hydride. In each case the product was the unsubstituted 3-thienyl alcohol XII. Reductive dehalogenation is common in the thiophene series, and has been accomplished with sodium amalgam,¹² aluminum amalgam¹³ and palladium on charcoal,¹⁴ but to our knowledge this is the first report of reductive dehalogenation by lithium aluminum hydride in the thiophene series.

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Experimental¹⁵

5-Bromo-3-thenoic Acid (II).—A solution of 46 g. (0.29 mole) of bromine in 225 ml. of glacial acetic acid was added slowly to a stirred solution of 38 g. (0.30 mole) of 3-thenoic acid (I)¹⁶ in 350 ml. of glacial acetic acid at room temperature. The mixture was stirred for 15 minutes, and then poured into 2 liters of cold water. The white precipitate was washed with water, and recrystallized from hot water, yielding 42 g. (69%) of white needles, melting at 117-118°.

Anal. Calcd. for C₅H₃O₂SBr: S, 15.46; neut. equiv., 207. Found: S, 15.21; neut. equiv., 206.

5-Bromo-3-thenoyl Amides IV.—5-Bromo-3-thenamide (IVa) was obtained by refluxing II in excess thionyl chloride, and pouring the reaction mixture into cold ammonium hydroxide. Recrystallizing from water yielded white plates melting at 100-101°.

Anal. Calcd. for C₅H₄ONBr: S, 15.52; N, 6.80. Found: S, 15.43; N, 6.70.

Warming the crude acid chloride with aniline in benzene produced the anilide IVb, which was recrystallized from dilute ethanol, and melted at 142-143°.

Anal. Calcd. for C₁₁H₈ONBr: S, 11.34; N, 4.97. Found: S, 11.29; N, 5.09.

2,5-Dibromo-3-thenoic Acid (III).—A solution of 2 g. (0.01 mole) of II in 25 ml. of glacial acetic acid was warmed with an excess (5-6 g.) of bromine, and the mixture poured into water and decolorized with bisulfite. The white powder thus obtained was recrystallized once from water to give 1.0 g. of III, melting at 175-176°.

Anal. Calcd. for C₅H₂O₂SBr₂: S, 11.20; neut. equiv., 286. Found: S, 11.02; neut. equiv., 286.

When either I or V⁴ was treated as above, the same product was obtained as shown by melting point and mixed melting point.

(11) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 504.

(12) W. Steinkopf and H. Jacob, *Ann.*, **515**, 273 (1935).

(13) I. Rinkes, *Rec. trav. chim.*, **55**, 991 (1936).

(14) R. Mozingo, *et al.*, *THIS JOURNAL*, **67**, 2092 (1945).

(15) All melting points uncorrected.

(16) E. Campaigne and W. M. LeSuer, *Org. Syntheses*, **33**, 94 (1953).

5-Chloro-3-thenoic Acid (VI).—Chlorine gas was bubbled into a solution of 3 g. (0.023 mole) of I in 200 ml. of glacial acetic acid at room temperature until the weight increase was 1.6 g. (0.023 mole). After standing a few minutes, the mixture was poured into 1 l. of ice-water, stirred and let stand overnight in the refrigerator. A small quantity of white crystals which deposited were collected, and the mother liquor ether-extracted, the extract dried and the ether removed to leave another small quantity of white powder. The combined precipitates were collected and recrystallized from hot water to yield 1.5 g. (40%) of VI, melting at 156-157°.

Anal. Calcd. for C₅H₃O₂SCl: S, 19.75; neut. equiv., 162. Found: S, 19.61; neut. equiv., 160.

A mixture of this substance with 2-chloro-3-thenoic acid (IX)⁴ (in. p. 163°) melted from 125-142°, showing that these acids are different.

5-Chloro-3-thenoyl Amides, VIII.—These derivatives were prepared in the same manner as the bromo-amides. 5-Chloro-3-thenamide (VIIIa), recrystallized from water as white needles melting at 135-136°.

Anal. Calcd. for C₅H₄ONSCl: N, 8.68. Found: N, 9.04.

5-Chloro-3-thenanilide (VIIIb), a white microcrystalline powder from 50% ethanol, melted at 170-171°.

Anal. Calcd. for C₁₁H₈ONSCl: N, 5.91; S, 13.50. Found: N, 6.15; S, 13.56.

2,5-Dichloro-3-thenoic Acid (VII).—Chlorine gas was bubbled into a solution of 3 g. of I in 100 ml. of glacial acetic acid at room temperature until the gain in weight exceeded 3.2 g. After standing for one-half hour, the reaction mixture was worked up as before to yield 2 g. of an acid melting at 147-148°. This same substance was obtained by similar chlorination of either VI or IX⁴ in acetic acid, and was proved to be 2,5-dichloro-3-thenoic acid by comparison to an authentic sample obtained from 2,5-dichloro-3-methylthiophene.⁴

5-Nitro-3-thenoic Acid (X).—A mixture of 20 ml. of concd. nitric acid (sp. gr. 1.42) and 11.5 ml. of 96% sulfuric acid was mechanically stirred in a tall beaker and cooled to -10° by a Dry Ice-methanol-bath. The temperature was kept below -5° while 5 g. (0.039 mole) of I was added in small portions. The reaction mixture was poured over ice and steam distilled. Ether extraction of the distillate gave no organic products. The aqueous residue upon cooling deposited 4.1 g. of yellow needles which after three recrystallizations from benzene melted at 145-146°.

Anal. Calcd. for C₅H₃O₄NS: N, 8.09; neut. equiv., 173. Found: N, 8.01; neut. equiv., 173.

5-Nitro-3-thenoyl Amides, XI.—Prepared from the acid chloride as previously described, 5-nitro-3-thenamide (XIa), recrystallized from water as light tan needles melting at 162-163°.

Anal. Calcd. for C₅H₄O₃N₂S: N, 16.24. Found: N, 15.92.

5-Nitro-3-thenanilide (XIb), recrystallized from 50% ethanol in light tan plates melting at 179-180°.

Anal. Calcd. for C₁₁H₈O₃N₂S: N, 11.30. Found: N, 11.29.

Attempted Nitration of 5-Nitro-3-thenoic Acid.—A series of seven experiments were conducted, in which 5-g. samples of X were stirred into a nitrating mixture of 2 parts of concd. nitric acid and 1 part of concd. sulfuric acid at various temperatures and the reaction prolonged to various times.

TABLE I

RECOVERY OF 5-NITRO-3-THENOIC ACID (X) USING MIXED ACID AT VARIOUS CONDITIONS

Exp. No.	T, °C.	Time, min.	Recovered X, %
1	-10	20	95
2	+10	30	95
3	25	60	92
4	40	60	96
5	80	60	80
6	110	90	75
7	140	120	50

The reaction mixture was worked up as described for X, above, but only 5-nitro-3-thenoic acid could be recovered. No evidence of further nitrated products was obtained. The results of these experiments are presented in Table I.

Attempted Preparation of *N'*-(α -Pyridyl)-*N'*-(5-bromo-3-thenyl)-*N,N*-dimethylethylenediamine.—A solution of 16.4 g. (0.1 mole) of *N'*-(α -pyridyl)-*N,N*-dimethylethylenediamine¹⁷ in 200 ml. of pyridine was treated with the crude acid chloride prepared from 15 g. (0.12 mole) of II. After warming for eight hours, the pyridine was vacuum distilled and the residue poured into ice-water. An ether extract of this mixture was extracted with dilute hydrochloric acid and the acid solution Norited and neutralized cold with dilute sodium hydroxide. The oil which precipitated was extracted with ether, dried, and the ether removed to yield 13 g. of a dark brown oil. Distillation of this oil yielded 8 g. (32%) of a pale orange oil, boiling at 193–197° (1 mm.). Reduction of this oil with lithium aluminum hydride in ethyl ether¹⁸ yielded 2 g. of a pale yellow oil, boiling at 165–170° (1 mm.). This was dissolved in 10 ml. of isopropyl alcohol and 0.7 ml. of concd. hydrochloric acid added. After standing overnight in a refrigerator, the mixture was cooled in an ice-methanol mixture, and the crystals collected. After drying, they melted at 168–169°, and a mixed melting point with the monohydrochloride of *N'*-(α -pyridyl)-*N'*-(3-thenyl)-*N,N*-dimethylethylenediamine⁴ was not depressed.

(17) We are indebted to C. M. Suter, of the Sterling-Winthrop Research Institute, for a sample of this compound.

(18) R. Nystrom and W. Brown, *THIS JOURNAL*, **69**, 1197 (1947).

Reduction of Halogenated Acids with Lithium Aluminum Hydride.—When 42 g. (0.20 mole) of II was reduced in ether with an equimolar amount of lithium aluminum hydride¹⁸ an alcohol was obtained in 30% yield which boiled at 88–90° (10 mm.). It contained no halogen, by sodium fusion test, and was similar in properties to 3-thenyl alcohol XII previously synthesized by McCarthy,¹⁹ b.p. 71° (4 mm.). The aqueous layer from the reduction reaction was treated with barium nitrate to remove the sulfate ion, and then tested for bromide with silver nitrate. A copious precipitate which darkened on standing indicated free bromide ion.

A mixture of 2 ml. of the alcohol and 1 ml. of α -naphthyl isocyanate was heated on a steam-bath for five minutes, cooled, and the brown solid which formed recrystallized from carbon tetrachloride in long white needles which melted at 133–134°. 3-Thenyl- α -naphthylurethan, prepared from an unequivocal sample of 3-thenyl alcohol¹⁹ melted at 132–133°, and a mixed melting point was not depressed.

Anal. Calcd. for C₁₆H₁₃O₂NS: S, 11.98; N, 5.24. Found: S, 12.07; N, 5.18.

Reduction of a sample of VII under the same conditions produced 35% of 3-thenyl alcohol, as shown by its boiling point, 86–88° (10 mm.), and conversion to an α -naphthylurethan, m.p. 132–133°, which did not depress the melting point of the authentic sample.

(19) W. C. McCarthy, unpublished Thesis, Indiana Univ., 1949.

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3-Substituted Thiophenes. VII. Derivatives of 3-Aminothiophene

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The syntheses of *N*-substituted 3-aminothiophenes have been investigated. These were prepared by the application of the Hofmann hypobromite rearrangement procedure to 3-thenamide, followed by reaction with the appropriate acid chloride or anhydride. It is significant that 2-thenamide fails to undergo the Hofmann rearrangement while 3-thenamide gives high yields of the corresponding amine under the conditions used. Several *N*-substituted 3-aminothiophenes were prepared including the benzoyl, acetyl, *p*-toluenesulfonyl, *p*-acetylamino benzenesulfonyl and *p*-aminobenzenesulfonyl derivatives. Preliminary physiological tests on 3-acetamidothiophene and *N'*-3-thienylsulfanilamide were unpromising. A series of substitution reactions of 3-acetamidothiophene were studied. Included in these reactions were mono- and dihalogenation, diazo-coupling and nitration. The positions of halogen substitution were unequivocally proved. In the case of monosubstitution, the 2-position was found to be the most reactive. Where disubstitution occurred, the entering substituents attacked the 2- and 5-positions of the molecule. The following 3-acetamidothiophene derivatives were prepared and characterized: 2-bromo, 2,5-dibromo, 2-chloro-, 2,5-dichloro-, 2-iodo, 2,5-diiodo, 2-nitro and 2-*p*-nitrophenylazo.

The preparation of 3-aminothiophene, as the hydrochloride stannic chloride double salt, was accomplished by the tin and aqueous hydrochloric acid reduction of 3-nitrothiophene as early as 1933 by Steinkopf and Hopner.² From this double salt, the benzoyl and acetyl derivatives were prepared. Due to the difficulty encountered in obtaining 3-nitrothiophene, this approach to 3-aminothiophene and its derivatives leaves much to be desired. With the now readily available 3-thenoic acid and subsequent 3-thenamide, as reported by Campaigne and LeSuer,³ the well-known Hofmann hypobromite rearrangement of the amide seemed like a logical and more convenient synthesis of the amine. However, this approach to the preparation of 2-aminothiophene from the more readily available 2-thenamide is conspicuous by its absence in the greater volume of literature dealing with 2-

substituted thiophenes. With 3-thenamide at hand, the Hofmann reaction was carried out and found to be a satisfactory method for the preparation of derivatives of 3-aminothiophene.

The rearrangement reaction was accomplished by adding the amide to a cold solution (0–5°) of sodium hypobromite and sodium hydroxide, stirring at this temperature for about an hour after the amide dissolved completely, and then warming to 65–70° for an additional hour. During this time, the reaction mixture turned deep red in color but the solution remained clear. It was found that by employing an inert atmosphere of nitrogen during the reaction, a better yield of the desired product could be obtained. Attempts to isolate the amine by distillation under a nitrogen atmosphere or as the hydrochloride failed. Distillation yielded only a tar, whereas addition of dry hydrogen chloride formed a green polymer in an ethereal solution of the amine. The benzoyl and acetyl derivatives were prepared by adding benzoyl chloride or acetic anhydride to the basic reaction mixture from

(1) Taken in part from the Thesis submitted by P.A.M. in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, February, 1952.

(2) W. Steinkopf and T. Hopner, *Ann.*, **501**, 174 (1933).

(3) E. Campaigne and W. LeSuer, *THIS JOURNAL*, **70**, 1555 (1948).