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-dimethylethylenediamine[17] 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 ether[18] 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-dimethylethylenediamine[4] 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 hydride[18] 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 alcohol[19] melted at 132–133°, and a mixed melting point was not depressed.

*Anal.* Calcd. for $C_{16}H_{13}O_2NS$: 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.

BLOOMINGTON, INDIANA

---

[CONTRIBUTION NO. 615 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

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

BY E. CAMPAIGNE AND PEARLE A. MONROE[1]

RECEIVED DECEMBER 28, 1953

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*-acetylaminobenzenesulfonyl 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).

which the desired derivative separated in good yield. Arylsulfonation of the amine was accomplished in a pyridine solution. This necessitated the extraction of the amine with ether, replacement of the ether with pyridine, followed by heating to 70° with the appropriate sulfonyl chloride. The *p*-toluenesulfonyl and *p*-acetylaminobenzenesulfonyl derivatives were prepared in this way. The *p*-aminobenzenesulfonyl derivative was obtained by dilute hydrochloric acid hydrolysis of the *p*-acetylaminobenzenesulfonyl compound.

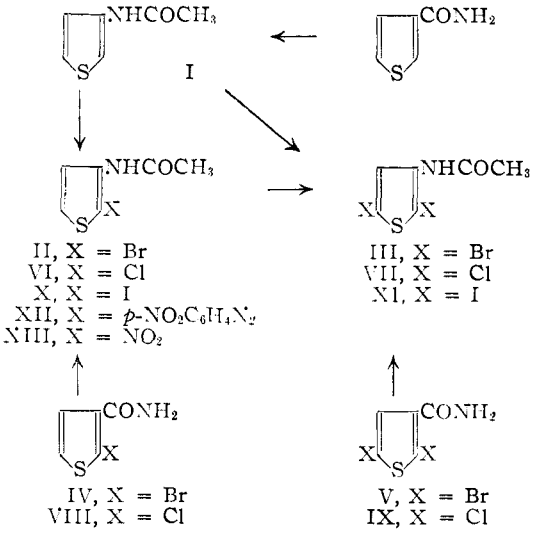
Under the same Hofmann conditions which successfully rearranged 3-thenamide to 3-aminothiophene, 2-thenamide did not undergo rearrangement, but was hydrolyzed to yield ammonia and 2-thenoic acid. This again emphasizes the great differences in reactivity between 2- and 3-substituted thiophenes.

In view of conflicting reports on the bacteriocidal activity of N′-2-thienylsulfanilamide,[4] N′-3-thienylsulfanilamide was submitted to the Sterling-Winthrop Research Institute for testing, and found to be ineffective against tuberculosis in *in vivo* tests in mice. On the other hand, while 2-acetamidothiophene, in contrast to acetanilide, has been reported to be completely inactive,[5] a preliminary study on the analgetic action of 3-acetamidothiophene (I) by the Sterling–Winthrop group, showed it to have an activity comparable to phenacetin and acetanilide, although side effects were greater for I.

Substitution reactions of 2-acetamidothiophene were reported by Steinkopf,[5] and have been studied more recently by Hurd and his co-workers.[6–8] Nitration, bromination, mercuration and sulfonation occur primarily in the 5-position, with a second substituent entering the 3-position. A halogen may be replaced by nitro, that in the 5-position being most susceptible.[7] Although acetanilide will not couple with diazonium salts, 2-acetamidothiophene coupled readily with *p*-nitrobenzenediazonium chloride in acid solution to form an azo dye.[6]

3-Acetamidothiophene (I) has been found to undergo bromination, chlorination, iodination, coupling with *p*-nitrophenyldiazonium chloride and nitration. With bromine in acetic acid, I was converted directly to 2,5-dibromo-3-acetamidothiophene (III). Monobromination was accomplished by refluxing I with an equimolar amount of N-bromosuccinimide in chloroform, to form 2-bromo-3-acetamidothiophene (II). II was converted to III by excess bromine in acetic acid. The structure of II and III was confirmed by their unequivocal syntheses from the known 2-bromo-3-thenoic acid,[9] and 2,5-dibromo-3-thenoic acid,[10] *via* a Hofmann rearrangement of the amides IV and V, followed by acetylation.

Chlorine in acetic acid or chloroform caused excessive oxidation, and no organic products could be isolated. Sulfuryl chloride in chloroform converted I to 2-chloro-3-acetamidothiophene (VI), but N-chlorosuccinimide proved to be the reagent of choice, giving either VI or 2,5-dichloro-3-acetamidothiophene (VII) in good yield, depending on the ratio of reagents. The identities of VI and VII were again confirmed by rearrangement and acetylation of the amides VIII and IX, derived from the known 2-chloro-[9] and 2,5-dichloro-3-thenoic[11] acids.




With equimolar amounts of I and iodine monochloride in glacial acetic acid, a monoiodo derivative was readily obtained, while with twice as much iodine monochloride in the same solvent, a diiodo derivative was obtained. These were assigned the configurations of 2-iodo-3-acetamidothiophene (X) and 2,5-diiodo-3-acetamidothiophene (XI) by analogy to the bromination and chlorination reactions. The reaction of I with *p*-nitrophenyldiazonium chloride in acid solution was found to take place readily to produce a purple azo dye, probably XII, which had indicator properties, and melted with decomposition at 185°. This compound is quite analogous to the purple substance melting at 250° with decomposition which Hurd and Priestley[6] obtained from 2-acetamidothiophene. It should be noted that I did not react with phenyldiazonium chloride under similar conditions. Nitration was accomplished with concentrated nitric acid in acetic anhydride. Regardless of concentration of the acid, only one nitro group could be introduced at −5°, while higher temperatures caused destruction of the molecule. The mononitro derivative, melting at 122–123°, was assigned structure XIII, by analogy. The hope that 5-nitro-3-thenamide[10] would rearrange under the Hofmann procedure to yield the isomeric 5-nitro-3-acetamidothiophene could not be realized, since only hydrolysis of the amide occurred. Nor could either of the bromo groups in III be satisfactorily replaced by nitro groups using fuming nitric acid as described by Priestley and Hurd[7] for 3,5-dibromo-2-acetamidothiophene.

The formulas and properties of the various derivatives of 3-aminothiophene which have been

(4) A. R. Frisk, *Acta Med. Scand. Suppl.*, **142**, 1 (1943); *C. A.*, **38**, 4692 (1944); J. Kimmig, *Arch. Dermatol. Syphilis*, **186**, 156 (1947); *C. A.*, **43**, 3097 (1949).

(5) W. Steinkopf, *Ann.*, **403**, 17 (1914).

(6) C. D. Hurd and H. M. Priestley, THIS JOURNAL, **69**, 859 (1947).

(7) H. M. Priestley and C. D. Hurd, *ibid.*, **69**, 1173 (1947).

(8) C. D. Hurd and J. Moffat, *ibid.*, **73**, 613 (1951).

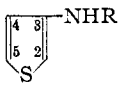
(9) E. Campaigne and W. M. LeSuer, *ibid.*, **71**, 333 (1949).

(10) E. Campaigne and R. C. Bourgeois, *ibid.*, **76**, 2445 (1954).

(11) H. D. Hartough and L. G. Conley, *ibid.*, **69**, 3096 (1947).

TABLE I

DERIVATIVES OF 3-AMINOTHIOPHENE



| No. | Compound | Method | Yield, % | M.p., °C.[a] | Formula | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 1 | R = $CH_3CO$ | A | 70 | 147–148[b] | $C_6H_7NOS$ | 9.92 | 9.79 |
| 2 | R = $C_6H_5CO$ | A | 82 | 153–154[b] | $C_{11}H_9NOS$ | (15.79)[c] | (15.50)[c] |
| 3 | R = $p$-$CH_3C_6H_5SO_2$ | B | 33 | 105–106 | $C_{11}H_{11}NO_2S_2$ | 5.54 | 5.76 |
| 4 | R = $p$-$CH_3CONHC_6H_4SO_2$ | B | 45 | 172–173 | $C_{12}H_{12}N_2O_3S_2$ | 9.47 | 9.56 |
| 5 | R = $p$-$H_2NC_6H_4SO_2$ | [d] | 82 | 166–168 | $C_{10}H_{10}N_2O_2S_2$ | 11.06 | 11.26 |
| 6 | 2-Br, R = $CH_3CO$ | A | 78 | 87–89 | $C_6H_6NOSBr$ | 6.36 | 6.50 |
| | | S[e] | 91 | 88–89 | | [f] | |
| 7 | 2,5-diBr, R = $CH_3CO$ | A | 61 | 118–119 | $C_6H_5NOSBr_2$ | (10.70)[c] | (10.69)[c] |
| | | S[e] | 97 | 118 | | [f] | |
| 8 | 2-Cl, R = $CH_3CO$ | A | 55 | 85–86 | $C_6H_6NOSCl$ | 7.98 | 7.83 |
| | | S[e] | 74 | 85–86 | | [f] | |
| 9 | 2,5-diCl, R = $CH_3CO$ | A | 51 | 108–109 | $C_6H_5NOSCl_2$ | 6.67 | 6.47 |
| | | S[e] | 71 | 108–109 | | [f] | |
| 10 | 2-I, R = $CH_3CO$ | S[e] | 56 | 109–110 | $C_6H_6NOSI$ | 5.24 | 4.94 |
| | | | | | | (47.53)[g] | (47.41)[g] |
| 11 | 2,5-diI, R = $CH_3CO$ | S[e] | 65 | 166–167 | $C_6H_5NOSI_2$ | 3.56 | 3.58 |
| | | | | | | (64.6)[g] | (64.5)[g] |
| 12 | $p$-$NO_2C_6H_4N_2$, R = $CH_3CO$ | S[e] | 86 | 185 dec. | $C_{12}H_{10}N_4O_3S$ | 18.62 | 18.37 |
| 13 | 2-$NO_2$, R = $CH_3CO$ | S[e] | 83 | 122–123 | $C_6H_6N_2O_3S$ | 15.05 | 14.48 |
| | | | | | | (17.20)[c] | (17.69)[c] |

[a] All melting points uncorrected. [b] In agreement with melting points reported by Steinkopf and Hopner.[2] [c] % Sulfur. [d] Prepared by hydrolysis of compound 4 in dilute hydrochloric acid. [e] Prepared by direct substitution, see Experimental. [f] A mixed melting point with the compound prepared by method A showed no depression. [g] % Iodine.

prepared in this investigation are collated in Table I.

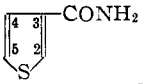
## Experimental[12]

**3-Thenamides.**—3-Thenoic acid[13] (128 g., 1 mole) was converted to the chloride by refluxing for six hours with 250 ml. of thionyl chloride. The excess thionyl chloride was removed by distillation with benzene. After cooling, the contents of the flask was poured slowly into an excess of ammonia water with stirring. The amide, filtered and recrystallized from hot water, weighed 111 g. (87.5%). The various other halogenated 3-thenamides listed in Table II were prepared from the known halogen acids[9,10] in equally good yield in the same manner.

**5-Nitro-3-thenamide.**—To a solution of 20 ml. of concentrated nitric acid, d. 1.42, and 15 ml. of concentrated sulfuric acid, d. 1.84, previously cooled to 10°, was added in small portions with stirring 5 g. (0.0394 mole) of 3-thenamide. After all the amide had been added, the solution was stirred for another ten minutes. The nitrating mixture was then poured into 100 ml. of ice-water to precipitate the nitroamide. The amide was filtered and recrystallized from hot water to yield 4.5 g. (66.5%) of pale yellow needles. The formulas and properties of the thenamides prepared and used are listed in Table II.

TABLE II

3-THENAMIDES



| Compound | M.p., °C.[a] | Formula | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|
| 3-Thenamide | 178–179 | | [b] | [b] |
| 2-Bromo- | 135–137 | $C_6H_4NOSBr$ | 6.80 | 6.92 |
| 2,5-Dibromo- | 147–148 | $C_6H_3NOSBr_2$ | 4.92 | 5.02 |
| | | | (56.09[c]) | (56.14[c]) |
| 2-Chloro- | 120–121 | $C_6H_4NOSCl$ | 8.67 | 8.81 |
| 2,5-Dichloro- | 115–116 | $C_6H_3NOSCl_2$ | 7.15 | 7.32 |
| 5-Nitro- | 166–167 | | [d] | [d] |

[a] All m.p.'s uncorrected. [b] A mixed m.p. with a sample prepared by LeSuer[3] showed no depression. [c] % Bromine. [d] A mixed m.p. with a sample prepared by Bourgeois[10] showed no depression.

(12) All melting points uncorrected.

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

**Hofmann Rearrangement of Amides. Method A.**—The rearrangement and acylation may be effected directly in the alkaline solution. The preparation of 3-acetamidothiophene (I) serves to illustrate this method. A sodium hypobromite solution was prepared by dropping 7.2 ml. of bromine with stirring into a solution of 22 g. of sodium hydroxide in 180 ml. of ice-cold water. To the clear yellow solution in a flask through which nitrogen was passed slowly was added 12.7 g. (0.1 mole) of 3-thenamide. The mixture was stirred for one hour after all the amide had dissolved and then warmed to 70–80° for about 45 minutes, during which time the clear solution became dark red in color. The solution was cooled in ice and 20 ml. of acetic anhydride added slowly with stirring. (For the benzamido derivative, benzoyl chloride was used.) The reaction was soon complete and the precipitate was filtered and recrystallized from hot water or water–alcohol mixture, which, after treatment with Norite, deposited white plates on cooling. The bromo- and chloro-amides were rearranged and acetylated in the same way (see Table I).

**Method B.**—The sulfonylation reactions were more readily effected in ether–pyridine solutions. The preparation of 3-$p$-toluenesulfonamidothiophene serves to illustrate this technique. After rearranging 0.03 mole of 3-thenamide as described before, the solution was cooled and extracted three times with a total of 50 ml. of ether. Pyridine (50 ml.) and 6 g. (0.0315 mole) of $p$-toluenesulfonyl chloride were added to the ether solution. The mixture was heated on a steam-bath to remove the ether, followed by heating to reflux for one-half hour, and then poured into 200 ml. of water, cooled and filtered. The precipitate was recrystallized first from an alcohol–water mixture and then from 50% acetic acid to yield 2.5 g. of pure product.

**Attempted Isolation of 3-Aminothiophene Hydrochloride.**—A hypobromite degradation was carried out on 3-thenamide as described previously. The cooled reaction mixture was extracted with ether, and the combined ether extracts dried thoroughly over Drierite. Dry hydrogen chloride gas was passed into the ether solution, which instantly began to turn green in color, as a precipitate formed. The tarry precipitate was insoluble in water and organic solvents and was not characterized further.

**Attempted Distillation of 3-Aminothiophene.**—A dried ether solution of the amine, obtained from a hypobromite

degradation of 3-thenamide, was subjected to vacuum distillation under a nitrogen atmosphere. After the ether had been removed and heat applied to the distilling flask, the residue decomposed leaving a tar in the distillation flask and no distillate was obtained.

**Attempted Hofmann Rearrangement of 2-Thenamide.**—Using a hypobromite solution prepared as described, 3.81 g. (0.03 mole) of 2-thenamide was added and stirred for one hour. During the heating period which followed, the odor of ammonia became very apparent. Addition of acetic anhydride to the cooled reaction mixture until the solution was acidic, yielded 3 g. of solid, which after recrystallization was found to melt at 126–127°, and did not depress the melting point of an authentic sample of 2-thenoic acid.

**Substitution Reactions of 3-Acetamidothiophene. 2-Bromo-3-acetamidothiophene** (II).—To a boiling solution of 1.41 g. (0.01 mole) of I in 30 ml. of chloroform was added 1.76 g. (0.01 mole) of N-bromosuccinimide. After the initial reaction ceased, the mixture was heated for ten minutes. The chloroform was evaporated on a steam-bath and the residue was dissolved in hot water, treated with Norite, and cooled to yield 2 g. of crystals.

**2,5-Dibromo-3-acetamidothiophene** (III).—To a solution of 1.41 g. (0.01 mole) of I in 15 ml. of glacial acetic acid was added 3.2 g. (0.02 mole) of bromine in 15 ml. of glacial acetic acid. The mixture was stirred for 20 minutes at room temperature, and then poured into ice-water. The precipitate was filtered and recrystallized from an alcohol–water mixture. The white needles obtained weighed 2.9 g. and melted at 118°. Using only a mole/mole ratio of amide and bromine under similar conditions, the same 2,5-dibromo compound was obtained in half the yield.

**b. From 2-Bromo-3-acetamidothiophene.**—A solution of 3 g. (0.0136 mole) of 2-bromo-3-acetamidothiophene in 20 ml. of glacial acetic acid was treated with a slight excess of bromine (2 g.) in 5 ml. of glacial acetic acid. The resulting solution was stirred for 15 minutes at room temperature and then poured into 50 ml. of ice-water. The precipitation was soon complete and the product recrystallized from an alcohol–water mixture, forming 3 g. (73%) of 2,5-dibromo-3-acetamidothiophene. A mixed melting point with a sample obtained from either 3-acetamidothiophene or 2,5-dibromo-3-thenamide was 118–119°.

**2-Chloro-3-acetamidothiophene** (VI). **a. From I and Sulfuryl Chloride.**—To a solution 1.41 g. (0.01 mole) of I in 20 ml. of chloroform was added 1.35 g. (0.01 mole) of sulfuryl chloride in 10 ml. of chloroform. The mixture was refluxed for two hours and the chloroform evaporated on a steam-bath. The brown residue was treated with Norite and recrystallized from hot water three times to yield 0.7 g. (40%) of white plates, melting at 84–85°.

**b. From I and N-Chlorosuccinimide.**—To 1.41 g. (0.01 mole) of 3-acetamidothiophene in 50 ml. of warm chloroform was added in small portions 1.34 g. (0.01 mole) of N-chlorosuccinimide, and the mixture was refluxed for 15 minutes. The chloroform was removed by evaporation with a stream of air, the residue was dissolved in a small volume of hot water and filtered from Norite. The cooled filtrate yielded 1.3 g. of white plates having a melting point of 85–86°. A mixed melting point with the sample obtained from the sulfuryl chloride reaction was 84–86°.

**2,5-Dichloro-3-acetamidothiophene** (VII).—To 1.41 g. (0.01 mole) of I in 50 ml. of warm chloroform was added 2.7 g. (0.02 mole) of N-chlorosuccinimide in small portions. The mixture was refluxed for 20 minutes and the chloroform evaporated. The residue was dissolved in a hot alcohol–water mixture and filtered from charcoal. The filtrate, after diluting with water, yielded 1.4 g. of white needles.

**Attempted Chlorination with Chlorine Gas.**—To 1.41 g. (0.01 mole) of I in 25 ml. of glacial acetic acid was added 1.42 g. (0.02 mole) of chlorine as evidenced by the increase in weight. The solution was diluted with water but no material precipitated. No chloro derivatives could be obtained by solvent extraction. A test with barium chloride showed the presence of sulfate in the aqueous solution.

With chloroform as the solvent, chlorine gas again did not yield any identifiable chloro products.

**2-Iodo-3-acetamidothiophene (X).**—To a solution of 1.41 g. (0.01 mole) of I in 30 ml. of glacial acetic acid was added 1.63 g. (0.01 mole) of iodine monochloride in 17 ml. of glacial acetic acid. Water (75 ml.) was added and the solution heated slowly to 80° (about 20 min.) and maintained at that temperature for 45 minutes until the iodine color disappeared. More water was added and the solution alllowed to cool in an ice-bath. The precipitate was filtered and recrystallized from hot water, yielding 1.5 g. of white needles.

**2,5-Diiodo-3-acetamidothiophene (XI).**—To 1.41 g. (0.01 mole) of I in 25 ml. of glacial acetic acid was added 3.25 g. (0.02 mole) of iodine monochloride in 15 ml. of glacial acetic acid. Fifty milliliters of water was added and the solution warmed. A precipitate appeared instantly. A little 5% sodium bisulfite solution was added to remove the iodine present. After cooling, the precipitate was collected and recrystallized from a methanol–water mixture, forming 2.21 g. of crystals.

***p*-Nitrophenylazo-3-acetamidothiophene (XII).**—To 1.38 g. (0.01 mole) of *p*-nitroaniline in 15 ml. of water and 3 ml. of concentrated hydrochloric acid was added with cooling 0.75 g. of sodium nitrite in 5 ml. of water. The filtered diazonium chloride solution was added dropwise to 1.41 g. (0.01 mole) of I in 25 ml. of absolute ethanol. The solution immediately became purplish-red in color. After the diazonium chloride solution had been added, a purple precipitate started to form. A little water was added to complete the precipitation. The product was filtered, washed with aqueous alcohol, and finally with water. The dried azo compound weighed 2.5 g. and decomposed at 185°.

An alcoholic solution of the azo compound was purple in acid and yellow in base.

**Attempted Preparation of Phenylazo-3-acetamidothiophene.**—A cold diazotized solution of 1 g. of aniline was mixed with 2.5 g. of I in 60 ml. of 50% ethanol containing 3 g. of sodium acetate. The solutions were shaken together vigorously at room temperature and, upon standing, a light yellow precipitate appeared. This substance proved to be unreacted I, recovered in 80% yield.

**2-Nitro-3-acetamidothiophene (XIII).**—To a solution of 1.5 g. of I in 25 ml. of acetic anhydride, cooled to −5°, was added with stirring 0.8 ml. of concentrated nitric acid, d. 1.42, at the rate of 1 drop/4 sec. When all the nitric acid had been added, the mixture was stirred for 15 minutes and then poured into 100 ml. of ice-water. When the acetic anhydride had dissolved, the solution was neutralized with solid sodium carbonate. The precipitate was filtered and recrystallized from hot water, yielding 0.5 g. of yellow needles having a melting point of 122–123°. The reaction filtrate was extracted with ether, to give another 0.3 g. of the material after recrystallization from water. Using the same procedure but employing 2 ml. of concentrated nitric acid, there was isolated a total of 1.54 g. of the same material.

**Attempted Hofmann Rearrangement of 5-Nitro-3-thenamide.**—To a solution of 2.4 ml. of bromine in 7.2 g. of sodium hydroxide in 60 ml. of water at 0° was added 5.16 g. of 5-nitro-3-thenamide. The solution was heated to 70°. During this time, the odor of ammonia became prevalent, indicating that hydrolysis was occurring. No acetamido compound could be isolated after acetic anhydride had been added.

5-Nitro-N-bromo-3-thenamide was prepared by adding 2 g. of the amide to a hypobromite solution. The N-bromo compound was precipitated by pouring it into acetic acid. The compound was added to a solution of 5 g. of sodium hydroxide in 50 ml. of water previously heated to 90°. Hydrolysis again occurred as evidenced by the evolution of ammonia. No rearrangement product could be identified.

**Attempted Replacement of Bromine by Nitro.**—To a solution of 1 ml. of fuming nitric acid (d. 1.50) in 3 ml. of acetic anhydride at 15° was added 1 g. of 2,5-dibromo-3-acetamidothiophene. After one-half hour, the solution was poured into 25 ml. of ice-water, and neutralized with solid sodium bicarbonate. No organic products could be recovered by ether extraction.

BLOOMINGTON, INDIANA