[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH & DEVELOPMENT DEPARTMENT]

The Reaction of Thiophene with Formaldehyde and Salts of Hydroxylamine[1]

BY HOWARD D. HARTOUGH

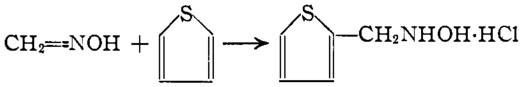
The reaction of thiophene with formaldehyde and ammonium chloride was recently reported from these laboratories.[1a] At the same time Holdren and Hixon reported the Mannich reaction had been extended to 2-methylfuran.[2] They also reported that hydroxylamine hydrochloride gave unidentified products with 2-methylfuran.

Sometimes prior to these publications it had been found in our laboratories that hydroxylamine salts would undergo a type of Mannich reaction with thiophene. This reaction has been studied in considerable detail. It had also been found that acetone, furan, and phenol undergo a similar reaction but with the exception of the thiophene series no attempt was made to study the composition of the products other than to determine that nitrogenous bases were formed:

In the thiophene series the following amines have been isolated: 2-thenylhydroxylamine (2-(hydroxylaminomethyl)-thiophene), I; di-(2-thenyl)-hydroxylamine, II; and di-(5-hydroxymethyl-2-thenyl)-hydroxylamine hydrochloride, III; and polymeric amines of unknown structure, IV.

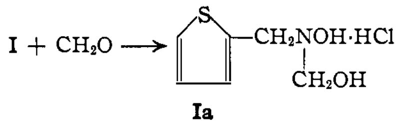
Compound I was formed in 78% yields by the reactions

(1) $CH_2O + NH_2OH.HCl \longrightarrow CH_2{=}NOH + HCl + H_2O$

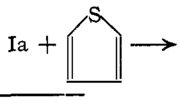
(2)


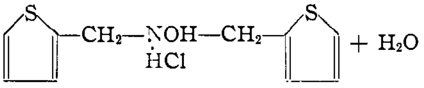
Hydrochloride of I

I could not be isolated from any reaction mixture if the reaction was not run stepwise with initial formation of formaldoxime. Introduction of aqueous formaldehyde to a slurry of thiophene and hydroxylamine hydrochloride gave II in 48% yields along with more complex amines, IV. It is believed that II is formed from the interaction of I with formaldehyde and thiophene.

(3)


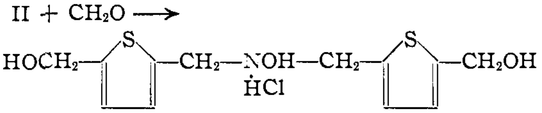
Ia

(4)




Hydrochloride of II
+
Hydrochloride of IV

Ia, however, has not been isolated. Compound III is formed in 36% yields along with IV when all of the reactants are mixed together and are allowed to react rapidly. Compound II apparently reacts further with formaldehyde.

(5)


Hydrochloride of III
+
Hydrochloride of IV

Amines of type IV are extremely complex and could be formed by condensation of I and III, Ia and II, or by the condensation of III with more hydroxylamine hydrochloride. The structure of the basic unit of the polymeric amines of type IV has been subjected to only a preliminary study by oxidation. Besides brown oxides of nitrogen, 2-thiophenealdehyde, V, 2-thiophenecarboxylic acid, VI, and 2,5-dicarboxylic acid. VII, have been obtained.

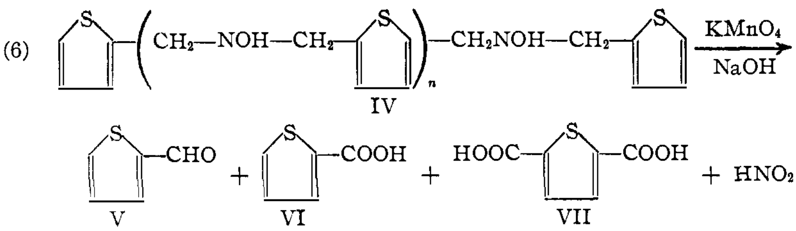
Compounds I and II are stable enough toward heat to have definite melting points. The free base of III decomposes slowly at room temperature and could not be obtained pure. Boiling of I in alcohol causes decomposition. No crystalline derivatives of these compounds and of IV could be prepared. The phenyl isothiocyanate derivatives can be obtained as crystalline materials by carrying out the reaction in an ice-bath but subsequent purification at room temperature leads to rapid decomposition with evolution of a gas. Acyl halides react with extreme violence to give unidentifiable products. The amine salts of I, II and III are crystalline but do not exhibit definite melting points, decomposing above 150°. Mixtures of I, II, III and IV as the free bases decompose violently when heated to about 150° and consequently cannot be separated by distillation. At 100° III and IV polymerize to give resinous bodies. The tendency of the free bases in amine IV to polymerize with heat indicated loss of water between methylol groups and thiophene or through the hydroxylamine radical to produce imine type compositions known for their ability to resinify. This observation was further supported when I showed increased nitrogen and sul-

---

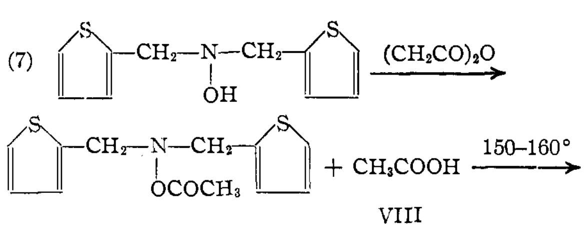
[1] This paper was presented before the Organic Division of the American Chemical Society at the Atlantic City meeting. April 16, 1947.

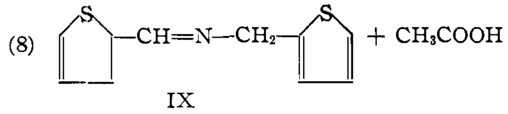
[1a] Hartough, Lukasiewicz and Murray, THIS JOURNAL, **68**, 1389 (1946).

[2] Holdren and Hixon, *ibid.*, **68**, 1198 (1946).

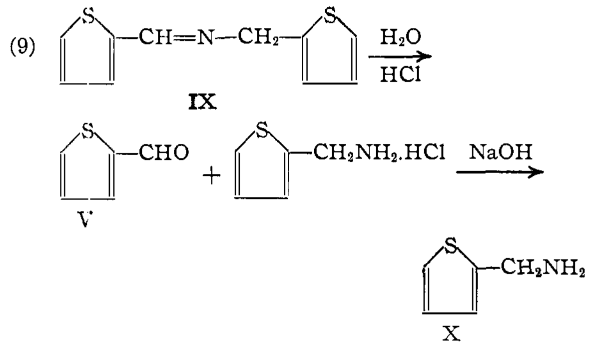


fur contents when heated at 100° on a steam-bath. Further proof was presented for imine structures when 2-thiophenealdehyde was steam-distilled from a hydrochloric acid solution of amine IV. Compound II is the most stable toward heat treatment of all of these amines. It fails to lose water in boiling benzene or in the presence of a few per cent. of iodine in boiling benzene. Acetic anhydride, however, forms a fairly stable acetate derivative, VIII, which when pyrolyzed at 150–160° gave N-(2-thenyl)-2′-thenaldimine, IX.





Compound IX can be easily hydrolyzed into its components, 2-thiophenealdehyde, V, and 2-thenylamine, X, by use of 2 *N* hydrochloric acid.



The respective yields of V and X were 68 and 95%. It has been previously reported that N-benzylphenylhydroxylamine could be dehydrated with heat and the corresponding N-phenylbenzaldimine could be split with 2 *N* hydrochloric acid to benzaldehyde and aniline.[3]

Either aqueous formaldehyde (35–37%) or polymeric formaldehyde may be used in these reactions. Aqueous formaldehyde is preferred if compounds I, II or III are desired. Paraformaldehyde in the presence of acetic acid[4] tends to give products with higher contents of both sulfur and nitrogen indicating imine formation. The corresponding amine IV types tend to polymerize more rapidly than those produced from aqueous formaldehyde.

It is obvious that nitrogenous products of type IV are very complex. Compositions containing numerous methylol groups and/or increased nitrogen contents can be formed by varying the molar concentrations of the formaldehyde and/or the hydroxylamine salts in the reaction mixture. Thus many types of sub-resinous amines of type IV can be "tailor-made" to suit the type resin desired as the end-product. Table I lists the analyses of several of these products.

While formaldoxime reacted readily with thiophene to give I, attempts to condense ketoximes with thiophene in the presence of hydrochloric acid were unsuccessful. Benzaldehyde gave only benzaldoxime and failed to condense with thiophene. No other aldoximes were tried.

It is advantageous to maintain the temperature of the reaction below 70° since above that temperature ring rupture with evolution of hydrogen sulfide takes place and no definite products can be isolated. If temperatures are maintained below 65° no color formation is noted in the reaction mixtures, and II or III, as the hydrochlorides, were crystallized as water-white salts from the reaction mixture and the free base of IV was obtained as a light yellow oil after neutralization of the aqueous solution with caustic. This oil polymerizes slowly at 100° to give light yellow resins.

The reaction is generally applicable to electropositively substituted thiophenes. 2-Chlorothiophene and 2-*t*-butylthiophene react readily and analyses of the products indicate mixtures of amines of types I and II.

While hydroxylamine hydrochloride is the preferred salt of amines I, II and III are desired, amine IV types are readily obtainable from commercial grades of the acid sulfate and sulfate salts of hydroxylamine.

Experimental

Preparation of 2-Thenylhydroxylamine (I) **and Di-2-(thenyl)-hydroxylamine** (II).—To 85 g. (1 mole) of 36% formaldehyde solution was added 70 g. (1 mole) of hydroxylamine hydrochloride. After the heat of reaction subsided the mixture was allowed to cool to room temperature and to stir for thirty minutes. No odor of formaldehyde could be detected in the solution but the odor of hydrochloric acid was very strong. To this well-agitated mixture was added 84 g. (1 mole) of thiophene. The temperature began to rise almost immediately. A maximum temperature, 53°, was reached after one hour. The reaction mixture was stirred for two and one-half hours longer

---

(3) Utzinger, *Ann.*, **556**, 50 (1944).

(4) Previous work on the Mannich reaction with polymeric formaldehyde and ammonium chloride with thiophene indicated that acetic acid was necessary to depolymerize the formaldehyde at a lower temperature, see ref. 1.

TABLE I

ANALYSES OF SOME TYPE IV AMINES

Moles of reactants used			Analyses, %	
C_4H_4S	CH_2O	$NH_2OH \cdot HCl$	Sulfur	Nitrogen
1	1	1	23.1	8.8
1	3	1	17.9[a]	2.8[a]
			20.8[b]	7.0[b]
1	4	1	19.1	6.9
1	4	2	13.7	9.4
1	2	2	18.9	10.5

[a] Benzene soluble portion. [b] Benzene insoluble portion.

and then cooled to 5° in an ice-bath to induce crystallization of di-(2-thenyl)-hydroxylamine hydrochloride. This was filtered off, dried and weighed. Twenty-four grams (9% yield) was obtained. After two recrystallizations from a 5% solution of hydrochloric acid it darkened at 150° and melted with decomposition at 171-172°.

Anal. Calcd. for $C_{10}H_{12}ClNOS_2$: S, 24.5; N, 5.44. Found: S, 24.6; N, 5.45.

A portion of the hydrochloride was neutralized with 20% sodium hydroxide solution to give di-(2-thenyl)-hydroxylamine (II). This white crystalline product was dissolved in benzene and precipitated by addition of petroleum ether. After repeating this purification the product melted at 60-62°.

Anal. Calcd. for $C_{10}H_{11}NOS_2$: C, 53.3; H, 4.9; N, 6.2; S, 28.4. Found: C, 53.0; H, 4.7; N, 6.0; S, 28.1.

The aqueous filtrate was neutralized with 40% sodium hydroxide and the 2-thenylhydroxylamine (I) was extracted three times with 50 ml. of thiophene. The product was crystallized from the thiophene by addition of petroleum ether followed by cooling to give 102 g. (78% yield) of product. After repeating this process the product melted at 58-60°.

Anal. Calcd. for C_5H_7NOS: N, 10.8. Found: N, 10.6.

Oxidation of I with alkaline potassium permanganate gave 2-thiophenecarboxylic acid, m. p. 129-130°, which was identified by a mixed melting point with an authentic sample.

Di-(2-thenyl)-hydroxylamine (II) and Amine IV.—To 544 g. (6.5 moles) of thiophene and 455 g. (6.5 moles) of hydroxylamine hydrochloride at 28° was added 540 g. (6.5 moles) of 36% formaldehyde portionwise over a period of five to ten minutes. The heat of reaction caused the temperature to rise to 65° where it was controlled by means of an ice-bath. When external cooling was no longer necessary the reaction was allowed to continue with stirring until it had cooled to room temperature (25°); three hours were required. Crystals began to form at about 50° and at 25° the formation seemed complete. 408 g. (48% yield) of di-(2-thenyl)-hydroxylamine hydrochloride was filtered off. After caustic neutralization and purification as described above the free amine II melted at 60-62°. Ninety-five grams of thiophene was recovered from the filtrate. The aqueous portion of the filtrate was treated with 40% sodium hydroxide solution and amine IV extracted with benzene. After evaporation of the benzene 345 g. of amine IV was obtained. Heating at 100° gave a light yellow thermoplastic resinous material.

Di-(5-hydroxymethyl-2-thenyl)-hydroxylamine (III).—To a mixture of 42 g. (0.5 mole) of thiophene and 35 g. (0.5 mole) of hydroxylamine hydrochloride was added 42 g. (0.5 mole) of 36% formaldehyde solution. The mixture was heated and boiled under reflux at 76° for about twenty-five minutes or until the solution became entirely homogeneous and clear. The material was then cooled and 21 g. (36% yield) of crystals were filtered off. After recrystallization from 100 ml. of water (at times crystallization had to be induced with addition of a minimum amount of concentrated hydrochloric acid) the white crystals darkened at 150° and melted at 157-160° with decomposition.

Anal. Calcd. for $C_{12}H_{16}ClNO_3S_2$: C, 44.7; H, 4.9; Cl, 11.0; N, 4.4; S, 20.0. Found: C, 44.2; H, 4.1; Cl, 11.0; N, 4.6; S, 20.3.

The material was not stable as the free base and quickly polymerized to a viscous sub-resinous oil that was only partially soluble in benzene.

Preparation of N-(2-Thenyl)-2′-thenaldimine (IX).—To an ice-cold solution of one mole (225 g.) of di-(2-thenyl)-hydroxylamine in 600 ml. of benzene was added slowly 150 g. of acetic anhydride. The mixture was refluxed three hours on a steam-bath, cooled, water washed and then washed with 10% sodium carbonate solution until neutral. The benzene was removed by distillation and the crude acetate (VIII) transferred to a Claisen flask and the pressure reduced to 4.0 mm. When the flask temperature reached 150-160° white fumes were noticed and 58.5 g. of acetic acid along with 8 g. of 2-thiophenealdehyde was collected in the Dry Ice trap. When pyrolysis was completed 73 g. (35% yield) of the N-(2-thenyl)-2′-thenaldimine (IX) distilled at 157-168° at 4 mm. The residue, 103 g., was a red polymeric oil which may have contained more product. The distillate slowly crystallized and after two recrystallizations from ASTM naphtha melted at 55.5-56.5°.

Anal. Calcd. for $C_{10}H_9NS_2$: N, 6.71. Found: N, 6.65.

Hydrolysis of N-(2-Thenyl)-2′-thenaldimine with 2 *N* Hydrochloric Acid.—To 30 g. of N-(2-thenyl)-2′-thenaldimine was added 200 ml. of 2 *N* hydrochloric acid solution and the mixture steam distilled. The distillate was extracted with ether and after evaporation of the ether 11 g. (68% yield) of 2-thiophenealdehyde (V) was obtained which was identified as the semicarbazone; m. p. 218-219° (uncor.) (lit.[5] reports melting point of 227-228°).

Anal. Calcd. for $C_6H_7N_3OS$: N, 24.74. Found: N, 24.93.

The acid residuum of the steam distillation was extracted with benzene to remove 6 g. of a dark red tar which was not identified. Neutralization of the water layer with potassium hydroxide followed by extraction with ether and subsequent evaporation of the ether gave 15.5 g. (95% yield) of 2-thenylamine (X). X was identified by conversion to N,N′-(2-thenyl)-phenylthiourea by treating it with phenyl isothiocyanate according to standard procedures. After two recrystallizations from 75% alcohol the product melted at 123.5-124.5°.

Anal. Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.29. Found: N, 11.36.

Oxidation of Amine IV with Alkaline Permanganate.—The amine IV used in this reaction was prepared by the reaction of two moles of formaldoxime with one mole of thiophene. It was originally hoped that 2,5-di-(hydroxylaminomethyl)-thiophene could be obtained but only amines of type IV were found. Twenty grams of this amine was mixed with 40 g. of sodium hydroxide in 300 ml. of water and heated to boiling. Forty grams of potassium permanganate in 300 ml. of water was slowly added. 2-Thiophenealdehyde was steam distilled as it formed and 4.6 g. was collected and identified by conversion to the semicarbazone. The manganese dioxide was filtered off, the water solution concentrated on the steam-bath to 200-ml. volume and acidulated. The crystalline acids (6.0 g.) were recrystallized once from water, dried, and digested with hot benzene, the insoluble portion (2.5 g.) being 2,5-thiophenedicarboxylic acid.

Anal. Calcd. for $C_6H_4O_4S$: neut. equiv., 172. Found: neut. equiv., 178.

The dicarboxylic acid was converted to the dimethyl ester by standard procedures. After two recrystallizations from methyl alcohol it melted at 147-148° (lit.[6] reports 151°).

2-Thiophenecarboxylic acid, 3.5 g., was obtained by evaporation of the benzene solution. After recrystalliza-

---

[5] Reichstein, *Helv. Chim. Acta*, **13**, 349 (1930).

[6] Demuth, *Ber.*, **18**, 3024 (1885).

tion from water it melted at 128–129°. A mixed melting point with an authentic sample (m. p. 129–130°) melted at 128–129°.

Reaction of Hydroxylamine Hydrochloride and Formaldehyde with 2-Chlorothiophene.—To a mixture of 30 g. (0.26 mole) of 2-chlorothiophene and 21 g. (0.25 mole) of 36% formaldehyde solution was added 17.5 g. (0.25 mole) of hydroxylamine hydrochloride. The temperature rose from 28 to 36°. The mixture was boiled under reflux at 94° for thirty minutes and allowed to cool slowly to room temperature. After standing sixteen hours, 16 g. of crystals were filtered off. These were washed with benzene, dried and analyzed without further purification. They correspond within fair limits to 5-chloro-2-thenylhydroxylamine hydrochloride.

Anal. Calcd. for C_5H_6ClNOS: S, 16.0; N, 7.0. Found: S, 16.1; N, 6.5.

The benzene washings of the filtrate and crystalline material were combined and the soluble amine hydrochloride obtained by evaporation of the benzene, yielding 24 g. of a red viscous oil that contained 5.8% nitrogen.

Reaction of Hydroxylamine Hydrochloride with Formaldehyde and 2-*t*-Butylthiophene.—In a similar manner to 2-chlorothiophene above, a 0.25-mole run was made with 2-*t*-butylthiophene. The crystalline amine hydrochloride, 23 g., upon analysis appeared to be a mixture of 5-*t*-butyl-2-thenylhydroxylamine hydrochloride and di-(5-*t*-butyl-2-thenyl)-hydroxylamine hydrochloride. The benzene soluble portion, 53 g., which was an orange viscous oil, upon analysis was indicated to be a mixture of the two above-mentioned compounds perhaps complicated with amines of type III or IV.

Anal. Calcd. for $C_9H_{16}ClNOS$: Cl, 16.1; N, 6.3; S, 14.4. Calcd. for $C_{18}H_{28}ClN_2OS_2$: Cl, 10.0; N, 3.9; S, 17.7. Found for crystalline product: Cl, 13.1; N, 5.3; S, 15.3. Found for benzene-soluble product: Cl, 11.8; N, 5.1; S, 15.7.

Reaction of Hydroxylamine Hydrochloride and Formaldehyde with Furan.—To a mixture of 68 g. (1 mole) of furan and 70 g. (1 mole) of hydroxylamine hydrochloride cooled to 20° was slowly added 81 g. (0.95 mole) of 36% formaldehyde over a period of one hour. The temperature meanwhile rose to 32°. The reaction mixture was stirred for one hour longer, cooled and neutralized with 40% sodium hydroxide solution. Fifty-four grams of a brown oily product containing 8.6% nitrogen was extracted from the neutralized mixture with benzene.

Reaction of Hydroxylamine Hydrochloride and Formaldehyde with Phenol.—To 47 g. (0.5 mole) of phenol and 35 g. (0.5 mole) of hydroxylamine hydrochloride was added 42 g. (1.5 mole) of 36% formaldehyde solution. The temperature was maintained between 20 and 30° by means of an ice-bath. After the heat of reaction subsided the mixture was heated slowly from 20 to 58° over a period of five hours. After cooling the mixture was neutralized with 40% sodium hydroxide solution and 56 g. of a viscous red oil was extracted with benzene which, when analyzed, contained 6.3% nitrogen.

Reaction of Hydroxylamine Hydrochloride and Formaldehyde with Acetone.—To 58 g. (1 mole) of acetone and 83 g. (1 mole) of 36% formaldehyde solution was added 70 g. (1 mole) of hydroxylamine hydrochloride. The temperature rose from 25° to the reflux temperature, 70°, and had to be controlled at 70° by means of an ice-bath. The mixture was allowed to cool to room temperature, was neutralized with 40% sodium hydroxide solution, and extracted with benzene to yield 27 g. of a yellow viscous oil that contained 10.4% nitrogen. The yellow oil gave a 2,4-dinitrophenylhydrazone, m. p. 178–180° (uncor.). This indicates that the carbonyl group is still intact and reaction took place with the methyl group.

Acknowledgments.—The author is grateful to Mr. Everett H. Murray, Jr., for technical assistance and to Dr. Darwin E. Badertscher for his advice and interest in this problem. The method used in converting di-(2-thenyl)-hydroxylamine to N-(2-thenyl)-2′-thenaldimine was suggested by Dr. John W. Schick.

Summary

1. Hydroxylamine salts and formaldehyde have been found to undergo a reaction of the Mannich type with thiophene, furan, phenol, and acetone. No attempt was made to identify any of the products from phenol, furan and acetone.

2. 2-Thenylhydroxylamine, di-(2-thenyl)-hydroxylamine, di-(5-hydroxymethyl-2-thenyl)-hydroxylamine and other amines of unknown constitution have been prepared for the first time from the reaction of hydroxylamine hydrochloride and formaldehyde with thiophene.

3. These amines lose water easily to give imine type structures which polymerize rapidly to resinous products.

4. N-(2-Thenyl)-2′-thenaldimine has been prepared for the first time and some of its physical constants ascertained.

PAULSBORO, N. J. RECEIVED JANUARY 8, 1947