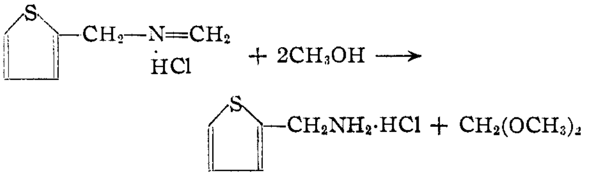
[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, A DIVISION OF SOCONY-VACUUM OIL CO., INC., RESEARCH AND DEVELOPMENT DEPARTMENT]

Aminomethylation of Thiophene. III.[1,2] Improved Synthesis of the 2-Thenylamines

BY HOWARD D. HARTOUGH AND SEYMOUR L. MEISEL

The reactivity of the methylene radical in N-(2-thenyl)-formaldimine has been demonstrated previously.[2] It has also been shown that in the aminomethylation of thiophene the 2-thenylamine (I) is formed as a secondary product by the reaction of N-(2-thenyl)-formaldimine (II) with thiophene and not as a primary product as originally believed. Di-(2-thenyl)-amine (III) was also shown to form in this reaction when acetic acid was present in the mixture.

It has now been found that if methanol is added to the reaction mixture after completing the reaction of thiophene, formaldehyde and ammonium chloride, the methylene group of N-(2-thenyl)-formaldimine is cleaved and 2-thenylamine is formed in 40–60% yields.



This reaction has been extended to 2-methylthiophene, 3-methylthiophene and 2-chlorothiophene. The yield of primary amine in some cases was not as great as might be expected. However, further study of the reaction variables should improve these yields.

It is of some significance to note that from 3-methylthiophene only the 3-methyl-2-thenylamine could be isolated. From prior work on the orientation of 3-methylthiophene[3,4] some of the 3-methyl-5-thenylamine would be expected.

When using aqueous formaldehyde to prepare 2-thenylamine, considerable amounts of a higher boiling liquid were isolated. This material on oxidation gave 2,5-thiophenedicarboxylic acid. Analysis of the phenylthiourea of this substance indicated that it was N-methyl-N-(5-hydroxymethyl-2-thenyl)-amine. The formation of a nuclear methylol group in the reaction of thiophene, formaldehyde and hydroxylamine hydrochloride has been previously reported.[5]

Little, if any, pure III is formed in this reaction. Compounds boiling in the range of III are present but in such minor amounts that they have not been purified sufficiently for characterization. However, it was found that if the reaction is carried out using polymeric formaldehyde and a little acetic acid as a catalyst, good yields of III are obtained by treating the reaction mixture with methanol to convert all of II to I. In this manner, yields of III as high as 40% were also obtained.

2,5-bis-(Aminomethyl)-thiophene has not been isolated although its precursor, 2,5-bis-(methyleneiminomethyl)-thiophene, has been shown to be present.[2] Its solubility in water may be so great that it is not extracted from the reaction mixture with ether.

Experimental

2-Thenylamine.—To 420 g. (5 moles) of thiophene were added 1670 g. (20 moles) of 36% formaldehyde and 535 g. (10 moles) of ammonium chloride. The well-stirred mixture was heated until a temperature of 60° was reached. Heating was discontinued and the temperature was allowed to rise to 65°. The reaction temperature was maintained between 64 and 65° by means of an ice-bath. After thirty-five minutes the temperature began to fall. The temperature range is quite critical since too high a temperature will produce larger amounts of high boiling materials and too low a temperature will result in an incomplete reaction.

After the reaction mixture had cooled to room temperature, 1500 ml. of methanol was added. The mixture was stirred for an additional two hours and then allowed to stand overnight.

The alcohol was removed by steam distillation and the mixture was neutralized with 40% caustic (10 moles) and extracted with ether. The ether layer was dried over Drierite, and the ether removed by distillation. The residue was distilled through a Claisen-type distilling head to yield 255 g. (45%) of 2-thenylamine, b. p. 63–65° (4 mm.), n^{20}_{D} 1.5628, and 45 g. of higher boiling material, b. p. 100–135° (4 mm.).

When theoretical amounts of formaldehyde and ammonium chloride are used the yields range from 50–60% based on reacted thiophene. However, less than 50% of the thiophene reacts. With the above procedure no thiophene is recovered.

The higher boiling material formed from this reaction was partially investigated. Oxidation of a redistilled center cut, b. p. 123–124°, n^{30}_{D} 1.5578, gave 2,5-thiophenedicarboxylic acid, m. p. 358–359°. A mixed melting point with an authentic sample[6] gave no depression. This cut yielded a phenylthiourea, m. p. 98.5–99° after three recrystallizations from alcohol, whose analyses indicated that the cut was N-methyl-N-(5-hydroxymethyl-2-thenyl)-amine.

Anal. Calcd. for $C_{14}H_{16}N_2OS_2$: C, 57.53; H, 5.48; N, 9.63; S, 21.92. Found: C, 57.28; H, 5.61; N, 9.76; S, 21.92.

2-Thenylamine and Di-(2-thenyl)-amine.—If paraformaldehyde is substituted for 36% formaldehyde solution and acetic acid is added, appreciable amounts of di-(2-thenyl)-amine are obtained when the reaction is carried out as described above. From 420 g. of thiophene, 300 g. of paraformaldehyde, 265 g. of ammonium chloride and 100 ml. of acetic acid there was obtained 110 g. of 2-thenylamine (19%) and 195 g. of di-(thenyl)-amine (38%), b. p. 162–165° (5 mm.). The hydrochloride of di-(2-thenyl)-amine melted at 250–251° and gave no depression with the hydrochloride of an authentic sample.

5-Methyl-2-thenylamine.—A mixture of 196 g. of 2-methylthiophene, 336 g. of 36% formaldehyde and 108 g.

---

[1] Paper I in this series, Hartough, Lukasiewicz and Murray, THIS JOURNAL, **70**, 1146 (1948).

[2] Paper II, Hartough, Koft, Meisel and Schick, *ibid.*, **70**, 4013 (1948).

[3] Hartough and Kosak, *ibid.*, **69**, 3093 (1947).

[4] Schick and Hartough, *ibid.*, **70**, 1645 (1948).

[5] Hartough, *ibid.*, **69**, 1355 (1947).

[6] Prepared by alkaline permanganate oxidation of 5-methyl-2-thiophenecarboxylic acid.

TABLE I

DERIVATIVES OF 2-THENYLAMINES

Derivative thenylamine	Hydrochloride				Phenylthiourea				Picrate			
	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2-Thenylamine	188–189	C_5H_8ClNS	[a]	[a]	123.5–124	$C_{12}H_{12}N_2S_2$	[a]	[a]	181–182	$C_{11}H_{10}N_4O_7S$	16.38	16.21
5-Methyl-2-	197–198	$C_6H_{10}ClNS$	8.59	8.68	133–134	$C_{13}H_{14}N_2S_2$	[a]	[a]	201–202[b]	$C_{12}H_{12}N_4O_7S$	15.75	15.29
3-Methyl-2-	224–226[b]	$C_6H_{10}ClNS$	8.59	8.68	137–138	$C_{13}H_{14}N_2S_2$	10.68[c]	10.90[c]	[d]	$C_{12}H_{12}N_4O_7S$	15.75	15.47
5-Chloro-2-	280–282[b]	$C_5H_7Cl_2NS$	7.61	7.37	119.5–120	$C_{12}H_{11}ClN_2S$	9.83	9.83	201–202[b,e]	$C_{11}H_9ClN_4O_7S$	14.89	14.91
t-Butyl-2-[g]	[f]				129–130	$C_{16}H_{20}N_2S_2$	9.24	9.43[h]	[f]			

[a] Previously analyzed in Ref. 1. [b] Closed tube, decomposes. [c] Calcd.: S, 24.42. Found: S, 24.48. [d] Turns brown at 190°, black at 207°; no definite melting point observed. [e] Turns brown at 197°. [f] Could not be isolated as a crystalline product. [g] The α-naphthylurea was also made, m. p. 185–186°. *Anal.* Calcd. for $C_{20}H_{22}N_2OS$: N, 8.28. Found: N, 8.55. [h] Calcd.: C, 63.16; H, 6.57; S, 21.05. Found: C, 63.51; H, 6.84; S, 21.19.

of ammonium chloride was stirred for four hours. The temperature was maintained at 35–40° by means of an ice-bath. During the reaction crystals of di-(5-methyl-2-thenyl)-amine hydrochloride precipitated. These were separated from the mixture and crystallized from water; yield, 150 g. (57%); m. p. 216–217°.[7] The reaction mixture, at this point, was worked up according to the procedure described for 2-thenylamine. About 40 g. of amine was obtained; yield 16%; b. p. 67–68° (3 mm.); $n^{20}D$ 1.5514.

5-Chloro-2-thenylamine.—To 119 g. of 2-chlorothiophene was added 60 g. of paraformaldehyde, 54 g. of ammonium chloride and 20 g. of glacial acetic acid. The mixture was stirred for two hours at 70–75° and then allowed to cool. As cooling proceeded crystals of di-(5-chloro-2-thenyl)-amine hydrochloride precipitated. These were removed and digested with hot water to remove the ammonium chloride. About 26 g. of the hydrochloride was obtained, m. p. 238–240°.[8]

Unreacted 2-chlorothiophene (50 g.) was recovered from the filtrate.

Sixteen grams (18% based on reacted 2-chlorothiophene) of 5-chloro-2-thenylamine was obtained by previously described procedures; b. p. 69–71° (2 mm.); $n^{20}D$ 1.5630.

3-Methyl-2-thenylamine.—The procedure used was exactly the same as that used for 2-thenylamine except that no initial heating was necessary. The temperature was maintained at 45–50° by means of an ice-bath for forty-five minutes. From 496 g. of 3-methylthiophene there was obtained 207 g. (33°) of 3-methyl-2-thenylamine; b. p. 78° (4 mm.); $n^{20}D$ 1.5606.

The 3-methyl-2-thenylamine was oxidized to 3-methyl-2-thiophenecarboxylic acid, m. p. 146–147°, by the method described by Rinkes[9] (32%). A mixed melting point with authentic 3-methyl-2-thiophenecarboxylic acid[10] gave no depression. All attempts to find a second isomer were unsuccessful.

***t*-Butyl-2-thenylamine.**[11]—The procedure used for the preparation of *t*-butyl-2-thenylamine is the same as that for 2-thenylamine with the exception that the *t*-butyl-2-thenylamine as the hydrochloride is soluble in the *t*-butylthiophene layer rather than in the aqueous layer. From 140 g. of *t*-butylthiophene, 166 g. of 36% formaldehyde and 53.6 g. of ammonium chloride 68 g. of unreacted *t*-butylthiophene was recovered and there was obtained 29 g. of material, b. p. 75–82° (2 mm.), $n^{20}D$ 1.5048 and 5 g. of higher boiling material, b. p. 100–125° (2 mm.), $n^{20}D$ 1.5230. The first cut undoubtedly contains material other than *t*-butyl-2-thenylamine since in making derivatives very low yields were obtained. Higher boiling cuts were not investigated.

Since the thenylamines have a tendency to react with carbon dioxide very readily and form carbamates, they were all analyzed as their derivatives. The carbamate of 2-thenylamine was made by allowing a thin layer of the amine on a watch glass to stand in air. Since the carbamate decomposed when attempts were made to recrystallize it from solvents, it was purified by sublimation; m. p. 83–85°.

Anal. Calcd. for $C_6H_7NO_2S$: N, 8.92. Found: N, 9.09.

Properties of some of the derivatives of the thenylamines appear in the following table. The phenylthioureas and picrates were prepared by standard procedures.[12] The hydrochlorides were prepared in an alcoholic-aqueous acid mixture and precipitated with ether. They were recrystallized from an alcoholic-ether mixture.

Acknowledgment.—The authors are grateful to Dr. Darwin E. Badertscher for advice and interest in this work.

Summary

A new and improved synthesis of the 2-thenylamines has been developed through the aminomethylation reaction and a mechanism is proposed. Three new thenylamines have been prepared and characterized. 3-Methylthiophene orientated exclusively to the 2-position in this reaction. Hydrochlorides, phenylthioureas, and picrates of these amines were prepared and characterized.

PAULSBORO, NEW JERSEY RECEIVED JULY 7, 1948

---

[7] Ref. 1 lists m. p. of 216–217°.

[8] Ref. 1 lists m. p. of 240–242°.

[9] Rinkes, *Rec. trav. chim.*, **53**, 543 (1934).

[10] Hartough and Conley, THIS JOURNAL, **69**, 3097 (1947).

[11] The *t*-butylthiophene used in this experiment was found to contain about equimolar quantities of the 2- and 3-*t*-butylthiophenes.

[12] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1945, pp. 148, 149.