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PREPARATION OF THIOPHENE-2-ALDEHYDE AND SOME SUBSTITUTED THIOPHENE ALDEHYDES[1]

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In the course of studies on the catalytic condensation of carbonyl compounds conducted in this laboratory (1), it was found necessary to prepare thiophene-2-aldehyde as well as certain substituted thiophene aldehydes. The methods for preparing these compounds as recorded in the literature are tedious and result in either low or, at best, fair yields. In Table I are summarized the data on the most important procedures applied in the literature.

The utilization of N-methylformanilide in the presence of phosphorus oxychloride for the production of aldehydes has been found applicable with certain carbocyclic and heterocyclic compounds containing particularly reactive positions (12). Since the nuclear sulfur atom in thiophene activates the α-hydrogen atoms, it was thought that this method might be useful in the thiophene series. It was found that thiophene-2-aldehyde could be obtained in 65–70% yields by this procedure, and various substituted thiophene aldehydes in yields ranging from 45 to 85%.

The aldehydes, upon analyses of freshly distilled samples, gave slightly too high values for carbon (range 0.4–0.7%). Therefore, the semicarbazones and acids of these compounds were prepared, and gave entirely satisfactory analyses. The positions of the constituents on the thiophene ring were determined by converting the aldehydes to the corresponding known thiophene carboxylic acids by alkaline permanganate oxidation. The collected data on the compounds prepared are recorded in Table II.

In the application of the N-methylformanilide synthesis to 2-bromothiophene, 5-chlorothiophene-2-aldehyde, instead of the expected 5-bromothiophene-2-aldehyde, was obtained, due to the replacement of the bromine atom by chlorine.

The presence of alkyl substituents on the thiophene ring gave rise to higher yields of the aldehyde than was the case with thiophene itself. This is to be expected, as the alkyl groups enhance the activity of the free α-position in the ring and tend to prevent side reactions. On the other hand, the presence of halogen on the ring made the replacement more difficult, and the reaction mixture had to be heated for a longer period of time; furthermore, the over-all yields were somewhat lower. The entering aldehyde group occupied the α-position adjacent to the nuclear sulfur, and in no case was the β-aldehyde isomer obtained.

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Attempts to utilize the N-methylformanilide synthesis with 2-nitrothiophene, 2-acetylthiophene, and thianaphthene (benzothiophene) were of no avail. However, it was found possible to prepare thianaphthene-3-aldehyde by the following procedure. Chloromethylation of thianaphthene, although previously reported unsuccessful (15), was effected by employing the method of Darzens

TABLE I

PREPARATION OF THIOPHENE ALDEHYDES AS RECORDED IN LITERATURE

AUTHORS	METHOD	COMPOUND PREPARED	YIELD
Biedermann (2) Barger and Easson (3) du Vigneaud *et al.* (4)	Acetylation of thiophene to yield 2-acetylthiophene. Then alkaline permanganate oxidation of 2-acetylthiophene followed by decarboxylation of the resulting 2-thiopheneglyoxylic acid.	Thiophene-2-aldehyde	40–50% based on thiophene
du Vigneaud *et al.* (4) Grishkevich-Trokimovskii (5) Vlastelitza (6) Weygand (7) Gattermann (8)	Iodination of thiophene followed by the action of magnesium and ethyl orthoformate on 2-iodothiophene to yield thiopheneal-dehyde acetal. Acid hydrolysis yields the free aldehyde.	Thiophene-2-aldehyde 5-Methyl thiophene-2-aldehyde 5-Bromothiophene-2-aldehyde	30–40% based on thiophene 10% based on dibromothiophene
Reichstein (9)	Thiophene, HCN, HCl, an hydrous aluminum chloride at low temperature.	Thiophene-2-aldehyde	10% based on thiophene
Barger and Easson (3)	Rosenmund reduction of 2-thenoyl chloride.	Thiophene-2-aldehyde	10–20% based on thenoyl chloride
Dunn, Waugh, and Dittmer (10) Blicke and Leonard (11)	Thiophene, HCl, and formaldehyde with cooling to yield 2-thienyl chloride. Formation of addition compound with urotropine and subsequent hydrolysis to yield thiophene-2-aldehyde.	Thiophene-2-aldehyde	20–25% based on thiophene

and Lévy (16) with modifications. Then, by formation and subsequent hydrolysis of the urotropine addition product of 3-chloromethylthianaphthene, thianaphthene-3-aldehyde was obtained. Because attempts to chloromethylate 2-nitrothiophene and 2-acetylthiophene proved unsuccessful, this procedure could not be used to obtain the aldehydes from these compounds.

The *one step* synthesis of thiophene aldehydes with good yields should greatly simplify the preparation of certain compounds, in which a benzene ring is re-

TABLE II

THIOPHENE ALDEHYDES PREPARED BY N-METHYLFORMANILIDE SYNTHESIS

STARTING MATERIAL	ALDEHYDE							SEMICARBAZONE			ACID					
	Product	Yield, %	B.P. °C/mm.	Anal.				M.P. °C	Anal.		M.P. °C	M.P. in Lit. °C	Anal.			
				Calc'd		Found			Cac'd N%	Found N%			Calc'd		Found	
				C%	H%	C%	H%						C%	H%	C%	H%
Thiophene	Thiophene-2-aldehyde	65–70	66–67/4	53.55	3.59	53.95	3.75	220–221 [a]	24.83	24.97	129–130	129–130 [b]	46.86	3.14	46.75	3.10
2-Methylthiophene	5-Methylthiophene-2-aldehyde	80–85	81–82/6	57.11	4.80	57.64	4.71	207–208	22.93	23.03	137–138	137–138 [b]	50.69	4.26	50.93	4.07
3-Methylthiophene	3-Methylthiophene-2-aldehyde	80–85	83–85/5	57.11	4.80	57.50	4.50	208–209	22.93	22.99	147–148	147–148 [b]	50.69	4.26	50.86	4.31
2-Ethylthiophene	5-Ethylthiophene-2-aldehyde	75–80	91–92/5	59.97	5.75	60.70	5.17	194–195	21.30	21.43	71	71 [c]	53.85	5.15	53.77	4.94
2-Propylthiophene	5-Propylthiophene-2-aldehyde	80–85	108–109/5	62.30	6.54	63.03	6.33	186–187	19.89	19.85	58	57 [c]	56.44	5.92	56.31	5.68
2-Chlorothiophene	5-Chlorothiophene-2-aldehyde	50–55	89–90/6.5	40.96	2.06	41.50	2.37	199–200	20.63	20.78	152–153	153–153.5 [b]	36.93	1.86	37.18	1.94

[a] Ref. (9) gives m.p. 227–228°; Ref. (5) gives m.p. 213°; Ref (21) gives m.p. 218–219° (uncor.).
[b] Ref. (13).
[c] Ref. (14).

placed by a thiophene or substituted thiophene ring. For example, β-2-thienylalanine, the isostere of phenylalanine has been prepared from thiophene-2-aldehyde, and used in biological and metabolic studies (3, 4).

EXPERIMENTAL

Materials. Thiophene, 3-methylthiophene, and 2-acetylthiophene were obtained through the courtesy of Dr. W. M. Holaday and Dr. G. A. Harrington of the Socony Vacuum Oil Company; thianaphthene, 2-chlorothiophene, 2-methylthiophene, and 2-nitrothiophene through the courtesy of Dr. L. C. Kemp, Jr. and his associates of the Texas Company; 2-chloro- and 2-bromo-thiophene through the courtesy of the Michigan Chemical Corporation; and 2-nitrothiophene through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company. 2-Ethyl- and 2-propyl-thiophene were prepared by a modified Wolff-Kishner reduction of the semicarbazones of 2-acetyl- and 2-propanoyl-thiophene (18). 2-Propanoylthiophene was prepared according to Hartough and Kosak (19).

General procedure for the preparation of thiophene aldehydes. The procedure utilized was essentially the same for all of the thiophene compounds with the exception of 2-chloro- and 2-bromo-thiophene.

Thiophene-2-aldehyde. Thiophene (21 g., 0.25 mole), 48 g. of phosphorus oxychloride (0.31 mole), and 45 g. of N-methylformanilide (0.32 mole) were mixed in a 500-cc. round-bottom flask fitted with a ground glass reflux condenser. The reaction is exothermic, and, if the mixture is allowed to stand for some time, the temperature will slowly rise. However, to reduce the time, it was customary to heat the preparation cautiously on a steam-bath until evolution of hydrogen chloride gas commenced. At this point, heating was discontinued and cooling immediately applied to prevent excessive decomposition. With larger quantities of reactants, some care must be exercised, as insufficient cooling at this point will lower the yield considerably. After the initial reaction had subsided, the reaction mixture was heated for twenty minutes on a steam-bath to complete the reaction. At the end of this period, cooling was again applied and the contents of the flask carefully neutralized with excess aqueous sodium acetate. The mixture was then steam distilled, the distillate extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over anhydrous sodium sulfate, and rectified. There was obtained 19 g. (68%) of thiophene-2-aldehyde (b.p. 66–67°/4 mm.). The semicarbazones and acids were prepared according to methods already described (17). The acids were purified by recrystallization from water, and finally by sublimation *in vacuo*. The semicarbazones were recrystallized from alcohol.

5-Chlorothiophene-2-aldehyde. 2-Chlorothiophene (35.6 g., 0.3 mole), 66 g. of phosphorus oxychloride (0.43 mole), and 58 g. of N-methylformanilide (0.43 mole) were mixed in a 500-cc. round-bottom flask fitted with a ground glass reflux condenser. Heating on a steam-bath caused only slight evolution of HCl. Therefore, heating was continued with a free flame until the reaction began. The reaction was allowed to proceed without cooling, and after the initial vigorous reaction had subsided, the mixture was heated on a steam-bath for one hour. Following the same isolation procedure described above, there was obtained 22.5 g. (51%) of 5-chlorothiophene-2-aldehyde, (b.p. 89–90°/6.5 mm.). A small prerun of 2-chlorothiophene (3 g.) was recovered during rectification.

When 2-bromothiophene was used as a starting product, 5-chlorothiophene-2-aldehyde was obtained. In this case, 32.58 g. of 2-bromothiophene (0.2 mole), 52 g. of phosphorus oxychloride (0.33 mole), and 45 g. of N-methylformanilide (0.33 mole) were brought into reaction. Heating on a steam-bath caused a vigorous evolution of HCl, and cooling was applied. After the reaction had subsided, the flask was heated on a steam-bath for 1 hour. Following the usual isolation procedure, there was obtained 17 g. of 5-chlorothiophene-2-aldehyde (58%), (b.p. 88–91°/6 mm.). The semicarbazone and acid prepared from this compound showed no depression of melting point when mixed with authentic samples obtained from 5-chlorothiophene-2-aldehyde.

3-Chloromethylthianaphthene. Dry HCl was passed into a suspension of 43 g. of trioxymethylene in 512 g. of acetic acid, until 58 g. was absorbed. Then 134 g. (1 mole) of thianaphthene was added to the clear solution. The solution became warm, and was placed in the icebox overnight. The mixture was then poured into 2 l. of water and extracted with ether. After washing the ether extract with water and 5% sodium bicarbonate solution, drying over sodium sulfate, and rectifying, there was obtained 120 g. of 3-chloromethylthianaphthene, (b.p. 149–156°/11 mm.). Refractionation yielded 116 g. (63%), (b.p. 152–153°/11 mm.) (m.p. 39–40°).

Anal. Calc'd for C_9H_7ClS: Cl, 19.41. Found: Cl, 19.24.

Thianaphthene-3-aldehyde. 3-Chloromethylthianaphthene (18.25 g., 0.1 mole), 14.02 g. of urotropine (0.1 mole), and 100 cc. of chloroform were refluxed for 1 hour. At the end of this time, the crystalline addition product was filtered off, air dried, and decomposed with 300 cc. of water. The solution was steam distilled and the thianaphthene-3-aldehyde came over slowly. The distillate was extracted with ether, the ether extract washed with water, 5% sodium bicarbonate solution and water again, dried over sodium sulfate, and the ether removed. There was obtained 5.1 g. (31%) of thianaphthene-3-aldehyde. Recrystallization from alcohol gave white crystals, (m.p. 58°). Komppa and Weckman (20) reported 58°.

Anal. Calc'd for C_9H_6OS: C, 66.63; H, 3.73.
Found: C, 66.88; H, 3.68.

SUMMARY

1. The N-methylformanilide synthesis has been shown to be applicable to the preparation of thiophene-2-aldehyde and some substituted thiophene aldehydes.

2. The following aldehydes and their semicarbazones, which are not listed in the literature, were prepared: 3-methylthiophene-2-aldehyde, 5-ethylthiophene-2-aldehyde, 5-propylthiophene-2-aldehyde, and 5-chlorothiophene-2-aldehyde.

3. 3-Chloromethylthianaphthene was prepared by chloromethylation of thianaphthene. Thianaphthene-3-aldehyde was obtained from 3-chloromethylthianaphthene.

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