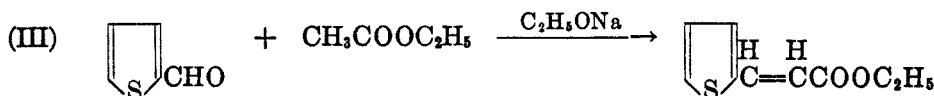
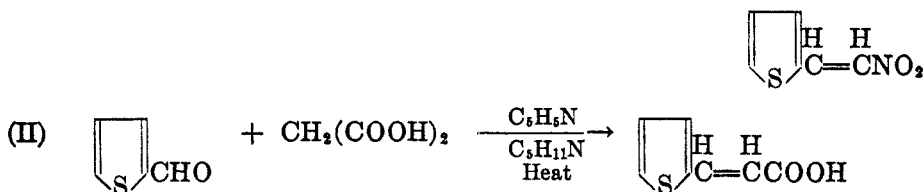
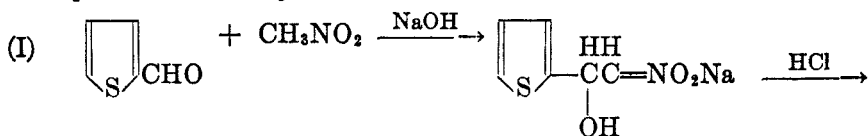


STUDIES IN THE THIOPHENE SERIES. III. CONDENSATIONS OF THIOPHENEALDEHYDES¹

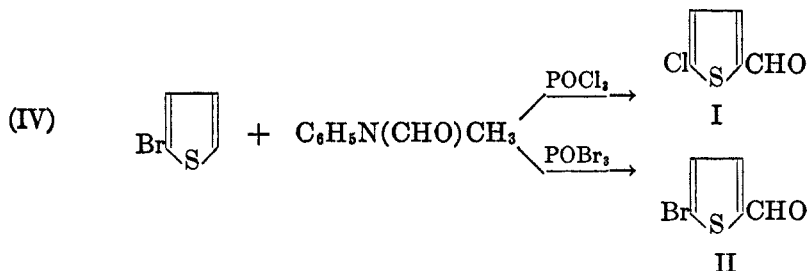
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In continuation of studies in the thiophene series (1a, b) conducted in this laboratory, it was decided to apply some typical aromatic aldehyde condensations to thiophenealdehydes to determine the feasibility of these reactions and the effect of various substituent groups. The syntheses reported in this communication include condensations with nitromethane and nitroethane and subsequent dehydration of the nitro alcohol to yield unsaturated nitro compounds; the Perkin reaction (Doebner modification) to yield acrylic acids and the Claisen condensation to give acrylic esters. These reactions may be indicated for 2-thiophenecarboxaldehyde as follows:



As mentioned in the first paper of this series, in using N-methylformanilide and phosphorus oxychloride for the preparation of thiophenealdehydes, it was found that starting with 2-bromothiophene a replacement of the bromine atom took place, yielding mainly 5-chloro-2-thiophenecarboxaldehyde (I). However, if phosphorus oxybromide was substituted for the oxychloride, it was possible to obtain 5-bromo-2-thiophenecarboxaldehyde (II) in yields of 50-55%:



¹ This investigation was aided, in part, by a grant from the Office of Naval Research. The analyses were carried out by M. Bier of this Department.

In the condensations of the thiophenealdehydes with nitromethane, it was found that upon dehydration of the reaction products with hydrochloric acid the normal unsaturated nitro compounds were obtained. It has been previously reported (2) that the condensation of 2-thiophenecarboxaldehyde with nitromethane yielded a bright yellow volatile crystalline substance in 20% yield, which was considered to be the analog of ω -nitrostyrene. However, neither experimental details of the preparation nor an analysis of the compound were

TABLE I
CONDENSATION PRODUCTS OF THIOPHENEALDEHYDES AND NITROPARAFFINS

ALDEHYDE	CONDENSATION PRODUCT	YIELD, %	M.P., °C	ANAL.					
				Calc'd			Found		
				C	H	N	C	H	N
2-Thiophene carboxaldehyde	ω -Nitro-2-vinylthiophene	78	79-80 ^a	46.44	3.25	9.03	46.62	3.28	8.89
2-Thiophene carboxaldehyde	1-(2-thienyl)-2-nitropropene	44	68.5	49.69	4.17	8.28	49.77	4.38	8.24
3-Methyl-2-thiophene carboxaldehyde	3-Methyl- ω -nitro-2-vinylthiophene	14	66-67	49.69	4.17	8.28	49.81	4.26	8.12
5-Methyl-2-thiophene carboxaldehyde	5-Methyl- ω -nitro-2-vinylthiophene	48	79-81	49.69	4.17	8.28	49.90	4.31	8.29
5-Ethyl-2-thiophene carboxaldehyde	5-Ethyl- ω -nitro-2-vinylthiophene	32	56-57 ^b	52.44	4.95	7.65	52.70	5.23	7.85
5-Propyl-2-thiophene carboxaldehyde	5-Propyl- ω -nitro-2-vinylthiophene	26	36.5 ^b	54.79	5.62	7.10	54.60	5.64	7.25
5-Chloro-2-thiophene carboxaldehyde	5-Chloro- ω -nitro-2-vinylthiophene	72	84.5-85	38.01	2.14	7.40	38.20	2.28	7.60
5-Bromo-2-thiophene carboxaldehyde	5-Bromo- ω -nitro-2-vinylthiophene	69	91-92	30.78	1.72	5.99	31.10	2.03	6.18

^a Probably same compound reported in Ref. (2) in 20% yield; m.p. 79-83°.

^b Obtained from reaction mixture as oils, which were taken up in alcohol and crystallized upon cooling.

presented. By following the standard method (3) for the condensation of aldehydes and nitroparaffins, we obtained ω -nitro-2-vinylthiophene in 78% yield as well as various other substituted ω -nitrovinylthiophenes. It was also found possible to condense nitroethane with 2-thiophenecarboxaldehyde, but 1-nitropropane did not condense under the conditions employed, probably due to the lower reactivity of the active hydrogen in this compound. Table I summarizes the data available on these compounds.

The aldehyde-nitroparaffin condensation products listed in Table I were prepared by using dilute sodium hydroxide as the condensing agent. Previous

work from this laboratory (4) indicated that coordination compounds of the type $Mg[Al(OC_2H_5)_4]_2$ can be applied as catalytic agents in this type of condensation. While it was found that ω -nitrovinylthiophene could be obtained, the yields (20–30%) and the formation of tarry products lessen the effective use of this type of catalyst with thiophenealdehydes.

The yields reported in Table I indicate that the activity of the carbonyl group of the substituted thiophenealdehydes in this reaction is similar to the trends observed with substituted benzaldehydes (5). That is, a compound containing a halogen group in the *para* position will give approximately the same yield as the unsubstituted aldehyde, while a methyl group in any position will decrease the yield and this effect falls off in the order *ortho* > *para*. The lower yields obtained with the ethyl and propyl substituted aldehydes may be due to the fact that the resulting nitro compounds are low melting and are obtained as oils which crystallize with difficulty.

The Perkin reaction itself, using acetic anhydride and sodium acetate, does not work effectively with 2-thiophenecarboxaldehyde (6). However, the Doebner modification with malonic acid in pyridine solution gives excellent yields of 2-thienylacrylic acid (2). In applying this reaction to the substituted thiophenealdehydes, it was found that uniformly high yields of the corresponding acrylic acids in the range of 80–85% could be obtained.

The Claisen condensation utilizing sodium ethoxide and ethyl acetate to yield acrylic esters has not been previously applied to the thiophenealdehydes. Since in many cases in synthetic work it is advantageous to obtain the ester directly, it was deemed suitable to investigate this synthesis. It was found that it was better to run the reaction at a lower temperature than in the benzene series; for example at 0–5°, the yield of ethyl β -(2-thienyl)acrylate was 35%, while at –10 to –15° the yield was 49%. Table II summarizes the data on the acrylic acids and esters prepared.

The Claisen synthesis is not so successful as the Doebner modification, neither from the viewpoint of yields nor of convenience. Even when the temperature is kept at –10 to –15°, a rather large amount of tarry residue results from the Claisen condensation. The substituent groups apparently have no effect on the Doebner modification, while in the ester synthesis the maximum yields are obtained from the alkyl substituted aldehydes. In the case of the chloroaldehyde it was not found possible to obtain the acrylic ester directly, the main product being 5-chloro-2-thiophenecarboxylic acid.

In general, it appears that the reactions of the thiophenealdehydes are very similar to those exhibited by benzaldehydes and that the substituents exert a similar effect in both series. Previous workers have shown that thiophenealdehydes undergo such transformations as the simple and crossed Cannizzaro reactions (7), the Claisen-Schmidt condensation with ketones (8), and reactions with other compounds containing an active hydrogen atom such as hippuric acid and hydantoin (2). The benzoin condensation has also been applied to 2-thiophenecarboxaldehyde (1b). The reactions as covered in the present communication give further evidence that the thiophenealdehydes enter into the normal reactions characteristic of the aromatic aldehyde function.

TABLE II
ACRYLIC ACIDS AND ESTERS FROM THIOPHENEALDEHYDES

STARTING ALDEHYDE	ACRYLIC ACIDS					ACRYLIC ESTERS ^d							
	YIELD %	M.P., °C	ANAL.		ANAL.	YIELD %	B.P., °C/MM.	d ₄ ²⁰	n _D ²⁰	ANAL.			
			Calc'd	Found						Calc'd	Found		
		C	H	C	H	C	H	C	H	C	H		
2-Thiophenecarboxaldehyde	85	143-144 ^a	54.52	3.92	54.30	3.98	110-116/3.5	1.1439	1.5868	59.32	5.53	59.20	5.67
5-Methyl-2-thiophenecarboxaldehyde	82	165-166	57.12	4.79	57.20	4.75	116-122/5	1.1218	1.5834	61.19	6.16	61.26	6.21
3-Methyl-2-thiophenecarboxaldehyde	80	172-173	57.12	4.79	57.30	4.84	121-126/3	1.1365	1.5837	61.19	6.16	61.20	6.17
5-Ethyl-2-thiophenecarboxaldehyde	85	102-103	59.32	5.53	59.51	5.68	122-128/2	1.0968	1.5780	62.85	6.66	62.70	6.57
5-Propyl-2-thiophenecarboxaldehyde	83	109-110	61.19	6.17	61.13	6.23	135-140/2	1.0724	1.5708	64.24	7.14	64.23	7.28
5-Chloro-2-thiophenecarboxaldehyde	85	201-203d. ^b	44.52	2.67	44.70	2.80							

^a Ref. (2) gives 143-144°.

^b Darkens at 190°.

^c Acrylic ester not isolated; main product is 5-chloro-2-thiophenecarboxylic acid.

^d The acrylic esters were hydrolyzed by refluxing with 25% sodium hydroxide solution for three hours. Acidification and recrystallization of the product yielded the corresponding acrylic acids, confirmed in each case by a mixed m.p. with the acids obtained by the Doebner modification.

EXPERIMENTAL²

5-Bromo-2-thiophenecarboxaldehyde. In a round-bottom flask were placed 32.6 g. (0.2 mole) of 2-bromothiophene, 45 g. of *N*-methylformanilide (0.32 mole), and 95.5 g. (0.33 mole) of phosphorus oxybromide. Upon addition of the oxybromide, a vigorous reaction occurred. The reaction mixture was cooled until the evolution of hydrogen bromide had subsided and then heated on a steam-bath for an hour. Then cooling was again applied and the contents of the flask carefully neutralized with excess aqueous sodium acetate. The mixture was steam distilled, the distillate extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over sodium sulfate and rectified. There was obtained 20.5 g. (54%) of 5-bromo-2-thiophenecarboxaldehyde (9). B.p. 80–83/2 mm.

Semicarbazone, m.p. 200–201°.

Anal. Calc'd for $C_6H_5BrN_3OS$: N, 16.95. Found: N, 17.12.

Acid, m.p. 141–141.5°. Mixed m.p. with an authentic sample (10) showed no depression.

Anal. Calc'd for $C_6H_5BrO_2S$: C, 29.00, H, 1.46.

Found: C, 29.16, H, 1.60.

Condensations with nitroparaffins. The condensations with the nitroparaffins were run according to the method outlined in the literature. As an example, the reaction of 2-thiophenecarboxaldehyde with nitromethane is given.

ω -Nitro-2-vinylthiophene. 2-Thiophenecarboxaldehyde (37 g., 0.33 mole), nitromethane (20 g., 0.33 mole), and 75 cc. of methyl alcohol were mixed in a 3-neck flask fitted with a thermometer, a mechanical stirrer and a separatory funnel. The temperature was kept between 10–15°, while a solution of 14 g. of sodium hydroxide in 50 cc. of water was added slowly. A bulky precipitate formed during the addition of the alkali. After fifteen minutes standing, the pasty mass was converted to a clear solution by the addition of ice-water. This solution was added slowly to a hydrochloric acid solution (made by diluting 70 cc. of concentrated hydrochloric acid with 100 cc. of water). The yellow crystals so formed were recrystallized from an alcohol-water mixture with charcoal. There was obtained 40.5 g. (78%) of ω -nitro-2-vinylthiophene, yellow crystals, m.p. 79–80°.

The condensation utilizing magnesium aluminum ethoxide was run in the following manner: 2-Thiophenecarboxaldehyde (11.2 g., 0.1 mole), nitromethane (6 g., 0.1 mole), and 1 g. of magnesium aluminum ethoxide were placed in a flask in an ice-water bath. The flask was then stoppered and after two to three hours was removed from the ice-bath and allowed to stand twenty-four hours at room temperature. A large excess of hydrochloric acid was added and the mixture warmed on the steam-bath for twenty minutes. After ether extraction, drying and rectification, there was obtained 3.5 g. (23%) of ω -nitro-2-vinylthiophene, b.p. 155–170°/9 mm., which after recrystallization from an alcohol-water mixture had m.p. 79–80°.

Preparation of thienylacrylic acids. The method utilized was the same in all cases. As an example the preparation of 2-thienylacrylic acid is given.

2-Thienylacrylic acid. 2-Thiophenecarboxaldehyde (11.2 g., 0.1 mole), malonic acid (20.4 g., 0.2 mole), 50 cc. of dry pyridine, and 1 cc. of piperidine were heated on a steam-bath for two hours and then boiled for five minutes. After cooling, the solution was poured into water and treated with excess hydrochloric acid. Filtration and recrystallization from an alcohol-water mixture yielded 13.1 g. (85%) of 2-thienylacrylic acid, m.p. 143–144°.

Preparation of thienylacrylic esters. The procedure utilized was the same for all of the thiophene compounds and followed that given in the literature (11) with the exception that the temperature was kept at –10 to –15° during the addition of the thiophenealdehydes. The example presented outlines the basic procedure.

² The nitroparaffins used in this work were obtained through the courtesy of the Commercial Solvents Corporation and the phosphorus oxybromide was placed at our disposal by the Dow Chemical Company.

Ethyl β -(2-thienyl)acrylate. Sodium (7.2 g., 0.31 mole) was prepared in a finely divided form by heating in dry xylene and stirring vigorously while the mixture cooled to room temperature. The xylene was decanted off and to the sodium was added absolute ethyl acetate (115 cc., 1.2 mole) and 1 cc. of absolute ethyl alcohol. The flask was quickly cooled to -10° and 28 g. (0.25 mole) of 2-thiophenecarboxaldehyde was added slowly from a separatory funnel with agitation. The temperature was kept between -10° to -15° . After addition of the aldehyde, the stirring was continued for one hour and the temperature allowed to rise to $0-5^{\circ}$. Then 25 cc. of glacial acetic acid was added and the mixture was carefully diluted with water. The ester layer was separated and the water layer extracted with 20-25 cc. of ethyl acetate. The combined ester layer was washed with 6 *N* hydrochloric acid and dried over sodium sulfate. Fractionation yielded 22.2 g. (49%) of ethyl β -(2-thienyl)acrylate. B.p. $110-116^{\circ}/3.5$ mm.

SUMMARY

1. Methods are presented for the condensation of some thiophenealdehydes with nitroparaffins, malonic acid and ethyl acetate. Physical properties of the products obtained are recorded.

2. The effects of some substituent groups in the above condensations are discussed.

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