[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FORDHAM UNIVERSITY]

PREPARATION OF THIOPHANTHRENEQUINONE AND ITS DERIVATIVES.[1] I

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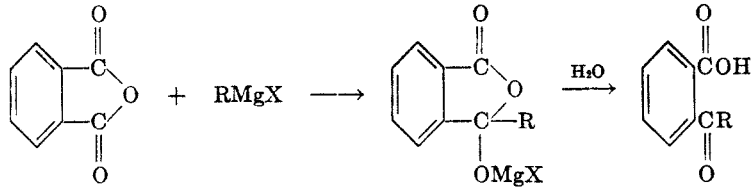
Due to the great importance of the series of dyes based on anthraquinones, it seemed of interest to investigate the thiophene analogs of this substance. The monothiophene analog of anthraquinone, α-thiophanthrenequinone, was first prepared by Steinkopf (1) in 25% yield. The first objective at the time this investigation was started was to find a suitable method for the preparation of 2-(2-thenoyl)benzoic acid in quantity and good yield. It seemed possible that the reaction of phthalic anhydride with 2-thienylmagnesium iodide would give the desired 2-(2-thenoyl)benzoic acid. This reaction was tried and a very good yield (over 90%) of the acid was obtained.

The effect of the solvent on the yield of the reaction product was studied using ether, dioxane, and anisole as solvents for the anhydride. The best yield (91%) was obtained using anisole. The effect of temperature on the yield of the acid was studied at 35°, 27°, and −10°. At 27° the yield of the acid was 91% and it did not change appreciably at 10° (92%), but dropped to 83% when the reaction temperature was maintained at 33–35° during the addition of the Grignard reagent. Slightly after the original report of our work, several patents by Lee and Weinmayr (2–6) appeared which described the preparation of 2-(2-thenoyl)benzoic acid and many of its substitution products by both a modification of Steinkopf's original Friedel-Crafts reaction and the Grignard method.

Buu-Hoï (7) has recently published the preparation of 2-(2-thenoyl)benzoic acid and its 5-methyl-, 5-chloro-, and 5-bromo-derivatives by the Friedel-Crafts method.

The successful result obtained in the preparation of 2-(2-thenoyl)benzoic acid led to the application of this method to the preparation of some substituted thenoylbenzoic acids, indicated by the following general reaction.



R = 2-thienyl-, 5-methyl-2-thienyl-, 5-ethyl-2-thienyl-, 2, 5-dimethyl-3-thienyl-, 5-chloro-2-thienyl-, 5-bromo-2-thienyl-.

The iodo derivatives of the thiophene compounds were generally prepared by

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the standard methods given in the literature with the exception of 5-chloro- and 5-bromo-2-iodothiophene which were prepared by the simple method of direct iodination of 2-chloro- and 2-bromo-thiophene respectively, rather than by the relatively involved procedures (8, 9) given in the literature for the preparation of these compounds. The experimental data for the thenoyl- and substituted thenoyl-benzoic acids have been summarized in Table I.

The keto acids described in Table I have been cyclized to the corresponding anthraquinone analogs. The ring closure of 2-(2-thenoyl)benzoic acid using phosphorus pentoxide or concentrated sulfuric acid was effected by Steinkopf (1) and the optimum yield of the cyclized compound obtained by these methods is about 45%. Recently, Weinmayr (2) and Buu-Hoï (7) have independently reported the preparation of α-thiophanthrenequinone in better yields.

TABLE I

THENOYL- AND SUBSTITUTEDTHENOYL-BENZOIC ACIDS

THIOPHENE PRECURSOR FOR RMgX	2-AROYLBENZOIC ACID	M.P., °C.	YIELD, %	EMPIRICAL FORMULA	ANALYSES			
					C		H	
					Cal'cd	Found	Calc'd	Found
2-Iodo-	2-Thenoyl-	145	91	$C_{12}H_8O_3S$	[d]			
5-Methyl-2-iodo-	5-Methyl-2-thenoyl-	137	60	$C_{13}H_{10}O_3S$	63.41	63.40	4.07	4.30
5-Ethyl-2-iodo	5-Ethyl-2-thenoyl-	105	87	$C_{14}H_{12}O_3S$	64.61	64.60	4.61	4.67
2,5-Dimethyl-3-thenoyl	2,5-Dimethyl-3-thenoyl-	127	62	$C_{14}H_{12}O_3S$	[e]			
5-Chloro-2-iodo-	5-Chloro-2-thenoyl	129–30	70	$C_{12}H_7ClO_3S$	54.03	54.30	2.62	2.83
5-Bromo-2-iodo-	5-Bromo-2-thenoyl	175	65	$C_{12}H_7BrO_3S$	46.30	46.25	2.25	2.93

[a] Reacted with phthalic anhydride in every case. [b] Yield calculated on the amount of anhydride used. [c] All analyses performed by Dr. F. Buhler of this Department. [d] Ref. 1. [e] Ref. 16.

In the present investigation the cyclization of the acids (Table I) has been effected by one (or more) of the following four general methods:

A. Heating the acid and phosphorus pentoxide.
B. Heating the acid and concentrated sulfuric acid.
C. Heating the acid and a mixture of aluminum chloride and sodium chloride.
D. Preparation of the acid chloride and cyclization with aluminum chloride in nitrobenzene.

The experimental data for the cyclized compounds are given in Table II.

The presence of the hetero atom in α-thiophanthrenequinone seemed to present interesting possibilities regarding orientation in this molecule. Steinkopf has reported (1) the preparation of a mononitro derivative of thiophanthrenequinone but did not prove its structure. It was therefore decided to study nitration and halogenation of α-thiophanthrenequinone. Nitration yielded a mono-nitro derivative identical with the one described by Steinkopf (1). This nitro compound was reduced to the amino derivative but attempts to convert it into the correspond-

ing chloro derivative through diazotization and the Sandmeyer reaction were unsuccessful. The N-benzoyl and N-acetyl derivatives of the monoaminothiophanthrenequinone were, however, obtained and characterized. Since our attempts to prove the structure of Steinkopf's nitrothiophanthrenequinone were unsuccessful, we turned to halogenation in the hope of being able to identify the positions taken by the entering group. Bromination of thiophanthrenequinone with bromine in glacial acetic acid in a sealed tube at a high temperature gave a bromo derivative which was identical with 2-bromothiophanthrenequinone obtained by the ring closure of 2-(5-bromo-2-thenoyl)benzoic acid. Thus it was indicated that electrophilic substitution favors the 2- position in thiophanthrene-

TABLE II

α-THIOPHANTHRENEQUINONE AND ITS DERIVATIVES

AROYLBENZOIC ACID	THIOPHANTHRENE-QUINONE	M.P., °C.	YIELD, %	EMPIRICAL FORMULA	ANALYSES			
					C		H	
					Calc'd	Found	Calc'd	Found
2-(2-Thenoyl)-	Unsubstituted	228	63	$C_{12}H_6O_2S$	[b]			
2-(5-Methyl-2-thenoyl)-	2-Methyl-	247–248	42	$C_{13}H_8O_2S$	68.42	68.27	3.51	3.60
2-(5-Ethyl-2-thenoyl)-	2-Ethyl-	235–236	23	$C_{14}H_{10}O_2S$	69.42	69.00	4.13	4.20
2-(2,5-Dimethyl-3-thenoyl)-	2,7-Dimethyl-	176	13	$C_{14}H_{10}O_2S$	[c]			
2-(5-Chloro-2-thenoyl)-	2-Chloro-	178	37	$C_{12}H_5ClO_2S$	58.02	58.00	2.01	2.27
2-(5-Bromo-2-thenoyl)-	2-Bromo-	180–181	27	$C_{12}H_5BrO_2S$	49.15	49.05	1.71	2.04

[a] Yield calculated on the basis of the acid used. [b] All analyses performed by Dr.F. Buhler of this department. [c] Ref. 16.

quinone and that by analogy Steinkopf's nitro compound is probably 2-nitrothiophanthrenequinone.

EXPERIMENTAL

A method for the preparation of 2-(thenoyl)benzoic acid has been described in detail and it is typical of the procedures used for the preparation of substituted 2-(2-thenoyl)-benzoic acids.

Preparation of 2-(2-thenoyl)benzoic acid. The Grignard reagent from 52.5 g. (0.2 mole) of 2-iodothiophene (10) in 200 ml. of anhydrous ether was run slowly into a mixture of 30 g. (0.2 mole) of phthalic anhydride and 300 ml. of freshly distilled anisole which was cooled externally with ice. The reaction was stirred vigorously during the addition of the Grignard reagent and for four hours after the addition. The cooled reaction mixture containing the magnesium complex was decomposed by the addition of 300 ml. of a cold saturated solution of ammonium chloride and then acidified with 6 *N* hydrochloric acid. The organic layer was separated, washed with water several times, and treated with 500 ml. of a 10% solution of sodium carbonate in three different portions. The aqueous alkaline layers were collected, cooled, and acidified by the dropwise addition of 6 *N* hydrochloric acid with vigorous stirring. The keto acid which precipitated was filtered and washed free of the mineral acid with water. The crude product was crystallized from boiling water. It was observed, how-

ever, that rapid addition of the mineral acid in the last step gave a gummy product which made subsequent operations difficult. The yield of 2-(2-thenoyl)benzoic acid, m.p. 145°, was 91%.

The above method was varied by changing the temperature of the condensation reaction. At 35° the yield of the keto acid dropped to 83% while at −10° it was 92%. Changing the solvent for the anhydride to ether or dioxane gave a lower yield (72–78%) than that when anisole was used as solvent.

Preparation of 2-(5-methyl-2-thenoyl)benzoic acid. 2-Methylthiophene was prepared according to the method given in the literature (11) and its 5-iodo derivative was obtained by a method analogous to that used to prepare 2-iodothiophene (12), b.p. 96°/23 mm., yield 88%.

The preparation of the Grignard reagent of 2-methyl-5-iodothiophene and its subsequent condensation with phthalic anhydride was effected according to the method described in the preceding case. The keto acid obtained was crystallized from water, m.p. 137° (4), yield 71%.

Preparation of 2-(5-ethyl-2-thenoyl)benzoic acid. 2-Ethylthiophene was prepared by the reduction (13) of 2-acetothienone (14) and its monoiodo derivative was obtained by direct iodination (12), b.p. 110°/16 mm. (14), yield 79%. The Grignard reagent from 2-ethyl-5-iodothiophene was condensed with phthalic anhydride according to the standard procedure. The crude 2-(5-ethyl-2-thenoyl)benzoic acid obtained was crystallized from water or xylene, m.p. 105°, yield 88%.

Preparation of 2-(2,5-dimethyl-3-thenoyl)benzoic acid. 2,5-Dimethyl-3-iodothiophene (15) was obtained by the direct iodination of 2,5-dimethylthiophene in the presence of yellow mercuric oxide as catalyst (12), b.p. 104–105°/15 mm., yield 63%. It was converted to the Grignard reagent, condensed with phthalic anhydride, and the crude reaction product obtained was crystallized from water, m.p. 127° (16), yield 62%.

Preparation of 2-(5-chloro-2-thenoyl)benzoic acid. The preparation of 2-chloro-5-iodothiophene was effected by direct iodination of 2-chlorothiophene in the presence of yellow mercuric oxide, b.p. 94°/12 mm. (9), yield 58%.

The Grignard reagent from 2-chloro-5-iodothiophene was condensed with phthalic anhydride and the reaction product obtained was crystallized from xylene or benzene, m.p. 129–130° (17), yield 70%.

Preparation of 2-(5-bromo-2-thenoyl)benzoic acid. 2-Bromothiophene was commercially available and its iodo derivative was prepared according to the standard method, b.p. 116°/13 mm., (8), yield 63%.

The preparation of the mono Grignard reagent of either 2-bromo-5-iodothiophene or 2,5-dibromothiophene was effected according to the usual method and the organomagnesium compound was then condensed with phthalic anhydride. The crude keto acid was crystallized from water or xylene, m.p. 175°, yield 65%.

Preparation of α-thiophanthrenequinone. The acid chloride from 4.6 g. (0.02 mole) of 2-(2-thenoyl)benzoic acid and 6.3 g. (0.03 mole) of phosphorus pentachloride was dissolved in benzene and treated with 7.8 g. (0.03 mole) of stannic chloride. The reaction was initially allowed to proceed at room temperature (27°) for one hour and then for an additional period of 4 hours at 70°. The crude reaction product was crystallized from glacial acetic acid; light yellow needles were obtained, m.p. 228° (1), yield 28%.

Using 4 g. (0.03 mole) of aluminum chloride as condensing agent and nitrobenzene as solvent the yield was 42% while raising the temperature to 140° for four hours raised the yield to 63%. Higher yields have been reported by Weinmayr (2) using similar procedures.

Preparation of 2-methyl-α-thiophanthrenequinone. 1. 2-(5-Methyl-2-thenoyl)benzoic acid (4.92 g.) was converted into the acid chloride with 6.3 g. (0.03 mole) of phosphorus pentachloride and cyclized by the dropwise addition of 7.8 g. (0.03 mole) of stannic chloride to the reaction mixture which was kept externally cooled with ice. After complete addition of stannic chloride, the reaction was allowed to proceed at 0° for three more hours and at 70° for an additional four hours. The crude 2-methylthiophanthrenequinone was crystallized

from benzene and petroleum ether, m.p. 247–248° (4), yield 42%. *2.* Another run was made in which the cyclization of the acid chloride obtained by treating 2-(5-methyl-2-thenoyl)-benzoic acid with thionyl chloride was carried out at room temperature (27°). A gummy material was obtained which yielded a small amount of 2-methylthiophanthrenequinone, m.p. 246–249°, yield 11%. *3.* 2-(5-Methyl-2-thenoyl)benzoic acid (5 g.) was intimately mixed with 20 g. of phosphorus pentoxide and heated at 145° for 2½ hours; then it was cooled and the product was isolated in the usual manner. The crude 2-methylthiophanthrenequinone obtained was crystallized from benzene and petroleum ether, m.p. 248°, yield 28%.

Preparation of 2-ethyl-α-thiophanthrenequinone. 2-(5-Ethyl-2-thenoyl)benzoic acid (3 g.) was intimately mixed with phosphorus pentoxide and heated at 120° for 2½ hours. The crude 2-ethylthiophanthrenequinone was crystallized from 80% acetic acid. It softened at 200° and melted at 235–236°, yield 23%.

Preparation of 2,7-dimethylthiophanthrenequinone. 2-(2,5-Dimethyl-3-thenoyl)benzoic acid (2 g.) was cyclized by heating a mixture of this acid with 12 g. of aluminum chloride and 3 g. of sodium chloride according to the procedure described by Steinkopf (16). The crude reaction product was crystallized from glacial acetic acid, m.p. 176°, yield 13%.

Preparation of 2-chlorothiophanthrenequinone. 1. 2-(5-Chloro-2-thenoyl)benzoic acid (5 g.) was converted to the acid chloride with phosphorus pentachloride. The cyclization reaction was then started with the acid chloride obtained using 3 g. of anhydrous aluminum chloride added at 0°, and allowed to proceed at room temperature (27°) for one hour and for three more hours at 90°. After removal of nitrobenzene by steam-distillation, the crude product was crystallized from hot ethyl alcohol; yellow-green needles of pure 2-chlorothio-phanthrenequinone were obtained, m.p. 178° (17), yield 37%. *2.* A mixture of 3 g. of 2-(5-chloro-2-thenoyl)benzoic acid and 8 g. of phosphorus pentoxide was heated at 135–140°. The reaction mixture was extracted with ether and the organic layer was treated in the usual manner. The crude reaction product was crystallized from ethyl alcohol, m.p. 178°, yield 30%.

Preparation of 2-bromo-α-thiophanthrenequinone. A mixture of 3 g. of 2-(5-bromo-2-thenoyl)benzoic acid and 10 g. of phosphorus pentoxide was heated at 140–145°. The reaction mixture was extracted with ether and the organic layer was treated in the usual manner. The crude product, m.p. 168–172°, yield 27%, was purified by sublimation. m.p. 180–181°.

Preparation of mononitro-α-thiophanthrenequinone (1). α-Thiophanthrenequinone (5 g.) was added in small portions to 60 ml. of fuming nitric acid while cooling with ice. The mixture was gently heated in a steam-bath for 1 hour, cooled, and then poured into 250 ml. of ice-cold water. The solid material which separated was collected, washed free from the mineral acid with water, and then crystallized from acetic acid. Deep yellow crystals were obtained m.p. 241–243°, yield 79%.

Reduction of mononitro-α-thiophanthrenequinone. Method A. A mixture of 5 g. of nitro-thiophanthrenequinone in 200 ml. of a 2% solution of sodium hydroxide was gradually added to a flask containing a solution of 10 g. of sodium sulfide and 5 g. of sodium hydroxide in 200 ml. of water at 70°. The reaction was allowed to proceed for 1 hour at 80° and the mixture filtered while hot. The filtrate contained the "leuco" compound which was oxidized by bubbling air through the mixture. The solid product which precipitated was collected and washed free of alkali with water. The crude brick-red amino compound could not be crystallized from the usual organic solvents. It melted at 240–243°, yield 63%. Sublimation of the crude compound did not give a purer product.

Anal. Calc'd for $C_{12}H_7NO_2S$: N, 6.11. Found: N, 6.01.

Method B. Nitrothiophanthrenequinone (5 g.) was stirred in 100 ml. of a 5% sodium hydroxide solution and gradually added to a flask containing a solution of 8 g. of sodium hydroxide and 35 g. of sodium hydrosulfite at 70°. The reaction was allowed to proceed at this temperature for a period of 1 hour and then filtered while hot. The filtrate on aeration precipitated the amino compound which was collected and washed free of the alkali with water. The crude compound obtained melted at 239–241°, yield 71%. Sublimation of the crude compound gave a product melting at 242–243°.

Preparation of N-acetylamino-α-thiophanthrenequinone. To 2 g. of the amino compound in a flask was added 30 ml. of acetic anhydride and the mixture was refluxed for three hours. After this period the reaction mixture was cooled and poured on crushed ice. The solid product which separated was collected, washed with water and then crystallized from ethyl alcohol, m.p. 220°, yield 73%.

Anal. Calc'd for $C_{14}H_9NO_3S$: C, 61.99; H, 3.32; N, 5.17.

Found: C, 62.33; H, 3.52; N, 5.08.

Preparation of N-benzoylamino-α-thiophanthrenequinone. The amino compound (4 g.) in dry benzene was benzoylated in the usual manner with benzoyl chloride and pyridine. After the solvent was removed under reduced pressure, the crude residue (m.p. 189–190°) obtained was purified by sublimation, m.p. 203°, yield (crude) 67%.

Anal. Calc'd for $C_{19}H_{11}NO_3S$: C, 68.47; H, 3.31; N, 4.20.

Found: C, 68.93; H, 3.27; N, 4.41.

Bromination of α-thiophanthrenequinone. A mixture of 3 g. of α-thiophanthrenequinone and 3.5 g. of bromine in 50 ml. of glacial acetic acid was heated in a sealed tube at 175–180° for 12 hours. After this period the tube was cooled, the seal broken, and the reaction product poured into crushed ice. The mixture was extracted with ether, and the ether solution was washed with water and then with three 100-ml. portions of a 15% sodium carbonate solution. The ether layer was washed free of alkali with water, dried over sodium sulfate, and the organic solvent removed under reduced pressure. The crude residue obtained melted at 177–180°, yield 63%. Sublimation of the crude compound gave a product melting at 181°. Mixture melting point of this compound with an authentic sample of 2-bromo-α-thiophanthrenequinone showed no depression.

SUMMARY

A convenient method has been found for the preparation of thenoyl- and substitutedthenoyl-benzoic acids in the reaction of phthalic anhydride and the Grignard reagent of a halothiophene or thiophene derivative. The following acids were prepared: 2-(2-thenoyl)-, 2-(5-methyl-2-thenoyl)-, 2-(5-ethyl-2-thenoyl)-, 2-(2,5-dimethyl-3-thenoyl)-, 2-(5-chloro-2-thenoyl)-, and 2-(5-bromo-2-thenoyl)benzoic acid.

The above acids were cyclized and the following diketone derivatives were obtained: α-thiophanthrenequinone, 2-methyl-, 2-ethyl-, 2,7-dimethyl-, 2-chloro-, and 2-bromo-α-thiophanthrenequinone.

An aminothiophanthrenequinone has been prepared by the reduction of the known mononitro-α-thiophanthrenequinone and its N-benzoyl and N-acetyl derivatives have been obtained.

Direct bromination of α-thiophanthrenequinone in a sealed tube yield 2-bromo-α-thiophanthrenequinone.

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