[Contribution from the Chemistry Department of Fordham University]

PREPARATION OF THIOPHANTHRENEQUINONES. III. THE THENOYLNITROBENZOIC ESTERS

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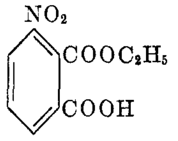
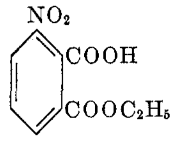
In a previous communication (1) we indicated a need for methods of preparation of 6-(2-thenoyl)-2- and 2-(thenoyl)-4-nitrobenzoic acids. It seemed possible that the Friedel-Crafts reaction of the appropriate half-ester acid chlorides of the nitrophthalic acids with thiophene would give the required acids.

There are two acid ethyl esters which theoretically could be obtained in the case of 3-nitrophthalic acid, *i.e.*, 2-carbethoxy-3-nitrobenzoic acid and 6-carbethoxy-2-nitrobenzoic acid. These acid ethyl esters will be referred to in the present discussion as the Ia ester and Ib ester, respectively.



Ia

(M.p. 111°)



Ib

(M.p. 157°)

There is some uncertainty in the literature about the details of half ester formation (2–5), but there is agreement that the anhydride and ethyl alcohol gives one half ester, while acid-catalyzed esterification gives the other and we have substantiated this. We prepared the acid ethyl ester of 3-nitrophthalic acid (m.p. 110–111°) according to the method described by Miller (6) and the isomeric acid ethyl ester (m.p. 157°) by the procedure of Bogert and Boroschek (7).

The Friedel-Crafts reaction of the acid chloride of each of the acid ethyl esters and thiophene gave one and the same product, an ethyl (2-thenoyl)nitrobenzoate. Hydrolysis of this ester gave an acid which was found to be identical with the acid obtained by us from the reaction of 3-nitrophthalic anhydride and 2-thienylmagnesium iodide which has been designated as 2-(2-thenoyl)-3-nitrobenzoic acid and on decarboxylation yielded 2-nitrobenzo-(2-thienone). Therefore, the product obtained from the Friedel-Crafts reaction can be designated as ethyl 2-(2-thenoyl)-3-nitrobenzoate. Thus the experimental data seemed to indicate the existence of dimorphous modifications of the acid ethyl esters of 3-nitrophthalic acid or the occurrence of rearrangement. The possibility of dimorphism was excluded on the basis of the following observations: (a) seeding of a supersaturated solution of one form with a crystal of the other form, or sublimation of each of the forms separately, did not yield a single compound which would correspond to the more stable of the two forms. (b) The two acid ethyl esters gave two different bromophenacyl derivatives.

The formation of one and the same ethyl thenoylnitrobenzoate from the

Friedel-Crafts reaction of the acid chloride of either Ia or Ib with thiophene and the fact that decarboxylation followed by hydrolysis of each of the acid ethyl esters of 3-nitrophthalic acid yielded one and the same nitrobenzoic acid (*i.e.*, 3-nitrobenzoic acid) indicated the possibility of a rearrangement having occurred in the Friedel-Crafts as well as in the decarboxylation reactions. The experimental data obtained established that rearrangement did not take place in the step involved in the formation of the acid chloride but did occur in the course of the condensation of the acid chloride half-ester and thiophene in the presence of stannic chloride. The acid chloride of the acid ethyl ester melting at 111° was rearranged to the acid chloride of the acid ethyl ester melting at 157°, which would therefore seem to be the more stable of the two isomeric acid ethyl esters of 3-nitrophthalic acid. This experimental observation and the fact that the Friedel-Crafts reaction of the acid chloride of either Ia or Ib with thiophene gave the ethyl ester of 2-(2-thenoyl)-3-nitrobenzoic acid, would indicate that the acid ethyl ester (m.p. 157°) is 6-carbethoxy-2-nitrobenzoic acid (Ib) and therefore the isomeric acid ethyl ester (m.p. 111°) should be designated as 2-carbethoxy-3-nitrobenzoic acid (Ia).

In a paper published just prior to our last report (1), Chase and Hey (8) have discussed ring-chain tautomerism in a number of acid halides of the half-esters of dibasic acids. Their work on the half methyl esters of 3-nitrophthalic acid parallels some of our work and reaches similar conclusions. However, due to certain variations in the two projects it seems worthwhile to publish the promised report (1) of our results.

It has been assumed in the preceding proof of structure that no rearrangement occurred in the process of the decarboxylation of thenoylnitrobenzoic acid. In order to confirm the structure assigned to Ia this compound was converted into its mono silver salt according to the procedure described by Zingaro and coworkers (9). The silver salt on treatment with bromine (10) followed by hydrolysis and decarboxylation yielded 3-nitrobromobenzene, thus further confirming that the original acid ethyl ester (m.p. 110°) must have been 2-carbethoxy-3-nitrobenzoic acid (Ia).

Attempts were made to study the probable mechanism of the esterification of 3-nitrophthalic anhydride by establishing the rate-determining step in the formation of the acid ethyl ester. Thus, the esterification of 3-nitrophthalic anhydride was effected using (a) molar proportions of the anhydride and sodium ethoxide in excess of ethyl alcohol, (b) anhydride dissolved in ethyl alcohol saturated with hydrochloric acid gas, (c) molar proportions of anhydride and ethyl alcohol in a non-polar solvent, *e.g.*, benzene, and (d) molar proportions of anhydride and ethyl chloride in benzene in the presence of stannic chloride. In all but the last run, pure Ib was obtained. The last experiment yielded a product melting at 150–154°. Repeated crystallization of this compound did not give a product with a sharper melting point. A mixture melting point determination of this compound and an authentic sample of Ib indicated that the latter compound was mainly Ib. Further, the fact that the reaction of 3-nitrophthalic anhydride and ethyl chloride in the presence of stannic chloride gave Ib indicated that the rearrangement of Ia might have proceeded *via* the formation of the anhydride.

The experimental observation that both Ia and Ib on decarboxylation and subsequent hydrolysis gave one and the same product, *i.e.*, 3-nitrobenzoic acid, indicated a rearrangement also in the process of decarboxylation. It was found that Ia on sublimation at 185° gave a mixture melting at 92–105°, which probably contained some Ib, 3-nitrophthalic anhydride, or both substances. The isomeric Ib also gave a mixture on sublimation which melted at 100–108°. Since the latter acid ethyl ester has not been found to rearrange, the mixture most probably contained an impurity of 3-nitrophthalic anhydride. Further, Ia did not rearrange on treatment with quinoline at room temperature (27°) or at 90° but did rearrange at 140° to Ib. Ib itself did not rearrange under these experimental conditions. It appears, therefore, that heat as well as the basic quinoline are factors responsible for the rearrangement of Ia to the isomeric Ib in the process of decarboxylation.

The Friedel-Crafts reaction of 3-nitrophthalic anhydride with benzene has been investigated by Lawrance (11) and he claims to have obtained the two theoretically possible benzoylnitrobenzoic acids. Lawrance claims to have established the structures of the two benzoylnitrobenzoic acids, by the Friedel-Crafts reaction of benzene and the acid chloride of 2-carbethoxy-3- and of 6-carbethoxy-2-nitrobenzoic acid followed by hydrolysis of the esters. This method of proving structures is subject to criticism from the point of view of the conflicting data which the author presents regarding the structures of the isomeric acid ethyl esters of 3-nitrophthalic acid and also in the light of our evidence for the rearrangement of the acid chloride of 2-carbethoxy-3-nitrobenzoic acid in the presence of a Friedel-Crafts catalyst [See also Chase and Hey (8).]

It has been shown on the basis of our experimental data (1) that the reaction of 3-nitrophthalic anhydride and phenylmagnesium bromide gave 2-benzoyl-3-nitrobenzoic acid melting at 238°. Additional evidence in support of our experimental data for this acid was obtained from the work of Hayashi (12) who prepared an acid presumed by him to be 2-benzoyl-3-nitrobenzoic acid which melted at 237°.

It will be noted that by taking into consideration the rearrangement of the acid chloride of 2-carbethoxy-3-nitrobenzoic acid in the Friedel-Crafts reaction and making on that basis the necessary correction in the interpretation of the experimental results presented by Lawrance, the melting point data for 2-benzoyl-3-nitrobenzoic acid found by this author (221°) and by us (238°) show relatively less disagreement. The lower-melting compound is probably an impure sample of the acid.

EXPERIMENTAL

Preparation of the acid ethyl ester of 3-nitrophthalic acid (m.p. 110–111°) (Ia). The acid ethyl ester was prepared according to the Fischer-Speier method. 3-Nitrophthalic acid (20 g.) was dissolved in 92 g. of absolute ethyl alcohol, the solution was saturated with dry hydrochloric acid gas, heated on a steam-bath for two hours, and left overnight at room temperature. After this period of time the solution was poured into water whereupon a turbidity appeared. The mixture was extracted with ether and the ether extract was treated with three 100-ml. portions of 10% sodium carbonate solution. The aqueous layer was separated, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was washed free of the mineral acid with water and dried over sodium sulfate. The crude acid ethyl ester, obtained after removal of ether under reduced pressure, was crystallized from benzene, m.p. 110–111°, yield 73%.

Preparation of acid ethyl ester of 3-nitrophthalic acid (m.p. 157°) (Ib) (7). 3-Nitrophthalic anhydride (20 g.) was dissolved in an excess of absolute ethyl alcohol, heated for five hours in a steam-bath, cooled, and poured into 300 ml. of water. Isolation in the manner described above gave crude acid ethyl ester which was crystallized from chloroform or benzene, m.p. 157°, yield 88%.

Friedel-Crafts reaction of 2-carbethoxy-6-nitrobenzoyl chloride (Ib) *with thiophene.* At room temperature, 5 g. of 2-carbethoxy-6-nitrobenzoic acid, m.p. 157°, was gradually added to 10 g. of thionyl chloride. The reaction flask was warmed gently on a steam-bath for two hours, then cooled, and the excess thionyl chloride removed under reduced pressure.

To a mixture of 5 g. of this half ester acid chloride and 1.6 g. of thiophene in 75 ml. of dry benzene was added dropwise, under reflux, 6 g. of stannic chloride. The reaction mixture was agitated and externally cooled during the addition and then for two hours longer. Dilute hydrochloric acid (100 ml.) was then added slowly, with stirring and external cooling. After adding some ether, the organic layer was washed with water, sodium carbonate solution, and water. After drying over sodium sulfate and removal of the organic solvents under reduced pressure, crude ethyl 2-(2-thenoyl)-3-nitrobenzoate remained and was recrystallized from petroleum ether. The pure material, representing a yield of 51%, melted at 114–115° (1).

Hydrolysis of ethyl 2-(2-thenoyl)-3-nitrobenzoate. A 5-g. sample of the ester obtained above was added to a mixture of 30 ml. of acetic acid and 12 ml. of 80% sulfuric acid. The mixture was heated on a steam-bath for 14 hours, cooled, and poured into crushed ice. The crude 2-(2-thenoyl)-3-nitrobenzoic acid which separated was washed with water and recrystallized from 80% acetic acid to give pure acid melting at 217° (1). The yield was 95%.

Friedel-Crafts reaction of 2-carbethoxy-3-nitrobenzoyl chloride with thiophene. In the manner described above, 2-carbethoxy-3-nitrobenzoic acid (Ia), m.p. 111°, furnished a 45% yield of ethyl 2-(2-thenoyl)-3-nitrobenzoate, which, after recrystallization from petroleum ether, melted at 114–115°. A mixture m.p. with the product of esterification of 2-(2-thenoyl)-3-nitrobenzoic acid showed no depression. Hydrolysis of the ester produced here in the manner described above gave 2-(2-thenoyl)-3-nitrobenzoic acid, melting at 215–217°.

Sublimation of the acid ethyl ester. A sample of the acid ethyl ester of 3-nitrophthalic acid (m.p. 111°) was sublimed at 185° under reduced pressure. The sublimate melted at 92–105°.

A sample of the acid ethyl ester (m.p. 157°) on sublimation under reduced pressure at 180° gave a sublimate melting at 100–118°.

Crystallization by seeding. A super saturated solution of the acid ethyl ester of 3-nitrophthalic acid (m.p. 111°) in benzene was seeded with a crystal of the acid ethyl ester (m.p. 157°). The compound which crystallized melted at 111°.

A super saturated solution of the acid ethyl ester (m.p. 157°) in benzene was seeded with a crystal of the acid ethyl ester (m.p. 111°). The compound which crystallized melted at 157°.

Preparation of p-bromophenacyl derivative of the acid ethyl ester (m.p. 111°). A solution of 2.5 g. of the acid ethyl ester (m.p. 111°) in 75 ml. of ethyl alcohol was made alkaline by addition of a cold dilute (0.5 *N*) sodium hydroxide solution and then made just acid by the dropwise addition of a 0.5 *N* hydrochloric acid solution. To this, 2.5 g. of *p*-bromophenacyl bromide was added and the mixture was allowed to reflux for 2 hours. The addition of a small quantity of ethanol at times was found necessary to dissolve any material which precipitated. After the reaction was completed, the flask was cooled to room temperature (27°) and the product was isolated. The solid residue obtained was dissolved in hot ethyl alcohol and then allowed to crystallize by external cooling with ice. The crystalline product was collected, m.p. 144–145°. The filtrate on addition of a few drops of water, deposited more crystalline material, m.p. 145°. Recrystallization of either crystalline fraction gave a compound melting at 145°, yield 2.9 g.

Anal. Calc'd for $C_{18}H_{15}BrNO_7$: C, 49.42; H, 3.43; N, 3.20; Br, 18.31.
Found: C, 49.81; H, 3.40; N, 3.29; Br, 18.50.

Preparation of p-bromophenacyl derivative of the acid ethyl ester (m.p. 157°). The procedure adopted to prepare this derivative was similar to that used above except that the reaction was allowed to proceed for 8 hours instead of 2 hours. The crude product obtained melted at 172–173°. Crystallization from 80% ethyl alcohol gave a product melting at 176°, yield 1 g.

Anal. Calc'd for $C_{18}H_{15}BrNO_7$: C, 49.42; H, 3.43; N, 3.20; Br, 18.31.
Found: C, 49.03; H, 3.22; N, 3.17; Br, 18.02.

Decarboxylation of the acid ethyl ester of 3-nitrophthalic acid (m.p. 157°). The acid ester (3 g.), 10 g. of freshly distilled quinoline, and 0.6 g. of copper powder were heated to 120° until no more carbon dioxide was evolved. The reaction flask was cooled to room temperature and the contents were filtered. Isolation in the usual manner gave a viscous liquid residue weighing 2.1 g. This was hydrolyzed by using a mixture of 15 ml. of acetic acid and 6 ml. of 80% sulfuric acid, and heating the reaction mixture in a steam-bath for two hours and then in an oil-bath at 120° for four more hours. The reaction mixture was cooled and the acid was isolated. The crude nitrobenzoic acid obtained after removing the ether under reduced pressure was crystallized from water, m.p. 140–141°, yield 89%.

A mixture m.p. of this acid with an authentic sample of 2-nitrobenzoic acid showed a depression of 25°; a mixture m.p. of the above acid and an authentic sample of 3-nitrobenzoic acid showed no depression.

Decarboxylation of the acid ethyl ester of 3-nitrophthalic acid (m.p. 111°). The decarboxylation was effected according to the above procedure and a viscous liquid was obtained and hydrolyzed. The crude product was crystallized from water, m.p. 140°, yield 80%.

A mixture m.p. of this acid and an authentic sample of 2-nitrobenzoic acid showed a depression of 17°. A mixture m.p. of this compound and an authentic sample of 3-nitrobenzoic acid showed no depression. A mixture m.p. of this acid and the nitrobenzoic acid obtained from the decarboxylation and subsequent hydrolysis of the acid ethyl of 3-nitrophthalic acid (m.p. 157°) showed no depression.

Reaction of the acid ethyl ester (Ia) (m.p. 111°) *with thionyl chloride.* To a 1-g. sample of the acid ethyl ester (m.p. 111°) was added 10 g. of thionyl chloride. After the initial reaction had subsided, the solution was gently heated in a steam-bath for 1 hour. After cooling, removing the excess of thionyl chloride *in vacuo*, and hydrolyzing, the half-ester acid obtained was found to melt at 111°. A mixture melting point of the compound and the acid ethyl ester (m.p. 111°) showed no depression.

Reaction of Ia acid chloride and stannic chloride in benzene. To a benzene solution of the half-ester acid chloride prepared as described above and kept at room temperature (27°) was added dropwise 3 g. of anhydrous stannic chloride, and the mixture was allowed to stand for three hours more and the product was isolated. The residue obtained melted at 154–156°. Crystallization from benzene gave a product melting at 157°. A mixture melting point of the compound and of an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression.

A similar run was made with the acid ethyl ester melting at 157°. The acid regenerated from the half-ester acid chloride melted at 157° and that obtained after treatment of the half-ester acid chloride with stannic chloride also melted at 157°.

Preparation of the silver salt of the acid ethyl ester (Ia) (9). To 10 g. of the acid ethyl ester (Ia) dissolved in 75 ml. of ethyl alcohol was added dropwise a 10% solution of sodium carbonate until the mixture was just alkaline. The solution was then made just acid by the dropwise addition of a cold, dilute (0.5 *N*) nitric acid solution. Silver nitrate (5.5 g.) was dissolved in 75 ml. of distilled water and this solution gradually was added to the solution of the sodium salt of the ethyl ester. Needle-shaped, white crystals of the silver salt immediately precipitated. The crystals were collected and washed with distilled water and ethanol. The silver salt was dried under reduced pressure at 70° for 6 hours, m.p. 214°, yield 94%.

Preparation of bromonitrobenzoic acid. Dry bromine (3.2 g.) in 50 ml. of carbon tetrachloride was added dropwise to a refluxing mixture of 6.9 g. of the silver salt of Ia (previously described) and 100 ml. of carbon tetrachloride. Heating was continued for an additional hour. After isolation, a deep brown viscous liquid residue weighing 2.8 g. was obtained.

The viscous liquid was hydrolyzed using a mixture of 6 ml. of 80% concentrated sulfuric acid and 15 ml. of acetic acid. The crude reaction product thus obtained was crystallized from toluene and petroleum ether (60–80°), m.p. 197°, yield 1.5 g.

Anal. Calc'd for $C_7H_4BrNO_4$: C, 34.15; H, 1.62; N, 5.69; Br, 32.52.
Found: C, 34.22; H, 1.47; N, 5.90; Br, 31.96.

Decarboxylation of the bromonitrobenzoic acid. One gram of the bromonitrobenzoic acid (m.p. 197°) was decarboxylated using 10 ml. of freshly distilled quinoline and 0.5 g. of copper powder at 140°. The crude reaction product melted over the range 49–53°. A deep yellow liquid distilled at 142°/19 mm. and solidified on cooling, m.p. 54–55°. A mixture melting point of this product and an authentic sample of *m*-bromonitrobenzene showed no depression.

Attempts to establish the mechanism of the rearrangement of the acid ethyl ester Ia (m.p. 111°). (*a*) Metallic sodium (0.31 g.) was reacted with 50 ml. absolute ethyl alcohol, to this was added 2.2 g. of 3-nitrophthalic anhydride, and the reaction mixture was refluxed in a steam-bath for 4 hours. At the end of this period the contents were poured into crushed ice and the product was isolated. The residue obtained melted at 157°. Crystallization from benzene did not change the melting point. A mixture melting point of this compound with an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression.

(*b*) To 50 ml. of absolute ethyl alcohol saturated with hydrochloric acid gas was added 2 g. of 3-nitrophthalic anhydride and the reaction mixture was refluxed in a steam-bath for 2 hours. At the end of this period it was cooled and poured into crushed ice. The residue obtained was found to melt at 155–157°. Crystallization of the crude product from benzene gave a compound melting at 157°. A mixture melting point of this compound and an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression.

(*c*) To a mixture of 2 g. of 3-nitrophthalic anhydride in benzene was added 0.8 ml. of absolute ethyl alcohol from a micro-pipette. The mixture was warmed gently on a steam-bath for 6 hours. At the end of this period it was cooled and the product was isolated. The crude product obtained was found to melt at 154–155°. Crystallization from benzene gave a product melting at 157°. A mixture melting point of this compound and an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression.

(*d*) The above experiment was repeated using anhydrous ether as a solvent instead of benzene. The product obtained melted at 157° and a mixture melting point determination with an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression.

(*e*) To a mixture of 2 g. of 3-nitrophthalic anhydride and 0.8 ml. of ethyl chloride in 50 ml. of dry benzene kept at room temperature (27°), 3 g. of stannic chloride was added and the reaction mixture was allowed to stand for 8 hours. It was then poured into 100 ml. of a cold dilute (1 *N*) hydrochloride acid solution and the product was isolated. The crude residue obtained melted at 149–153°. Crystallization from benzene gave a product melting at 150–154°. A purer product could not be obtained on repeated crystallization from other solvents. The mixture melting point of this compound and an authentic sample of the acid ethyl ester (m.p. 157°) was found to be 156–157°.

Reaction of the acid ethyl ester (Ia) *and quinoline.* To 2 g. of the acid ethyl ester (m.p. 111°) was added 15 ml. of freshly distilled quinoline and the mixture was allowed to stand at room temperature (27°) for 12 hours. At the end of this period the product was isolated; the residue obtained melted at 111°.

The above experiment was repeated maintaining the reaction temperature at 90°. The original acid ethyl ester (m.p. 111°) was recovered.

In another run the reaction temperature was maintained at 140° and the product obtained on crystallization from benzene melted at 157°, yield 1.1 g. A mixture melting point of this compound and an authentic sample of the acid ethyl ester (m.p. 157°) showed no depression. It is probable that in this run some of the acid ethyl ester (111°) was decarboxylated.

The above experiments were repeated using the isomeric acid ethyl ester (157°). In all the runs the original compound was obtained.

Preparation of the acid ethyl ester of 4-nitrophthalic acid. 4-Nitrophthalic acid (20 g.) was dissolved in 92 g. of absolute alcohol and the solution was saturated with dry hydrochloric acid gas. The reaction was allowed to proceed at room temperature (27°) for a period of 24 hours. The reaction mixture was then treated as described in the preparation of the acid ethyl ester of 3-nitrophthalic acid by this method.

The crude product obtained upon crystallization from benzene melted at 103–112°. Repeated crystallizations of this compound from other solvents did not yield a product with a sharper melting point.

In another run 10 g. of 4-nitrophthalic acid was reacted with 4 ml. of absolute ethyl alcohol in dry benzene at 50° for 4 hours and the crude reaction product upon crystallization from benzene gave a compound melting at 108–117°. Hydrolysis of the diethyl ester also yielded a mixture melting at 99–109°.

SUMMARY

1. The Friedel-Crafts reaction of the acid chlorides of 2-carbethoxy-3- and 6-carbethoxy-2-nitrobenzoic acid with thiophene yielded one and the same product, namely, the ethyl ester of 2-(2-thenoyl)-3-nitrobenzoic acid.

2. The rearrangement of 2-carbethoxy-3-nitrobenzoic acid and its acid chloride under various conditions has been reported.

3. Lawrance's (11) 6-benzoyl-2-nitrobenzoic acid has been shown to be 2-benzoyl-3-nitrobenzoic acid.

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