[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FORDHAM UNIVERSITY]

PREPARATION OF THIOPHANTHRENEQUINONES. II. THENOYLNITROBENZOIC ACIDS AND NITROTHIOPHANTHRENEQUINONES[1]

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Received December 26, 1951

At the time this investigation was begun, there was no information in the literature concerning the interaction of nitrophthalic anhydrides with Grignard reagents. The work described in the previous paper of this series (1) was, therefore, extended to the study of the reactions of nitrophthalic anhydrides and 2-thienylmagnesium halide. Such reactions are of importance primarily because they make it possible to obtain the various 2-(2-thenoyl)nitrobenzoic acids, which can then be converted into nitrothiophanthrenequinones having the nitro group in the isocyclic part of the molecule.

We have carried out the reaction between 3-nitrophthalic anhydride and 2-thienylmagnesium halide and that between 4-nitrophthalic anhydride and 2-thienylmagnesium halide in two different ways in each case.

According to the first of these schemes, wherein the solvent was anisole and the crude reaction product was purified by recrystallization from acetic acid, there was obtained in each instance only one of the two theoretically possible isomers, *i.e.*, 2-(2-thenoyl)-3-nitrobenzoic acid and 2-(2-thenoyl)-5-nitrobenzoic acid, respectively (Ia and Ic of Figure 1).

It has recently been found by Lee and Weinmayr (2), however, that the reaction of 3- and of 4-nitrophthalic anhydride with 2-thienylmagnesium bromide, when run somewhat differently, furnishes the two theoretically possible isomers in each case. In following this procedure, we find that two isomers are indeed produced. These authors have not given any proof for the structures which they have assigned to the four acids. The structures of our thenoylnitrobenzoic acids were established by identifying the products of their decarboxylation with the corresponding nitrobenzo(2-thienone) isomers of known structure, synthesized by the action of the appropriate nitrobenzoyl chloride on thiophene in typical Friedel-Crafts reactions. Our melting point and decarboxylation data show that the acids previously reported by Lee and Weinmayr (2) to be Ia and Ib actually correspond to the formulas Ib and Ia, respectively, and the acids previously reported by Lee and Weinmayr to be Ic and Id actually correspond to the formulas Id and Ic, respectively.

It occurred to us that the explanation for Ib and Id not having been isolated when the reactions were carried out according to the first scheme might lie in the rearrangement of these acids to Ia and Ic, respectively, due to the action of the acid medium used in their recrystallization. It was, in fact, found that the

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[1] Presented at the April 1950 meeting of the American Chemical Society in Philadelphia. Taken in part from the thesis of Renato Goncalves presented in partial fulfillment of the requirements for the Ph.D. degree, May 1951.

conversions Ib → Ia and Id → Ic can be effected by boiling acetic acid but even more satisfactorily by the action of warm concentrated sulfuric acid. Previous instances of similar rearrangements are known (3–5).

In two patents Lee and Weinmayr (6) and Fieser and Schroeder (7) have indicated that structures corresponding to our (2-thenoyl)nitrobenzoic acids have been obtained in the (2-thenoyl)chlorobenzoic acid series.

Other methods for preparing the isomeric (2-thenoyl)nitrobenzoic acids were also investigated. Accordingly, the Friedel-Crafts reactions of the nitrophthalic half-ester acid chlorides and thiophene were studied. Since there is considerable confusion in the literature concerning these isomeric esters, it was necessary to establish their structures conclusively. This work is the subject of a subsequent report (8). However, regardless of their structures the action of the acid chlorides of each of the acid ethyl esters shown in Figure 2 upon thiophene gave the same product, namely, ethyl 2-(2-thenoyl)-3-nitrobenzoate, identical with the ethyl ester of the 2-(2-thenoyl)-nitrobenzoic acid produced by the Grignard reaction as in Figure 1.

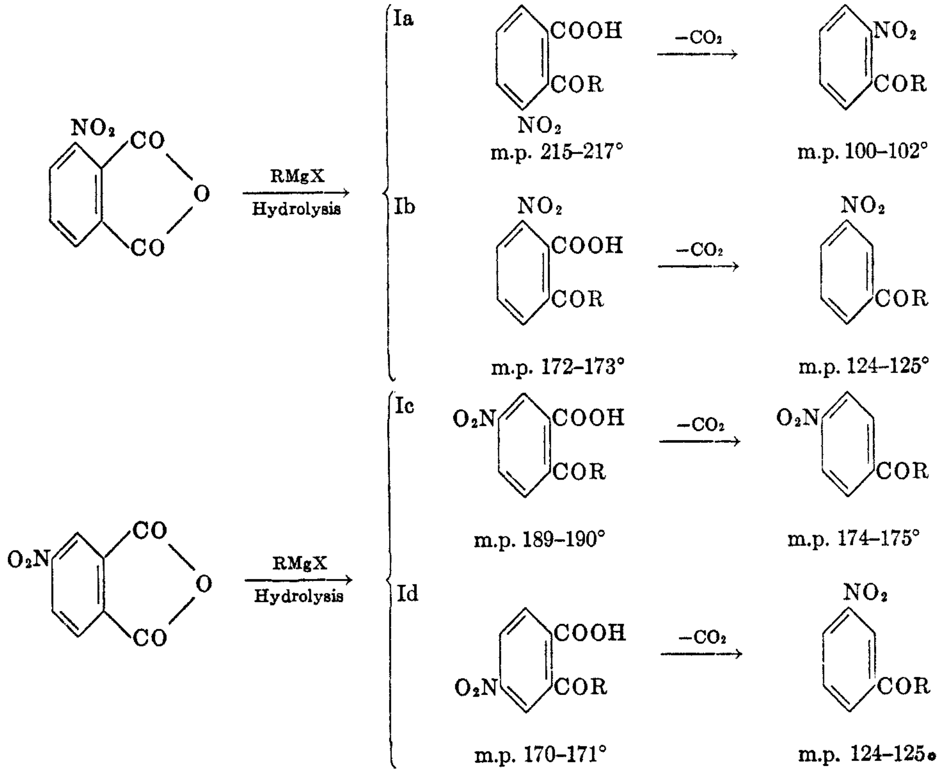

FIGURE 1 R = thienyl

Hydrolysis of this ethyl ester from the Friedel-Crafts reaction furnished an acid identical with Ia which, upon decarboxylation, yielded 2-nitrobenzo(2-thienone).

TABLE I

AROYLNITROBENZOIC ACIDS OBTAINED BY THE GRIGNARD REACTION

PRECURSOR FOR RMgX	NITRO-PHTHALIC ANHYDRIDE	METHOD	AROYLNITROBENZOIC ACID	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
							C		H		N	
							Calc'd	Found	Calc'd	Found	Calc'd	Found
2-Iodothiophene	3	A	2-(2-Thenoyl)-3-	215–217	53	$C_{15}H_7NO_5S$	51.99	52.05	2.52	2.52	5.05	5.35
Bromobenzene	3	A	2-Benzoyl-3-	238	40	$C_{14}H_9NO_5$	61.99	61.87	3.32	3.30	5.17	5.40
2-Bromothiophene	3	B	2-(2-Thenoyl)-3	215–217	42							
2-Bromothiophene	3	B	2-(2-Thenoyl)-6-	172–173	31		(2)					
2-Iodothiophene	4	A	2-(2-Thenoyl)-5-	196	56		(2)					
Bromobenzene	4	A	2-Benzoyl-5-	219–220	38	$C_{14}H_9NO_5$	61.99	61.68	3.32	3.25	5.17	5.15
2-Bromothiophene	4	B	2-(2-Thenoyl)-5	189–190	34	$C_{15}H_7NO_5S$	51.99	52.11	2.52	2.65	5.05	5.19
2-Bromothiophene	4	B	2-(2-Thenoyl)-4	170–171	19		(2)					

Since the pure isomeric acid ethyl esters of 4-nitrophthalic acid are not available, it was impossible to study their reactions.

The possibility of obtaining the desired acids by the Friedel-Crafts reaction of 3- and of 4-nitrophthalic anhydride and thiophene was also investigated. In the case of 3-nitrophthalic anhydride, a small yield of 2-(2-thenoyl)-3-nitrobenzoic acid was obtained, with none of the isomeric 6-(2-thenoyl)-2-nitrobenzoic acid being detected. With 4-nitrophthalic anhydride, 2-(2-thenoyl)-5-nitrobenzoic acid was obtained, with no 2-(2-thenoyl)-4-nitrobenzoic acid being detected.

IIa IIb

FIGURE 2

TABLE II

THENOYLNITROBENZOIC ACIDS OBTAINED BY THE FRIEDEL-CRAFTS REACTION

REACTANT[a]	ETHYL THENOYLNITROBENZOATE	M.P., °C.	YIELD, %	THENOYLNITROBENZOIC ACID[b]	M.P., °C.	YIELD, %
2-Carbethoxy-3-nitrobenzoyl chloride	2-(2-Thenoyl)-3-	114–115	43–46	2-(2-Thenoyl)-3-	215–217	88[c]
6-Carbethoxy-3-nitrobenzoyl chloride	2-(2-Thenoyl)-3-	114–115	51	2-(2-Thenoyl)-3-	215–217	95[c]
3-Nitrophthalic anhydride				2-(2-Thenoyl)-3-	215–217	19
4-Nitrophthalic anhydride				2-(2-Thenoyl)-5-	189	38

[a] The acid chloride or anhydride was reacted with thiophene in each case.

[b] By hydrolysis of the corresponding ester.

[c] Analysis for this ester will be found in the experimental part.

This investigation has been further extended to the study of the reaction of 3- and of 4-nitrophthalic anhydride with phenylmagnesium bromide. These reactions gave predominantly one benzoylnitrobenzoic acid in each case after crystallization from acetic acid. The products obtained by the decarboxylation of these benzoylnitrobenzoic acids have been compared with authentic samples of the corresponding nitrobenzophenones and it has been shown that the benzoylnitrobenzoic acids obtained are structurally the benzene analogs of the acids obtained in the thiophene series by this reaction.

2-(2-Thenoyl)-3-nitrobenzoic acid and 2-(2-thenoyl)-5-nitrobenzoic acid were cyclized to 8- and 6- nitrothiophanthrenequinone, respectively, barring any rearrangement during cyclization.

EXPERIMENTAL

2-(2-Thenoyl)-3-nitrobenzoic acid. (*Method A*). The Grignard reagent from 8.1 g. (0.3 mole) of magnesium turnings and 63 g. (0.3 mole) of 2-iodothiophene in 300 ml. of anhydrous ether was run into a flask containing a mixture of 57.9 g. (0.3 mole) of 3-nitrophthalic anhydride and 450 ml. of freshly-distilled anisole which was cooled externally with ice. The mixture was stirred vigorously during the addition of the Grignard reagent and then for four hours afterward. The cooled reaction mixture was then decomposed by the addition of 450 ml. of saturated ammonium chloride solution and acidified with 6 *N* hydrochloric acid. The organic layer was separated, washed with water, and then extracted with 750 ml. of 10% sodium carbonate solution used in three portions.

The extracts were cooled with ice and acidified by the dropwise addition of 6 *N* hydrochloric acid with vigorous stirring. The precipitated keto-acid was washed with water and crystallized from 80% acetic acid to give the pure acid melting at 215–217°. The yield was 53%.

Ethyl 2-(2-thenoyl)-3-nitrobenzoate. A solution of 5 g. of 2-(2-thenoyl)-3-nitrobenzoic acid in 50 ml. of absolute ethanol was saturated with dry hydrogen chloride. After heating on a steam-bath for two hours, and standing overnight at room temperature, the solution was poured into water and the resulting turbid mixture was extracted with ether. The ether extract was washed with sodium carbonate solution, then with water, and dried over sodium sulfate. After evaporation of the solvents under reduced pressure, the crude residue was crystallized from petroleum ether. The yield was 91% of ester melting at 115°.

Anal. Calc'd for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.61, N, 4.59.

Found: C, 55.00; H, 3.28; N, 4.61.

2-(2-Thenoyl)-5-nitrobenzoic acid. (*Method A*). In the manner described above for the isomeric acid, the Grignard reagent from 52.5 g. (0.25 mole) of 2-iodothiophene was reacted with 48 g. (0.25 mole) of 4-nitrophthalic anhydride. Crystallization of the crude product furnished the pure acid melting at 189–190°. The yield was 56%.

2-(2-Thenoyl)-3-nitrobenzoic acid and 2-(2-thenoyl)-6-nitrobenzoic acid. (*Method B*). According to the method of Lee and Weinmayr (2), the Grignard reagent from 2.7 g. (0.1 mole) of magnesium and 16.3 g. (0.1 mole) of 2-bromothiophene in 100 ml. of absolute ether was added over a period of ten minutes to a solution of 19.3 g. (0.1 mole) of 3-nitrophthalic anhydride in 275 ml. of dry benzene at 45° and then stirred for two hours longer at that temperature. The mixture was hydrolyzed by adding 300 ml. of water and 1 g. of magnesium oxide and refluxing for one hour. The mixture was filtered while warm and the aqueous layer, containing the organic acids as their magnesium salts, was separated and cooled. Addition of acetic acid to this solution until no further precipitate formed furnished crude 2-(2-thenoyl)-3-nitrobenzoic acid, which was washed with water and dried. The yield was 42.5%. Crystallization from nitrobenzene gave the pure acid melting at 215–217°. The filtrate from the above, still containing acetic acid, was strongly acidified with hydrochloric acid, whereupon crude 2-(2-thenoyl)-6-nitrobenzoic acid precipitated. This was washed with water and dried. The yield was 30.9%. Crystallization from chlorobenzene furnished the pure acid melting at 172–173°.

2-(2-Thenoyl)-5-nitrobenzoic acid and 2-(2-thenoyl)-4-nitrobenzoic acid. (*Method B*). These compounds were synthesized according to the method of Lee and Weinmayr as outlined above, except that 4-nitrophthalic anhydride was substituted for 3-nitrophthalic anhydride. Addition of acetic acid to the hydrolysate gave crude 2-(2-thenoyl)-5-nitrobenzoic acid in 34.2% yield. Crystallization from nitrobenzene afforded the pure acid melting at 189–190°.[2] 2-(2-Thenoyl)-4-nitrobenzoic acid precipitated in 19.2% yield when the filtrate from the above was made strongly acid with hydrochloric acid. The crude material was recrystallized from chlorobenzene to give the pure acid melting at 170–171°.[2]

2-Nitrobenzo-(2-thienone). To 16.7 g. (0.1 mole) of 2-nitrobenzoic acid and 75 ml. of dry benzene there was slowly added at room temperature, under reflux, 23 g. (0.11 mole) of phosphorus pentachloride. The reaction was allowed to proceed at this temperature for one hour and then for one hour at 100°, at the end of which time the mixture was cooled to room temperature. To this mixture containing the acid chloride, together with 9 g. (0.11

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[2] Lee and Weinmayr (2) report m.p. 149–150° for 2-(2-thenoyl)-5-nitrobenzoic acid.

mole) of thiophene and 50 ml. of dry benzene, there was added, dropwise and under reflux, 29 g. (0.11 mole) of stannic chloride, with stirring and external cooling with ice. After the addition of the stannic chloride, the mixture was stirred for two hours at room temperature and then externally cooled with ice. It was decomposed with 100 ml. of 4 *N* hydrochloric acid and extracted with ether. The organic layer was separated and washed with water, sodium carbonate solution, and water. The ether-benzene layer was dried over calcium chloride and the organic solvents were removed under reduced pressure. The residue was crystallized from petroleum ether (b.p. 60–75°) to give the pure ketone melting at 102°. The yield was 31%.

3-Nitrobenzo-(2-thienone). In the manner outlined above, the acid chloride from 16.7 g. (0.1 mole) of 3-nitrobenzoic acid furnished a 28% yield of this ketone, melting, after recrystallization from 95% ethanol, at 125°.

TABLE III
KETONES

PARENT AROYL NITROBENZOIC ACID	KETONE	BY DECARBOXYLATION		BY FRIEDEL-CRAFTS		ANALYSES					
						C		H		N	
		M.P., °C.	YIELD, %	M.P., °C.	YIELD, %	Calc'd	Found	Calc'd	Found	Calc'd	Found
2-(2-Thenoyl)-3-	2-Nitrobenzo-(2-thienone)	102	85	102	31	56.65	56.92	3.00	3.00	6.00	6.13
2-Benzoyl-3-	2-Nitrobenzophenone	105	88	105	18	(9)					
2-(2-Thenoyl)-5-	4-Nitrobenzo-(2-thienone)	174–175	80	175	63	56.65	56.72	3.00	3.28	6.00	5.97
2-Benzoyl-5-	4-Nitrobenzophenone	138	96	138	72	(3)					
2-(2-Thenoyl)-6-	3-Nitrobenzo-(2-thienone)	124–125	85	125	28	56.65	56.92	3.00	2.72	6.00	6.29
2-(2-Thenoyl)-4-	3-Nitrobenzo-(2-thienone)	124–125	83								

4-Nitrobenzo-(2-thienone). In the manner described above, the acid chloride from 16.7 g. (0.1 mole) of 4-nitrobenzoic acid furnished a 63% yield of this ketone, melting, after recrystallization from 95% ethanol, at 175°.

Decarboxylation of 2-(2-thenoyl)-3-nitrobenzoic acid. A 5-g. sample of the acid, 10 g. of freshly-distilled quinoline, and 1 g. of copper-bronze powder were heated by a flame in a small flask to 200° until a brisk evolution of carbon dioxide began. When the evolution of gas had ceased, the mixture was filtered while still warm and poured into 100 ml. of 4 *N* hydrochloric acid. The solid precipitate was washed with hydrochloric acid, water, sodium carbonate solution, and water. After two recrystallizations from petroleum ether (b.p. 60–75°), the 2-nitrobenzo-(2-thienone) melted at 102°. The yield was 85%. A mixture m.p. with the authentic sample prepared as above showed no depression.

Decarboxylation of 2-(2-thenoyl)-6-nitrobenzoic acid. In the manner outlined above, 5 g. of this acid furnished an 85% yield of 3-nitrobenzo(2-thienone), melting, after two recrystallizations from petroleum ether (b.p. 60–75°), at 124–125°. A mixture m.p. with the authentic sample prepared as above showed no depression.

Decarboxylation of 2-(2-thenoyl)-5-nitrobenzoic acid. In the manner described above, 2.5 g. of this acid gave an 80% yield of 4-nitrobenzo(2-thienone), melting, after two recrystallizations from petroleum ether (b.p. 60–75°), at 174–175°. A mixture m.p. with the authentic sample prepared as above showed no depression.

Decarboxylation of 2-(2-thenoyl)-4-nitrobenzoic acid. In the manner outlined above, 2.0 g. of this acid afforded an 83% yield of 3-nitrobenzo(2-thienone), melting, after two recrystallizations from petroleum ether (b.p. 60–75°), at 124–125°. A mixture m.p. with the authentic sample prepared as above showed no depression.

Rearrangement of 2-(2-thenoyl)-6-nitrobenzoic acid. A 1-g. portion of this acid, m.p. 172–173°, was dissolved in 6 ml. of concentrated sulfuric and maintained at a temperature of 60° for one hour. The solution was cooled and added dropwise, with stirring, to an excess of ice-water. The precipitated material, after washing with water, was recrystallized several times from nitrobenzene to give 2-(2-thenoyl)-3-nitrobenzoic acid, m.p. 215–217°. A mixture m.p. with an authentic sample showed no depression.

Rearrangement of 2-(2-thenoyl)-4-nitrobenzoic acid. In the manner outlined above, this acid, m.p. 170–171°, was converted into 2-(2-thenoyl)-5-nitrobenzoic acid, melting at 189–190°. A mixture m.p. with an authentic sample showed no depression.

Friedel-Crafts reactions of the half ethyl esters of 3-nitrophthalic acid. Both the half ester melting at 157° and the half ester melting at 111° (8) were converted to the corresponding acid chlorides with thionyl chloride. The acid chlorides were reacted with thiophene in the usual manner using stannic chloride as the catalyst. In each case an approximate 50% yield of ethyl 2-(2-thenoyl)-3-nitrobenzoate melting at 114–115° was obtained. A mixture melting point of this ester and the product of esterification of the acid obtained by the Grignard reagent (Ia) showed no depression. Hydrolysis of the ester with sulfuric acid in aqueous acetic acid gave 2-(2-thenoyl)-3-nitrobenzoic acid melting at 217°. A mixture melting point with the acid Ia showed no depression.

Friedel-Crafts reaction of 3-nitrophthalic anhydride with thiophene. A mixture of 10 g. of 3-nitrophthalic anhydride, 7 g. of aluminum chloride, and 100 ml. of nitrobenzene was heated to 80° and 5 g. of thiophene was added dropwise, under reflux, with stirring. After three hours of stirring at 80°, the mixture was a viscous mass, which was then decomposed by pouring into ice-cold 1 *N* hydrochloric acid. The nitrobenzene was then removed by steam-distillation, the residue being washed with dilute hydrochloric acid and then with water. Treatment of the solid with three 100-ml. portions of 15% sodium carbonate solution gave an extract which was filtered and then acidified with hydrochloric acid. The precipitated 2-(2-thenoyl)-3-nitrobenzoic acid was washed and recrystallized to give a 19% yield of pure material melting at 215–217°. A mixture m.p. with the corresponding acid Ia obtained from the Grignard reaction showed no depression.

Friedel-Crafts reaction of 4-nithrophthalic anhydride with thiophene. In the same manner, except that the reaction was carried out at 50°, 10 g. of 4-nitrophthalic anhydride afforded 2-(2-thenoyl)-5-nitrobenzoic acid. After recrystallization there was obtained a 38% yield of pure acid melting at 189–190°. A mixture m.p. with the corresponding acid Ia obtained from the Grignard reaction showed no depression.

2-Benzoyl-3-nitrobenzoic acid. The Grignard reagent from 40 g. (0.25 mole) of bromobenzene was condensed in the usual manner with 48 g. (0.25 mole) of 3-nitrophthalic anhydride in anisole. The crude reaction product was recrystallized from 80% acetic acid to give a 49% yield of keto-acid melting at 238° (3, 9).

2-Benzoyl-5-nitrobenzoic acid. The Grignard reagent from 40 g. (0.25 mole) of bromobenzene was condensed according to the usual procedure, with 48 g. (0.25 mole) of 4-nitrophthalic anhydride in anisole. Recrystallization of the crude reaction product gave a 38% yield of the pure acid, m.p. 219–220° (9).

Decarboxylation of 2-benzoyl-3-nitrobenzoic acid. By the usual method, 3 g. of the acid was decarboxylated at 200°, giving a product which on recrystallization from ethanol melted at 105°. The yield was 88%. A mixture m.p. with an authentic sample of 2-nitrobenzophenone (10) showed no depression.

Decarboxylation of 2-benzoyl-5-nitrobenzoic acid. According to the usual procedure, 3 g. of the acid was decarboxylated. The crude product was recrystallized from ethanol to give a 96% yield of pure ketone, m.p. 138°. A mixture m.p. with an authentic sample of 4-nitrobenzophenone (11) showed no depression.

Nitrothiophanthrenequinone. A 5-g. sample of 2-(2-thenoyl)-3-nitrobenzoic acid was treated with 5 g. of phosphorus pentachloride in 30 ml. of dry benzene at 80°. The acid chloride thus obtained was added to 3.5 g. of aluminum chloride in 50 ml. of nitrobenzene at 0°; the mixture was allowed to stand for two hours at room temperature and then was heated for 8 hours at 120°. After hydrolysis of the mixture with dilute hydrochloric acid and removal of the nitrobenzene by steam-distillation, the solid was washed with dilute acid, water, sodium carbonate solution, and water. The crude product was recrystallized from acetic acid to give a 40% yield of quinone melting at 231–233°.

Anal. Calc'd for $C_{12}H_5NO_4S$: C, 55.59; H, 1.93; N, 5.40.
Found: C, 55.82; H, 2.31; N, 5.39.

6-Nitrothiophanthrenequinone. In the manner described above, 5 g. of 2-(2-thenoyl) 5-nitrobenzoic acid furnished a 54% yield of this quinone, purified by sublimation *in vacuo*, m.p. 219–220°.

Anal. Found: C, 55.41; H, 2.20; N, 5.46.

SUMMARY

1. Various 2-(2-thenoyl)nitrobenzoic acids have been synthesized by several methods.
2. The structure of each of these acids has been proven through the characterization of the products of decarboxylation.
3. These acids have been cyclized to give nitrothiophanthrenequinones.

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