[Contribution from the Chemical Laboratory of Washington University]

STUDIES IN THE ANTHRONE SERIES.

I. THE CONDENSATION OF PHTHALIDE WITH AROMATIC COMPOUNDS[1]

By Al Steyermark with John H. Gardner

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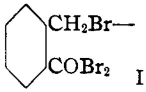
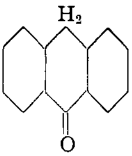
In view of the importance in medicine of certain anthrones and dianthrones such as those found in chrysarobin, it has seemed of interest to study methods for the determination of the structures of members of this class of compounds. Most of the work which has been done heretofore has been purely analytical in nature and consequently cannot be regarded as furnishing a final solution of the problem. The present work represents the beginning of a series of studies on the methods of synthesizing anthrones and the rules of orientation involved.

It was shown by Mayer and Fischbach[2] that ω-bromo-*o*-toluyl bromide (I) can be condensed with benzene by means of aluminum chloride to form anthrone (II). Using chlorobenzene, they obtained a product which they identified as 2-chloro-9-anthrone (III).



I



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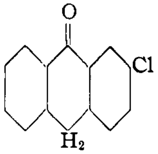
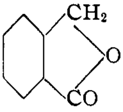
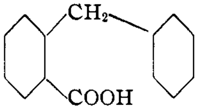


III

Since phthalide (IV) is related to ω-bromo-*o*-toluyl bromide as an acid anhydride to its bromide, it would be expected to undergo the same type of condensation reactions. As a matter of fact, King[3] obtained *o*-benzylbenzoic acid (V) by the condensation of phthalide with benzene. In the present investigation, it has been found that anthrone is formed in this reaction in somewhat greater quantities than the benzylbenzoic acid.



IV



V

In view of the work of Mayer and Fischbach and of King, and by analogy with the product obtained in the condensation of phthalic anhydride with toluene,[4] it would be expected that phthalide could be condensed with

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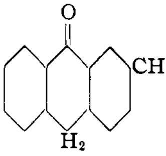
[1] Based upon a portion of a thesis submitted by Al Steyermark, Fellow in Chemistry and Physics, in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Washington University, June, 1930.

[2] Mayer and Fischbach, *Ber.*, **58**, 1251 (1925).

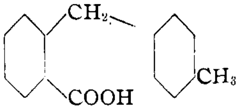
[3] King, This Journal, **49**, 562 (1927).

[4] Friedel and Crafts, *Ann. chim. phys.*, [6] 14, 447 (1888).

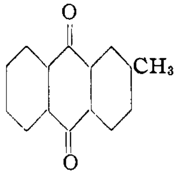
toluene with the formation of 2-methyl-9-anthrone (VI) and possibly *o*-(4-methylbenzyl)-benzoic acid (VII) as the principal products. However, on carrying out the reaction, the product was an oily mass, obviously a mixture, since all of the compounds which might have been expected to be formed are solids. On attempting to work up the product, a small amount of unchanged phthalide was the only pure substance which could be isolated. The crude product on oxidation gave a good yield of 2-methylanthraquinone (VIII), indicating the presence of either 2-methyl-9-anthrone (VI) or 2-methyl-10-anthrone (IX) or both.



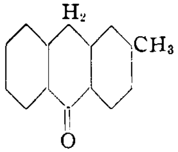
VI



VII

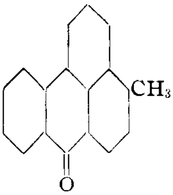


VIII

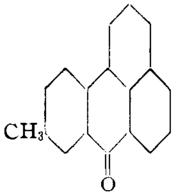


IX

As both isomers melt at practically the same temperature, it would be expected that they would exhibit practically the same solubilities in all solvents and consequently it would be impossible to separate them by fractional crystallization. This we have found to be the case. However, the benzanthrones which can be obtained from them[5] melt 30° apart and would be expected to differ markedly in their solubility relationships. This was found to be the case. 2-Methylbenzanthrone (X), m. p. 199°, is easily crystallized from a mixture of benzene and petroleum ether, while the isomeric 6-methylbenzanthrone (XI), m. p. 170°, is too soluble in benzene to be crystallized readily from it or from a mixture of benzene and petroleum ether.



X



XI

The oily mixture obtained from the condensation of phthalide with toluene was treated with glycerol and sulfuric acid and the product subjected to fractional crystallization from a mixture of benzene and petroleum ether. In this way, 2-methylbenzanthrone (X) was isolated, showing that

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[5] Steyermark with Gardner, This Journal, **52**, 4887 (1930).

2-methyl-10-anthrone was present in the original condensation product. From the character of that material and by analogy with the work of Mayer and Fischbach and of King, it is certain that the isomeric 2-methyl-9-anthrone was also formed, but it was found impossible to isolate it or the benzanthrone formed from it in the reaction with glycerol and sulfuric acid.

On condensing phthalide with chlorobenzene, there was obtained a red, oily mass which, on oxidation, yielded 2-chloro-anthraquinone, indicating the presence of either 2-chloro-9-anthrone or 2-chloro-10-anthrone or both. In this case neither the anthrones nor the corresponding benzanthrones could be isolated in a sufficiently pure state for identification. All indications point to the presence of both possible isomers.

From the results of Mayer and Fischbach and of King, it would be concluded that the condensation of phthalide with aromatic hydrocarbons and their derivatives takes place exclusively through the methylene group of phthalide with the formation of *o*-benzylbenzoic acids which may be dehydrated to anthrones. The present work demonstrates that the carboxyl residue also reacts, leading to the formation of benzoylbenzyl alcohols, which are dehydrated to anthrones.

Experimental

Anthrone.—Ten grams of phthalide was dissolved in 50 cc. of benzene in a 500-cc. flask provided with a reflux condenser and protected by a calcium chloride tube; 20 g. of anhydrous aluminum chloride was added and the mixture heated on the water-bath for ten hours. After cooling, 100 cc. of 1:1 hydrochloric acid was added and the excess benzene driven off with steam. The residue was cooled and the solid material filtered off; yield of light yellow needles from alcohol followed by recrystallization from 3:1 benzene–petroleum ether, 4 g. (28%), m. p. 152–154°. A mixed melting point with anthrone showed no depression.

For further identification, a portion was oxidized with chromic acid in glacial acetic acid, yielding anthraquinone, m. p. 282–284°. Another portion was methylated by the method of Meyer and Schlösser[6] to 9-anthranol methyl ether, m. p. 94–95°.

Condensation of Phthalide with Toluene.—A mixture of 15 g. of phthalide in 90 cc. of toluene with 30 g. of anhydrous aluminum chloride was heated for fifteen hours on the steam-bath. On working up the product as was done with anthrone, there was obtained an oily mass from which no pure compound could be isolated.

Oxidation of the Phthalide–Toluene Condensation Product.—Two grams of the crude product was dissolved in 15 cc. of glacial acetic acid and a solution of 0.6 g. of chromic acid in 6 cc. of 50% acetic acid was added. After heating on the water-bath for five minutes, the product was precipitated by the addition of water, giving nearly colorless needles from alcohol, m. p. 168–170°. A mixed melting point with 2-methylanthraquinone showed no depression.

Preparation of 2-Methylbenzanthrone from the Phthalide–Toluene Condensation Product.—The oily mass obtained in the condensation described above was dissolved in 150 cc. of 82% sulfuric acid and 20 g. of glycerol was added. The mixture was heated in an oil-bath at 125–130° for four hours. The red solution was then poured onto

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[6] Meyer and Schlösser, *Ann.*, **420**, 126 (1920).

cracked ice. The olive-green precipitate was extracted with 500 cc. of hot 1% sodium hydroxide solution. After washing with water and drying, the residue was extracted with hot benzene. After cooling and adding petroleum ether, the benzene extract deposited 3.5 g. of yellow needles of 2-methylbenzanthrone, m. p. 198.5–199°, from benzene and petroleum ether. A mixed melting point with 2-methylbenzanthrone prepared from 2-methyl-9-anthrone showed no depression.[5]

Anal. Subs., 0.1033: CO_2, 0.3403; H_2O, 0.0444. Calcd. for $C_{18}H_{12}O$; C, 88.49; H, 4.91. Found: C, 88.35; H, 4.81.

Condensation of Phthalide with Chlorobenzene.—A mixture of 10 g. of phthalide in 55 cc. of chlorobenzene with 20 g. of anhydrous aluminum chloride was heated in an oil-bath at 125–130° for fifteen hours. The resulting product was worked up as before. No pure compound could be isolated.

A portion of the crude condensation product on oxidation with chromic acid gave 2-chloro-anthraquinone, m. p. 206–207°. On attempting to prepare a chlorobenzanthrone, a mixture which could not be separated into its components was obtained.

Summary

1. Phthalide can be condensed with aromatic hydrocarbons and their derivatives with the formation of anthrones.
2. Condensation takes place both through the methylene and the carboxyl residues of phthalide resulting in the formation of a mixture of isomers and rendering the method unsuitable for the synthesis of anthrones of definite structure.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

STUDIES IN THE ANTHRONE SERIES.
II. THE SYNTHESIS OF SOME HYDROXYMETHYLANTHRONES[1]

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Since the most important of the naturally occurring anthrones are derived from 1,8-dihydroxy-3-methylanthraquinone and some related compounds, it has seemed of interest to study methods for the synthesis of hydroxy- and hydroxymethylanthrones which will afford definite proof of the structures of the products obtained. Most of the work which has been done on the determination of the structure of this class of compounds has been analytical in nature and has not always led to concordant results.[2] The only synthetic method which has been extensively investigated is the phthalaldehyde acid condensation method originated by Bistrzycki, which has been extended and improved by Adams and his students. The

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[1] Based upon a portion of a thesis submitted by Al Steyermark, Fellow in Chemistry and Physics, in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Washington University, June, 1930.

[2] Cross and Perkin, *J. Chem. Soc.*, 292 (1930), and previous papers by Perkin and his co-workers; Green, *ibid.*, 2341 (1927).