

been isolated and certain physical and chemical properties of these substances are described. An anhydrous crystalline base as well as a hydrated (the monohydrate) crystalline base has been prepared. A third crystalline modification of the base has been identified when the melted base is supercooled. This is believed to be a tautomeric form of benzothiazoleguanidine. The results of microscopical studies of these substances are presented.

BROOKLYN, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

STUDIES IN THE ANTHRONE SERIES.

III. THE SYNTHESIS OF 3-METHOXYPHTHALALDEHYDE ACID AND A NEW SYNTHESIS OF CHRYSAZIN^{1,2}

BY CHARLES A. NAYLOR, JR., WITH JOHN H. GARDNER

RECEIVED JULY 23, 1931

PUBLISHED NOVEMBER 5, 1931

As a number of the naturally occurring anthrone and anthraquinone derivatives are related to chrysazin, 1,8-dihydroxyanthraquinone, a convenient method for the synthesis of compounds of this type would be of value for the solution of some problems regarding the structure of these substances. The most promising method of attack is the phthalaldehyde acid condensation originated by Bistrzycki and his co-workers and improved by Adams and his students,³ provided that suitable starting materials can be obtained.

First of all, it was necessary to obtain a phthalaldehyde acid substituted in the position ortho to the aldehyde group with hydroxyl or a group which could be replaced by hydroxyl. A search of the literature suggested 3-nitrophthalaldehyde acid,⁴ but some preliminary experiments on the synthesis of anthraquinone derivatives through the condensation of nitrophthalaldehyde acids with phenols led to unexpected complications.⁵ Another method of attack was suggested by the work of Bentley, Robinson and Weizmann on the oxidation of 1,5-dihydroxynaphthalene monomethyl ether.⁶ They obtained in this way 3-methoxyphthalic acid and a compound which might have been, from the method of preparation, either

¹ Previous papers in this field are (a) Steyermark with Gardner, *THIS JOURNAL*, 52, 4884 (1930); (b) *ibid.*, 52, 4887 (1930).

² Based upon a portion of a thesis submitted by Charles A. Naylor, Jr., Fellow in Chemistry, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Washington University, June, 1931.

³ Brubaker and Adams, *THIS JOURNAL*, 49, 2279 (1927), give a bibliography of the work in this field.

⁴ Wegscheider and v. Dubrav, *Monatsh.*, 24, 805 (1903).

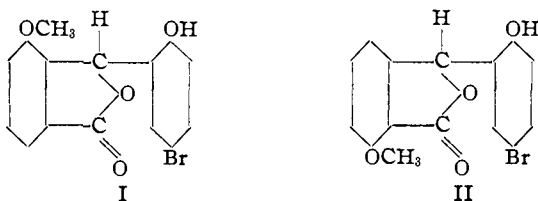
⁵ Rolf, "Thesis," Washington University, 1930.

⁶ Bentley, Robinson and Weizmann, *J. Chem. Soc.*, 91, 104 (1907).

3- or 6-methoxyphthalonic acid, the former being more probable. Since phthalonic acid can be converted into phthalaldehyde acid through the bisulfite compound,⁷ this suggested a method for the preparation of 3-methoxyphthalaldehyde acid.

On carrying out the oxidation of 1,5-dihydroxynaphthalene monomethyl ether with alkaline potassium permanganate, it was found that the reaction was very difficult to control. However, since it had previously been found that 1-naphthyl methyl ether is readily oxidized to phthalonic acid by potassium permanganate, the oxidation of 1,5-di-methoxynaphthalene was tried and found to proceed smoothly. The product was subjected to the procedure used by Tcherniac for the conversion of phthalonic acid into phthalaldehyde acid. In this way there was obtained a compound which, from its properties and analysis, might be either 3- or 6-methoxyphthalaldehyde acid, the former seeming the more probable.

In order to distinguish between the two possibilities, the methoxyphthalaldehyde acid was converted into an anthraquinone derivative. On condensation with *p*-bromophenol, there was obtained a substituted phthalide which might be represented by Formula I or II, depending upon whether the starting substance was 3- or 6-methoxyphthalaldehyde acid. Only one product was obtained at this point, showing that we were not dealing with a mixture of the two possible isomers. The phthalide was then reduced to the corresponding benzylbenzoic acid, which was dehydrated to an anthrone. This, on oxidation, yielded a product which agreed in all of its properties with the monomethyl ether of chrysazin (1,8-dihydroxyanthraquinone) as given by Oesterle and Haugseth.⁸ 6-Methoxyphthalaldehyde acid would have given the monomethyl ether of anthrarufin (1,5-dihydroxyanthraquinone).



The new product was demethylated to the corresponding dihydroxyanthraquinone, which was found to agree in all of its properties with chrysazin. As no chrysazin from other sources was available, the melting points of a mixture of the new product with anthrarufin and of a mixture of the acetates were determined. In each case, a decided depression was observed, demonstrating conclusively that the anthraquinone deriva-

⁷ Tcherniac, German Patents 79,693 (1895) and 86,914 (1896); Graebe and Trümpy, *Ber.*, **31**, 369 (1898).

⁸ Oesterle and Haugseth, *Arch. Pharm.*, **253**, 335 (1915).

tive was chryszin and that the starting material must have been 3-methoxyphthalaldehyde acid.

The use of 3-methoxyphthalaldehyde acid in the synthesis of some naturally occurring anthrone and anthraquinone derivatives is to be the subject of further investigation.

Experimental

Methylation of 1,5-Dihydroxynaphthalene.—Two hundred grams of 1,5-dihydroxynaphthalene was dissolved in 220 cc. of 10 *N* sodium hydroxide and 400 cc. of water in a 3-liter flask provided with a good mechanical stirrer, a reflux condenser and a dropping funnel. To this mixture 150 cc. of dimethyl sulfate was added in small portions during a period of forty-five minutes. The temperature was not allowed to rise above 70° and the reaction was allowed to continue until half an hour after the last addition of dimethyl sulfate. Two hundred cc. of 10 *N* sodium hydroxide and 200 cc. of water were added to destroy any excess of dimethyl sulfate. The stirring was continued for a few minutes, after which the mixture was allowed to cool. The brown insoluble residue of 1,5-dimethoxynaphthalene was removed by filtration, washed thoroughly with water, dried in air and finally in an oven at 100°. The filtrate was acidified with concd. hydrochloric acid and the resulting light brown precipitate of 1-hydroxy-5-methoxynaphthalene was washed and dried. The yield was 130 g. (55%) of the dimethyl ether and 100 g. (46%) of the monomethyl ether. No attempt was made to purify the products since the crude products were found satisfactory for subsequent procedures.

Methylation of 1-Hydroxy-5-methoxynaphthalene.—The procedure was identical with that used for the methylation of 1,5-dihydroxynaphthalene. The yield of crude dimethoxynaphthalene was quantitative.

3-Methoxyphthalaldehyde Acid.—In a 3-liter flask provided with a good mechanical stirrer, a reflux condenser and a dropping funnel, were placed 500 cc. of 0.5 *N* sodium hydroxide and 47 g. of 1,5-dimethoxynaphthalene. The mixture was heated to boiling and a boiling solution of 184 g. of potassium permanganate in 1500 cc. of water was added in small portions during one and one-half hours, with vigorous stirring. After the last addition of permanganate, the mixture was boiled for thirty to forty-five minutes to complete the oxidation. Any unchanged permanganate was reduced by the addition of 20 cc. of alcohol, and the mixture was cooled and filtered free of precipitated manganese dioxide. The filtrate was acidified with 150 cc. of concd. hydrochloric acid, evaporated to 500 cc., cooled and filtered. The filtrate was then neutralized with sodium hydroxide, 50 g. of sodium bisulfite was added and the mixture was evaporated to dryness on the steam-bath in a partial vacuum. The residue was stirred with 100 cc. of concd. hydrochloric acid and evaporated to dryness on the steam-bath in an open dish. The hydrochloric acid treatment and evaporation were repeated. The residue was extracted with benzene in a special type of continuous extractor designed in this Laboratory.⁹ The capacity of this extractor was sufficient for the simultaneous extraction of the residues from two oxidations. The benzene extract was distilled to remove the benzene and the resulting brown sirupy liquid was crystallized from 200 cc. of water using activated carbon for purification. On cooling the hot solution and allowing it to stand for twenty-four to forty-eight hours, the 3-methoxyphthalaldehyde acid separated out in fine, long, white needles which were recrystallized from water. The crystals were dried in air and finally in vacuum over phosphorus pentoxide. The substance melted to a turbid liquid at 121–122° and then seemed to solidify partially and remelt, the last particle disappearing at 144.8°; yield, 5–7 g. (11–16%) for a single oxidation.

⁹ Gardner and Kerone, *J. Chem. Ed.*, 7, 593 (1930).

Anal. Subs., 0.1032: CO_2 , 0.2260; H_2O , 0.0409. Calcd. for $\text{C}_9\text{H}_8\text{O}_4$: C, 60.00; H, 4.44. Found: C, 59.73; H, 4.40. *Neutral equivalent.* Subs., 0.2352: 13.60 cc. of 0.0973 *N* NaOH. Calcd. for $\text{C}_9\text{H}_8\text{O}_4$: neut. equiv., 180. Found: 177.85.

3-Methoxy-2-(2-hydroxy-5-bromophenyl)-phthalide (I).—In a 15-cm. evaporating dish 10 g. of 3-methoxyphthalaldehyde acid and 9.6 g. of *p*-bromophenol were thoroughly mixed and to the mixture 28 cc. of 85% sulfuric acid was added slowly with stirring. After the sirupy mass became homogeneous, it was allowed to stand at room temperature for twelve hours, at the end of which period it had partially solidified. The mixture was poured onto crushed ice and allowed to stand until the sticky product which formed at first became a heavy, white granular solid. The product was filtered, washed free of sulfuric acid and then treated with a small amount of ether to remove the excess *p*-bromophenol. It was crystallized from 95% alcohol forming fine, white needles, m. p. 198–200°. ¹⁰ Glacial acetic acid may also be used for crystallization. In either case crystallization was very slow. The yield of crude product was quantitative and that of the pure product 10.3 g. (55%).

Anal. Subs., 0.4109: 39.90 cc. of 0.0986 *N* AgNO_3 ; 34.54 cc. of 0.0977 *N* NH_4SCN . Calcd. for $\text{C}_{15}\text{H}_{11}\text{O}_4\text{Br}$: Br, 23.85. Found: Br, 23.81.

3-Methoxy-2-(2-hydroxybenzyl)-benzoic Acid.—A solution of 20 g. of 3-methoxy-2-(2-hydroxy-5-bromophenyl)-phthalide in 500 cc. of 10% sodium hydroxide was placed in a 1-liter round-bottomed flask and treated with 60 g. of powdered zinc. The mixture was heated almost to boiling for fifteen hours with mechanical stirring. The solution was then filtered from the zinc and an excess of concd. hydrochloric acid was slowly added to the filtrate. The resulting gummy, white precipitate was broken up, filtered and washed. It was dissolved in cold 10% sodium carbonate solution. The solution was filtered from undissolved impurities and an excess of hydrochloric acid was added to the filtrate. A gummy white precipitate formed which solidified on standing. It was filtered and washed free of hydrochloric acid. The product thus obtained was sufficiently pure for use in the preparation of the corresponding anthrone; yield, 12.5 g. (82%). The product was purified by crystallization from toluene, forming white, irregular plates, m. p. 185–186°.

Anal. Subs., 0.1020: CO_2 , 0.2609; H_2O , 0.0499. Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_4$: C, 69.77; H, 5.43. Found: C, 69.75; H, 5.44. *Neutral equivalent.* Subs., 0.2122: 8.50 cc. of 0.0973 *N* NaOH. Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_4$: neut. equiv., 258. Found: 256.6.

1-Hydroxy-8-methoxy-10-anthrone.—Ten grams of 3-methoxy-2-(2-hydroxybenzyl)-benzoic acid was suspended in 100 cc. of concentrated sulfuric acid and allowed to stand at room temperature until solution was complete. This required from two to three hours. The resulting dark red solution was then poured on ice to precipitate the anthrone. This was first obtained as a granular, yellow precipitate which, however, darkened in color and became sticky upon being washed with water. The precipitate was filtered, washed free of sulfuric acid and finally treated with cold 10% sodium carbonate solution to remove any unchanged benzylbenzoic acid. The crude anthrone was filtered, washed free of sodium carbonate and dried in the air. The product thus obtained was sufficiently pure for oxidation directly to the anthraquinone; yield, 2.7 g. (30%). The product was completely purified by several crystallizations from alcohol, using activated carbon the first time, forming pale yellow needles, m. p. 170–171°.

Anal. Subs., 0.0826: CO_2 , 0.2261; H_2O , 0.0363. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 75.00; H, 5.00. Found: C, 74.66; H, 4.89.

1-Hydroxy-8-methoxyanthraquinone (Chrysazin Monomethyl Ether).—A solution of 1.0 g. of crude 1-hydroxy-8-methoxy-10-anthrone in 100 cc. of glacial acetic acid

¹⁰ All melting points in this paper are corrected.

was treated with 0.55 g. of chromium trioxide dissolved in a few cc. of water. Oxidation at room temperature did not take place readily, so the mixture was heated for about thirty minutes on a steam-bath. The solution changed in color from greenish-yellow to violet and considerable heat was generated. On cooling and allowing to stand overnight, no crystals were deposited. The solution was heated to boiling, water added to turbidity, and the solution again allowed to cool. Small orange-yellow needles were deposited. These were removed by filtration and the precipitation by dilution was repeated. The crude material was crystallized from 95% alcohol forming fine, orange-red needles; yield, 0.3 g. (28%). The substance darkened at 150°, softened at 175° and melted at 196.8–198°. Oesterle and Haugseth⁸ give m. p. 198°.

Anal. Subs., 0.1093: CO₂, 0.2825; H₂O, 0.0401. Calcd. for C₁₅H₁₀O₄: C, 70.83; H, 3.93. Found: C, 70.49; H, 4.07.

1,8-Dihydroxyanthraquinone (Chrysazin).—To a solution of 1.0 g. of 1-hydroxy-8-methoxyanthraquinone in 125 cc. of glacial acetic acid was added 50 cc. of constant boiling hydrobromic acid. The mixture was boiled for twelve hours. During the boiling there separated out a small quantity of black material which was removed by filtration. The solution was allowed to stand overnight but no crystals were deposited. It was then heated to boiling, water added to turbidity and the solution cooled. A yellowish-brown compact solid was deposited. This was crystallized from dilute alcohol (1:1), forming golden-yellow plates, m. p. 192–193°; yield, 0.1 g. (11%). Liebermann¹¹ gives m. p. 191°; Green¹² gives orange-red at 160°, m. p. 193°.

Anal. Subs., 0.0498: CO₂, 0.1281; H₂O, 0.0143. Calcd. for C₁₄H₈O₄: C, 70.00; H, 3.33. Found: C, 70.15; H, 3.20.

No sample of 1,8-dihydroxyanthraquinone was available for comparison but a mixed melting point determination with 1,5-dihydroxyanthraquinone, m. p. 279.4–280.2°, was made. A mixture of equal amounts of the two substances melted over a range of 7.5° from 182.5 to 190°, proving that the compounds were not identical.

1,8-Diacetoxyanthraquinone (Diacetyl Chrysazin).—A mixture of 0.75 g. of 1,8-dihydroxyanthraquinone, 0.75 g. of freshly fused sodium acetate and 20 cc. of acetic anhydride was boiled for five hours. The acetic anhydride was removed by evaporation on the steam-bath and the resulting solid was washed with water and dried. It was purified by precipitation from glacial acetic acid solution by the addition of water and then crystallized from alcohol using activated carbon; yield, 0.35 g. (35%) of fine yellow plates which darkened at 190° and melted at 231–232°. Liebermann¹³ gives m. p. 227–232°.

Anal. Subs., 0.0853: CO₂, 0.2075; H₂O, 0.0280. Calcd. for C₁₈H₁₂O₆: C, 66.67; H, 3.70. Found: C, 66.35; H, 3.65.

A mixture of equal amounts of this substance and 1,5-diacetoxyanthraquinone, m. p. 243.6°, melted over a range of 21° from 189 to 210°, proving that the compounds were not identical.

Summary

1. 3-Methoxyphthalaldehyde acid has been prepared for the first time and its structure proved.
2. A new synthesis of chrysazin has been described.

ST. LOUIS, MISSOURI

¹¹ Liebermann, *Ann.*, **183**, 186 (1876).

¹² Green, *J. Chem. Soc.*, **129**, 2203 (1926).

¹³ Ref. 11. p. 188.