[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

STUDIES IN THE ANTHRONE SERIES. IV. THE SYNTHESIS OF THE ANTHRONES DERIVED FROM CHRYSOPHANIC ACID[1,2]

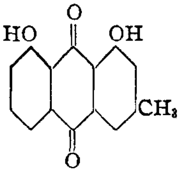
BY CHARLES A. NAYLOR, JR., WITH JOHN H. GARDNER

RECEIVED JULY 23, 1931 PUBLISHED NOVEMBER 5, 1931

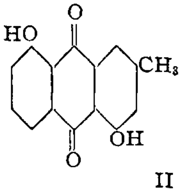
In order to obtain a better understanding of the relation between chemical constitution and physiological action among the compounds of the anthracene series, it is highly desirable that the constitution of certain naturally occurring medicinal products be fully elucidated. One of the most interesting of these drugs is chrysarobin, which has been found by a number of investigators to be a complex mixture of reduction products of the frequently found polyhydroxymethylanthraquinones, chrysophanic acid and emodin, and of emodin monomethyl ether. Although an enormous amount of analytical work has been done on this material, in no case have the exact structures of any of the active constituents been determined.[3]

The present work represents the beginning of an attempt to determine the exact constitution of chrysarobin by synthetic methods.

The first step was the development of a new method for the synthesis of chrysophanic acid which could leave no doubt as to the structure of the product obtained. Eder and Widmer[4] synthesized this compound by the benzoylbenzoic acid synthesis, starting with a condensation of 3-nitrophthalic anhydride and *m*-cresol. In this way they obtained two anthraquinone derivatives (I and II). Since the work of previous investigators indicated that chrysophanic acid is 1,8-dihydroxy-3-methylanthraquinone (I), Eder and Widmer assigned that structure to the synthetic



I



II

---

[1] Previous papers in this field are (a) Steyermark with Gardner, THIS JOURNAL, **52**, 4884 (1930); (b) *ibid.*, **52**, 4887 (1930); (c) Naylor with Gardner, *ibid.*, **53**, 4109 (1931).

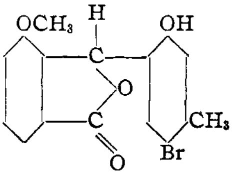
[2] Based upon a thesis submitted by Charles A. Naylor, Jr., Fellow in Chemistry, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Washington University, June, 1931.

[3] Eder and Hauser, *Arch. Pharm.*, **263**, 321, 436 (1925), give a review of the literature.

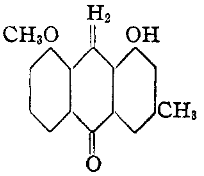
[4] Eder and Widmer, *Helv. Chim. Acta*, **5**, 3 (1922); *ibid.*, **6**, 419 (1923).

product which was found to be identical with chrysophanic acid. However, the method of synthesis does not in itself distinguish between the two compounds.

The present investigation began with a new synthesis of chrysophanic acid which could result in only one product and which consequently eliminated the last possible doubt as to the structure of this compound. By the condensation of 3-methoxyphthalaldehyde acid with *p*-bromo-*m*-cresol, there was obtained the substituted phthalide represented by Formula III. This was reduced to the corresponding benzylbenzoic acid, which was in turn dehydrated to 1-hydroxy-3-methyl-8-methoxy-10-anthrone (IV). This, on oxidation and demethylation, gave 1,8-dihydroxy-3-methylanthraquinone (I), which was found to be identical with natural chrysophanic acid obtained from chrysarobin and also with a sample of the synthetic material prepared by the method of Eder and Widmer.[4]

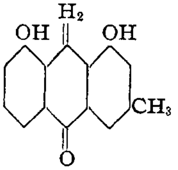


III

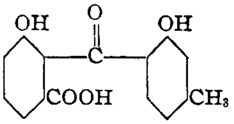


IV

Chrysophanic acid could conceivably be reduced to two isomeric anthrones. One of these occurs in natural chrysarobin, but no work has been done up to the present to determine which it is. As the next step in the present investigation, both isomers were prepared for comparison with the naturally occurring material. One of these, 1,8-dihydroxy-3-methyl-10-anthrone (V), was obtained by the demethylation of 1-hydroxy-3-methyl-8-methoxy-10-anthrone (IV), which was prepared as an intermediate step in the synthesis of chrysophanic acid. For further confirmation, 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)-benzoic acid (VI), obtained by the method of Eder and Widmer,[4] was reduced to the corresponding benzylbenzoic acid, which was in turn dehydrated to 1,8-dihydroxy-3-methyl-10-anthrone.

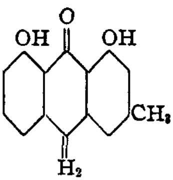


V



VI

The isomeric 1,8-dihydroxy-3-methyl-9-anthrone (VII) was obtained by the reduction of either the synthetic 1,8-dihydroxy-3-methylanthraquinone or of natural chrysophanic acid, as would be expected by analogy with the results of Steyermark and Gardner on related compounds.[1b] Its structure was proved by the fact that it differed in all of its properties from 1,8-dihydroxy-3-methyl-10-anthrone and also by the fact that the melting points of mixtures of the two compounds and of the acetates of the corresponding anthranols showed decided depressions.



VII

By the fractional crystallization of the product obtained by demethylating and then acetylating commercial chrysarobin, there was isolated a substance agreeing in its analysis and all of its properties with the acetate of 1,8-dihydroxy-3-methyl-9-anthranol. A mixed melting point with the synthetic material showed no depression. Since Eder has found that the acetate of the anthranol obtained by the reduction of emodin monomethyl ether melts at practically the same temperature as that derived from chrysophanic acid, and further that a mixture of the two compounds shows practically no depression in melting point,[5] the substance which was isolated from chrysarobin was subjected to a methoxyl determination, with a negative result, indicating definitely that it is the acetate of chrysophanic acid 9-anthrone. This investigation of the analysis of chrysarobin is to be continued.

Experimental

3-Methoxy-2-(-2-hydroxy-4-methyl-5-bromophenyl)-phthalide (III).—In a 15-cm. evaporating dish 10 g. of 3-methoxyphthalaldehyde acid and 10.4 g. of *p*-bromo-*m*-cresol 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, when it had partially solidified. The mixture was poured onto crushed ice and allowed to stand until the sticky product which first formed became a heavy, white granular solid. The product was filtered, washed free of sulfuric acid and treated with a small amount of ether to remove the excess of *p*-bromo-*m*-cresol. Purification was effected by crystallization from either alcohol or toluene; yield, 15.1 g. (79%) of irregular white plates, m. p. 243–244.6°.

Anal. Subs., 0.3619: 41.20 cc. of 0.0986 N $AgNO_3$; 30.82 cc. of 0.0977 N NH_4CNS. Calcd. for $C_{16}H_{13}O_4Br$: Br, 22.90. Found: Br, 22.98.

3-Methoxy-2-(2-hydroxy-4-methylbenzyl)-benzoic Acid.—A solution of 10 g. of 3-methoxy-2-(2-hydroxy-4-methyl-5-bromophenyl)-phthalide in 500 cc. of 10% sodium hydroxide was placed in a 1-liter round-bottomed flask and treated with 30 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. A gummy white precipitate formed which solidified on standing. The solid 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 which solidified on standing was formed. It was filtered and washed free of hydrochloric acid. The product so obtained was sufficiently pure for use in the preparation of the corresponding anthrone. For analysis, it was further purified by

---

[5] Eder, *Arch. Pharm.*, **254**, 1 (1916).

crystallization from 50% methyl alcohol using activated carbon; yield, 7.5 g. (96%) of white needles, m. p. 164–164.6°.

Anal. Subs., 0.0640: CO_2, 0.1649; H_2O, 0.0339. Calcd. for $C_{16}H_{16}O_4$: C, 70.59; H, 5.88. Found: C, 70.24; H, 5.89. *Neutral equivalent.* Subs., 0.1552: 5.88 cc. of 0.0973 *N* NaOH. Calcd. for $C_{16}H_{16}O_4$: neut. equiv., 272. Found: 272.0.

1-Hydroxy-3-methyl-8-methoxy-10-anthrone (IV).—Seven grams of 3-methoxy-2-(2-hydroxy-4-methylbenzyl)-benzoic acid was suspended in 70 cc. of concd. sulfuric acid and allowed to stand at room temperature until solution was complete. This required about two hours. The resulting dark green solution was then poured on ice to precipitate the anthrone. This was at first obtained as a granular light brown precipitate which became sticky upon being washed with water. The precipitate was 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 demethylation and for oxidation directly to the anthraquinone, yield, 2.0 g. (31%). The product was completely purified by several crystallizations from alcohol, using activated carbon the first time, forming fine orange-yellow needles, m. p. 173.8–175°.

Anal. Subs., 0.0550: CO_2, 0.1514; H_2O, 0.0267. Calcd. for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.08; H, 5.40.

1-Hydroxy-3-methyl-8-methoxyanthraquinone.—A solution of 3.0 g. of crude 1-hydroxy-3-methyl-8-methoxy-10-anthrone in 100 cc. of glacial acetic acid was treated with 1.57 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 green to greenish-violet and considerable heat was generated. On cooling a light brown amorphous solid was deposited. This was filtered and washed free of acetic acid. The product was crystallized from dilute alcohol using activated carbon; yield, 0.85 g. (20%) of orange needles, m. p. 202–204°.

Anal. Subs., 0.1011: CO_2, 0.2648; H_2O, 0.0400. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.43; H, 4.40.

1,8-Dihydroxy-3-methylanthraquinone (**Chrysophanic** Acid) (I).—To a solution of 0.5 g. of 1-hydroxy-3-methyl-8-methoxyanthraquinone in 100 cc. of glacial acetic acid was added 25 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. On cooling, a brown amorphous solid separated out and was removed by filtration. It was purified by solution in 5% sodium hydroxide, precipitation with carbon dioxide and crystallization from alcohol using activated carbon; yield, 0.25 g. (53%) of yellow plates, m. p. 193–194°.

Anal. Subs., 0.0949: CO_2, 0.2956; H_2O, 0.0330. Calcd. for $C_{15}H_{10}O_4$: C, 70.87; H, 3.94. Found: C, 70.80; H, 3.87.

A mixture of equal amounts of this substance, a sample of chrysophanic acid from chrysarobin, m. p. 193.6–194°, and a sample prepared by the synthesis of Eder and Widmer,[4] m. p. 195.6–196.2°, melted at 193–195°, showing the three compounds to be identical.

3-Hydroxy-2-(2-hydroxy-4-methylbenzoyl)-benzoic Acid (VI).—This substance was prepared according to the method of Eder and Widmer.[4]

1,8-Dihydroxy-3-methylanthraquinone (**Chrysophanic** Acid) (I).—This substance was also prepared according to the method of Eder and Widmer.[4]

1,8-Dihydroxy-3-methyl-9-anthrone (VII).—A mixture of 0.7 g. of 1,8-dihydroxy-3-methylanthraquinone, 2.1 g. of granulated tin and 35 cc. of glacial acetic acid was placed in a 200-cc. round-bottomed flask fitted with a reflux condenser. The mixture was boiled until the anthraquinone had completely dissolved. To the boiling solution five portions of 1 cc. each of concd. hydrochloric acid were added during the course of forty-five minutes. After the final addition the solution was boiled for forty-five minutes longer. The hot solution was filtered and upon cooling yellow needles were deposited. The material was crystallized from glacial acetic acid; yield, 0.57 g. (86%), m. p. 203.4–204°.

Anal. Subs., 0.1018: CO_2, 0.2792; H_2O, 0.0456. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 74.80; H, 4.98.

Acetate of 1,8-Dihydroxy-3-methyl-9-anthranol.—A mixture of 0.45 g. of 1,8-dihydroxy-3-methyl-9-anthrone, 0.5 g. of freshly fused sodium acetate and 10 cc. of acetic anhydride was boiled for five hours. The mixture was poured into water and boiled to decompose the excess acetic anhydride. The resulting yellow precipitate was filtered, washed with water and dried. After crystallization from glacial acetic acid, yellow needles were obtained, m. p. 236–237°; yield, 0.54 g. (79%).

Anal. Subs., 0.0782: CO_2, 0.1960; H_2O, 0.0341. Calcd. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.92. Found: C, 68.36; H, 4.85.

1,8-Dihydroxy-3-methyl-10-anthrone (V).—To a solution of 1.0 g. of crude 1-hydroxy-3-methyl-8-methoxy-10-anthrone in 100 cc. of glacial acetic acid, 50 cc. of constant boiling hydrobromic acid was added. The mixture was boiled for twelve hours. During the boiling a small quantity of black material separated out and 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 acetic acid (1:1) forming pale yellow needles, m. p. 179–180°; yield, 0.2 g. (21%).

Anal. Subs., 0.0845: CO_2, 0.2317; H_2O, 0.0369. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 74.78; H, 4.85.

3-Hydroxy-2-(2-hydroxy-4-methylbenzyl)-benzoic Acid.—One and one-half grams of 3-hydroxy-2-(2-hydroxy-4-methylbenzoyl)-benzoic acid, 6 g. of zinc dust, 6 cc. of water and 25 cc. of concd. ammonium hydroxide were heated in a 200-cc. round-bottomed flask for nine hours with mechanical stirring. During this time 5 cc. of ammonium hydroxide was added every half hour in order to maintain the concentration of ammonia. The mixture was then filtered and the filtrate acidified with hydrochloric acid. The white solid which precipitated was filtered, redissolved in dilute ammonium hydroxide and reprecipitated with hydrochloric acid. The crude benzylbenzoic acid was filtered and crystallized from 50% methyl alcohol using activated carbon; yield, 1.0 g. (70%) of white needles, m. p. 157–158°.

Anal. Subs., 0.1524: CO_2, 0.3868; H_2O, 0.0740. Calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43. Found: C, 69.21; H, 5.40.

1,8-Dihydroxy-3-methyl-10-anthrone (V).—Seven-tenths gram of 3-hydroxy-2-(2-hydroxy-4-methylbenzyl)-benzoic acid was dissolved in 7 cc. of concd. sulfuric acid and the solution was allowed to stand at room temperature for two hours. It was then poured onto cracked ice and the resulting yellow precipitate filtered, washed and crystallized from 95% ethyl alcohol using activated carbon; yield, 0.45 g. (69%) of pale yellow needles, m. p. 179.2–180°.

Anal. Subs., 0.1051: CO_2, 0.2872; H_2O, 0.0460. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 74.52; H, 4.87.

A mixture of equal amounts of this substance and the anthrone prepared by the demethylation of 1-hydroxy-3-methyl-8-methoxy-10-anthrone, m. p. 179–180°, melted sharply at 179–180°, indicating that the two compounds are identical.

A mixture of equal amounts of this substance and 1,8-dihydroxy-3-methyl-9-anthrone, m. p. 203.4–204°, melted over a range of 10°, from 150 to 160°, proving that the compounds are not identical.

Acetate of 1,8-Dihydroxy-3-methyl-10-anthranol.—A mixture of 0.3 g. of 1,8-dihydroxy-3-methyl-10-anthrone, 0.3 g. of freshly fused sodium acetate and 5 cc. of acetic anhydride was boiled for five hours. The mixture was poured into water and boiled to remove the excess acetic anhydride. The resulting brownish-yellow precipitate was filtered, dried and crystallized from glacial acetic acid; yield, 0.18 g. (40%) of yellow needles, m. p. 209–210°.

Anal. Subs., 0.0706: CO_2, 0.1771; H_2O, 0.0317. Calcd. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.92. Found: C, 68.42; H, 4.99.

A mixture of equal parts of this substance and of the acetate of 1,8-dihydroxy-3-methyl-9-anthranol, m. p. 236–237°, melted over a range of 15°, from 173 to 188°, proving that the compounds were not identical.

Demethylation and Acetylation of Chrysarobin.—A suspension of 10 g. of chrysarobin in 150 cc. of glacial acetic acid and 150 cc. of constant boiling hydrobromic acid was boiled under reflux for fourteen hours. The mixture was cooled and the resulting precipitate filtered out and dried in the air. It was then intimately mixed with 13 g. of anhydrous sodium acetate and dissolved in 130 cc. of acetic anhydride. The solution was boiled for one hour and poured onto ice. After standing overnight, the precipitate which formed was filtered off.

On crystallization from glacial acetic acid, there was obtained an almost insoluble fraction melting at 223–224°, with previous softening. After recrystallization from glacial acetic acid, the material melted at 236.6–237°, in agreement with the melting point of the acetate of 1,8-dihydroxy-3-methyl-9-anthranol. A mixed melting point using approximately equal amounts of the two substances showed no depression.

Anal. (Pregl). Subs., 4.549: CO_2, 11.275; H_2O, 2.070; ash, 0.065. Calcd. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.92. Found (corr. for ash): C, 68.56; H, 5.16.

A methoxyl determination showed no methoxyl groups to be present.

Summary

1. A new synthesis of chrysophanic acid which definitely proves its structure has been accomplished.

2. Methods for the preparation of both of the anthrones derived from chrysophanic acid have been developed.

3. It has been shown that the anthrone of chrysophanic acid which occurs in chrysarobin is the 9-anthrone.

ST. LOUIS, MISSOURI