lene has been prepared by methylation. It has in turn been transformed into 1,5-methoxynaphthoic acid by use of the Grignard reaction.

3. The hydroxynaphthoic acid known as the "1,5" has been methylated and the resulting methoxynaphthoic acid has been found to be identical with that made from the bromonaphthol.

4. The so-called "1,5"-hydroxynaphthoic acid is, therefore, the 1,5 acid as has been assumed and the so-called "1,8" acid is shown to be the true 1,8 acid.

5. It has been concluded, accordingly, that the 1,8- and not the 1,5-hydroxynaphthoic acid forms the lactone.

6. Naphthalene cannot, therefore, have the centroid structure proposed by Huggins and by inference, at least, his structure for benzene is made doubtful.

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POLYHYDROXY-METHYLANTHRAQUINONES. IV. CONDENSATION OF OPIANIC ACID WITH SUBSTITUTED PHENOLS. ORIENTATION IN THE PREPARATION OF ANTHRAQUINONES

BY R. A. JACOBSON[1] WITH ROGER ADAMS

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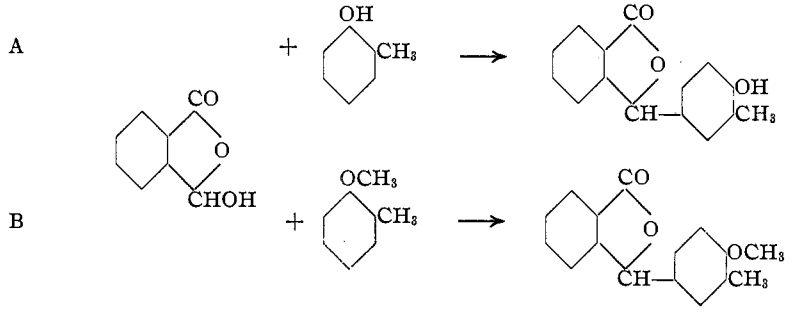
Satisfactory methods for the synthesis of polysubstituted, in particular, polyhydroxy and polyhydroxy-methyl substituted anthraquinones are of interest on account of the large number of natural products and commercially important synthetic products belonging to this class of compounds. Many natural products are isomeric trihydroxy-methylanthraquinones, the most important containing two hydroxyl groups in one ring and one hydroxyl with one methyl in the other. A study of the methods which make possible the synthesis of many of these latter compounds has been undertaken in this Laboratory and the successful preparation of emodin has already been accomplished.[2] However, not all of the isomeric forms may be synthesized by the methods available. In this communication is reported a further development in the methods which will allow the production of many hitherto unavailable polyhydroxy- and polyhydroxy-methylanthraquinones.

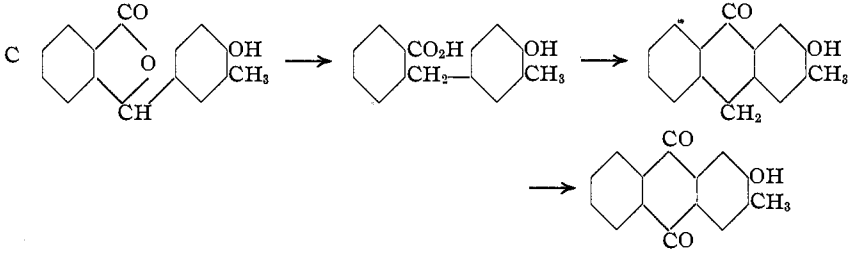
[1] This communication is an abstract of part of a thesis submitted by R. A. Jacobson in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] (a) Graves and Adams, THIS JOURNAL, **45**, 2439 (1923). (b) Gardner and Adams, *ibid.*, **45**, 2455 (1923). (c) Jacobson and Adams, *ibid.*, **46**, 1312 (1924).

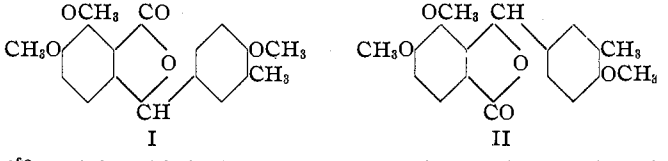
The new method is one similar to that discovered by Bistrzycki.[3] He condensed aromatic ortho aldehyde acids with cresol and cresol ethers as illustrated in A and B.



The aldehyde acid reacts in the tautomeric form and condenses *para* to the hydroxyl in phenols and *para* to the methoxyl in phenol ethers. By reduction of the products to benzyl-benzoic acids and subsequent conversion to anthraquinones as illustrated in Series C, the formation of the anthraquinone is accomplished.



Unfortunately, the phthalides thus produced from opianic acid (3,4-dimethoxy-2-carboxy-benzaldehyde) could not be reduced to the benzyl-benzoic acids, although the unsubstituted aldehyde acid derivatives were readily reduced and were then converted to anthraquinones. It seems surprising that the condensation products of opianic acid and substituted phenols such as (I) should not reduce in view of the fact that compounds of Type II are reduced quantitatively.



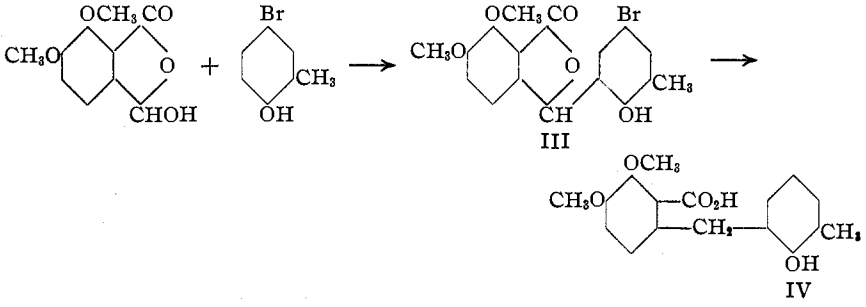
Bistrzycki[3c] explains this lack of reduction as due to that methoxyl group of the opianic acid residue which is *para* to the CH of the phthalide, although

[3] (a) Bistrzycki and Zen-Ruffinen, *Helvetica Chim. Acta*, **3**, 369 (1920). (b) Bistrzycki and Yssel de Schepper, *Ber.*, **31**, 2790 (1898). (c) Bistrzycki and Krauer, *Helvetica Chim. Acta*, **6**, 750 (1923).

according to the usual experience in examples of steric hindrance, the phthalide with the CH having two groups substituted *ortho* to it might be expected to reduce with greater difficulty instead of with less. It seems likely to the authors that the inactivity toward reducing agents lies more probably in some details of experimentation than in steric hindrance and this research has fully substantiated this view.

A more valuable synthesis than the one just discussed for producing naturally occurring polyhydroxy-methylanthraquinones, such as morindone, and various polyhydroxy-anthraquinones the constitution of which is in doubt, would be that in which the aldehyde acid is condensed *ortho* to the hydroxyl or methoxyl groups instead of *para*, and these products are then converted to anthraquinones. This communication describes a successful method for accomplishing this, using opianic acid as the aldehyde acid.

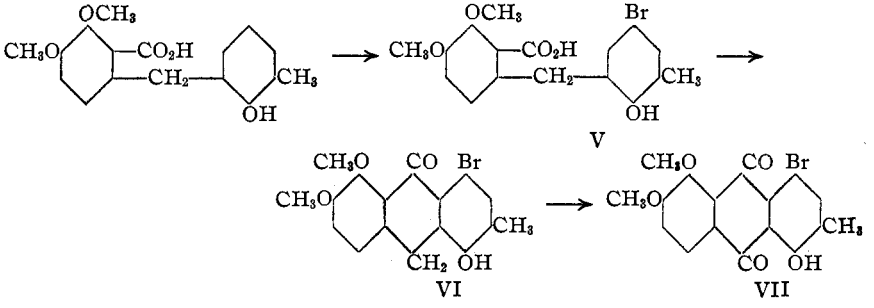
When opianic acid is condensed with *p*-bromophenol or *p*-bromo-*o*-cresol in the presence of 85% sulfuric acid the reaction takes place with surprising ease, the linkage being *ortho* to the hydroxyl group.



Judging from Bistrzycki's results the expectation would be against the reduction of these compounds. The results, however, showed that, under the proper conditions, zinc and sodium hydroxide readily reduce these compounds to benzyl-benzoic acid derivatives and at the same time replace the bromine atom by hydrogen (IV). This is conclusive evidence that the methoxyl group *para* to the CH of the phthalide is not the cause of the resistance to reduction of those compounds studied by Bistrzycki from opianic acid and *o*-cresol, guaiacol, etc., but that it depends on some other factor, possibly experimental conditions or reagents. A preliminary attempt to reduce the phthalide from opianic acid and *o*-cresol yielded a product which as yet has not been obtained crystalline, but nevertheless is completely soluble in sodium carbonate. A further study of the reduction of the phthalides prepared by Bistrzycki is contemplated.

The conversion of the benzyl-benzoic acids from the reduction of the phthalides from *p*-bromophenols and opianic acid to anthraquinones has not as yet been extensively studied. The conversion of 5,6-dimethoxy-

2-(2-hydroxy-3-methylbenzyl)benzoic acid (IV) to the anthrone took place with difficulty and only a poor yield resulted. This is undoubtedly due to the tendency toward sulfonation by means of the sulfuric acid used as a condensing agent. This was avoided by brominating the benzylbenzoic acid, the bromine atom entering *para* to the hydroxyl (V), a procedure similar to the bromination of certain benzoyl-benzoic acids before converting them to anthraquinones.[2c] The substituted product condenses very readily to the anthrone (VI), the reaction taking place almost quantitatively. By oxidation of the anthrone the anthraquinone (VII) is readily produced.

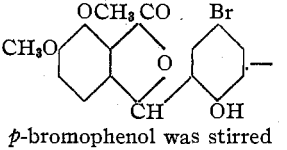


It is obvious that a method is available here for the synthesis of morindone provided the structure ordinarily assigned to it (1,2,5-trihydroxy-6-methylanthraquinone) is correct. The anthraquinone mentioned above (VII) is therefore a bromodimethyl ether of morindone. It gives a color reaction similar to morindone with concd. sulfuric acid. The application of the general method discussed above is being studied.

Experimental Part

5,6-Dimethoxy-2-(2-hydroxy-3-methyl-5-bromophenyl)phthalide. III.—In a 200-mm. evaporating dish 25 g. of opianic acid and 22.5 g. of *p*-bromo-*o*-cresol were thoroughly mixed, stirred and to the mixture 65 cc. of 85% sulfuric acid was added slowly. The mixture became liquid at first but solidified in 10 to 15 minutes. Water was added and the heavy granular solid filtered off and washed free from sulfuric acid. The product was recrystallized from acetic acid forming fine, white needles; m. p., 204–205°. Ethyl alcohol may also be used for recrystallization. The yield of crude product was quantitative and that of the pure product, 25 g. (55%).

Anal. Subs., 0.1990: AgBr, 0.0986. Calc. for $C_{17}H_{15}O_5Br$: Br, 21.08. Found: 21.08.

5,6-Dimethoxy-2-(2-hydroxy-5-bromophenyl)phthalide, 

An intimate mixture of 15 g. of opianic acid and 12.6 g. of *p*-bromophenol was stirred while to it was added slowly 39 cc. of 85% sulfuric acid. The mixture was allowed to stand for 12 hours, at the end of which time it had partially solidified. Water was then added, the product filtered off and washed free from sulfuric acid. It was purified by

recrystallization from dil. acetic acid from which it formed white needles; m. p., 219–220°. The yield of crude product was quantitative and that of the pure product 14 g., (54%).

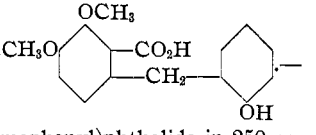
Anal. Subs., 0.2133: AgBr, 0.1101. Calc. for $C_{16}H_{13}O_5Br$: Br, 21.89. Found: 21.96.

5,6-Dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic Acid. IV.—A solution of 25 g. of 5,6-dimethoxy-2-(2-hydroxy-3-methyl-5-bromophenyl) phthalide in 500 cc. of 10% sodium hydroxide was placed in a 1-liter round-bottom flask and treated with 75 g. of powdered zinc (Baker's 96.4%). The contents were heated almost to boiling and mechanically stirred at this temperature for 15 hours. The zinc was filtered off and an excess of concd. hydrochloric acid added to the filtrate. The precipitate thus formed was gummy but on standing in the acid solution for a few minutes it solidified. The solid was broken up, filtered off and washed. It was dissolved in 10% sodium carbonate solution without heating. This solution was filtered from undissolved impurity and an excess of hydrochloric acid added to the filtrate. The gummy precipitate which formed soon solidified. It was filtered off and washed free from hydrochloric acid. The product thus obtained was sufficiently pure for use in forming its bromo derivative; yield, 18 g., or 90%. The product was completely purified by recrystallization from toluene forming white, rectangular plates; m. p., 137–138°.

Anal. Subs., 0.1711: CO_2, 0.4224; H_2O, 0.0910. Calc. for $C_{17}H_{18}O_5$: C, 67.52; H, 6.00. Found: C, 67.34; H, 5.95.

Attempts to reduce the substance with zinc dust and acetic acid resulted in the recovery of the lactone unchanged.

5,6-Dimethoxy-2-(2-hydroxybenzyl)benzoic Acid,



A solution of 12 g. of 5,6-dimethoxy-2-(2-hydroxy-5-bromophenyl)phthalide in 250 cc. of 10% sodium hydroxide solution was treated with 40 g. of powdered zinc (Baker's 96.4%). The procedure from this point was similar to that described above for the reduction of 5,6-dimethoxy-2-(2-hydroxy-3-methyl-5-bromophenyl)phthalide. Warming the gummy precipitate with hydrochloric acid hastened its solidification; yield of crude product, 7 g., or 74%. Purification was effected by dissolving in dry toluene and allowing the solution to evaporate spontaneously. The compound crystallized on the sides of the container while a certain amount of sticky material collected on the bottom. The compound formed white, irregular, oval crystals; m. p., 138.5–140°. Dry benzene may also be used for recrystallization.

Anal. Subs., 0.2166: CO_2, 0.5278; H_2O, 0.1060. Calc. for $C_{16}H_{16}O_5$: C, 66.64; H, 5.59. Found: C, 66.47; H, 5.47.

5,6-Dimethoxy-2-(2-hydroxy-3-methyl-5-bromobenzyl)benzoic Acid. V.—A solution of 22 g. of 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic acid in 130 cc. of glacial acetic acid was stirred and treated slowly with 12.8 g. of bromine (10% in excess of that calculated) in 15 cc. of acetic acid. Decolorization of the bromine occurred as fast as it was added. On cooling the solution with ice, 16 g. of the bromo acid separated. When the filtrate was concentrated an additional 2.8 g. was obtained; total yield, 18.8 g., or 67%. The product was crystallized from glacial acetic acid, forming thick, white needles; m. p., 190–191°.

Anal. Subs., 0.1788: AgBr, 0.0877. Calc. for $C_{17}H_{17}O_5Br$: Br, 20.96. Found: 20.87.

It was unnecessary to use recrystallized 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl)benzoic acid as the acid purified by precipitation from 10% sodium carbonate solution melted only slightly lower than the recrystallized product.

1,2 - Dimethoxy - 5 - hydroxy - 6 - methyl - 8 - bromo - 9,10 - dihydro - 9 - keto-anthracene. VI.—A solution of 6.2 g. of 5,6-dimethoxy-2-(2-hydroxy-3-methyl-5-bromobenzyl)benzoic acid in 60 cc. of concd. sulfuric acid was allowed to stand at room temperature for ten minutes. It was then poured slowly into 400 cc. of water containing ice while the mixture was stirred. The anthrone separated at once as a heavy, yellow precipitate; yield, 5.4 g., or 91%. A suitable solvent for recrystallization was not found; hence, the crude compound was oxidized directly to the corresponding anthraquinone for identification.

1,2-Dimethoxy-5-hydroxy-6-methyl-8-bromo-anthraquinone. VII.—A solution of 1 g. of crude 1,2-dimethoxy-5-hydroxy-6-methyl-8-bromo-9,10-dihydro-9-keto-anthracene in 10 cc. of glacial acetic acid was oxidized by adding 0.55 g. of chromium trioxide in 5 cc. of glacial acetic acid. From the solution, 0.25 g. of the anthraquinone separated. Recrystallization from glacial acetic acid gave yellow needles; m. p., 193–193.5°. The substance dissolved in sulfuric acid giving a deep blue solution.

Anal. Subs., 0.1556: AgBr, 0.0772. Calc. for $C_{17}H_{13}O_5Br$: Br, 21.19. Found: 21.11.

Summary

1. Aromatic aldehyde acids condense with various *p*-bromophenols by means of sulfuric acid to give substituted phthalides where condensation has taken place *ortho* to the hydroxyl group.

2. The phthalides thus produced are readily reduced with zinc and sodium hydroxide to benzyl-benzoic acids which can be converted to anthraquinones. The procedure outlined gives a method suitable for the synthesis of various natural products and polyhydroxy-methylanthraquinones.

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[CONTRIBUTION FROM THE UNIVERSITY OF BRISTOL]

THE CONSTITUTION OF CATECHIN. VII. 4,5,7,3′,4′-PENTAHYDROXY-FLAVAN

BY M. NIERENSTEIN

RECEIVED JULY 11, 1924 PUBLISHED DECEMBER 13, 1924

Of the many formulas that have been suggested for catechin,[1] Formulas I and III are still under consideration. These formulas have been proposed by A. G. Perkin[2] and they both represent catechin as a reduction product of quercetin (II).

[1] (a) Freudenberg, Böhme and Purrmann, *Ber.*, **55**, 1734 (1922). (b) Drumm, *Sci. Proc. Roy. Dublin Soc.*, **36**, 45 (1923). (c) Freudenberg, Orthner and Fikentscher, *Ann.*, **436**, 286 (1924).

[2] Perkin, *J. Chem. Soc.*, **81**, 1172 (1902); **87**, 405 (1905).