[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

TRIHYDROXY-METHYLANTHRAQUINONES. III. SYNTHESIS OF EMODIN

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With a view to developing a procedure which would allow the synthesis of several naturally occurring polyhydroxy methylanthraquinones that had not previously been synthesized, the study of the condensation of certain easily prepared phthalic anhydrides containing methoxyl groups with phenols was undertaken and the results have been published in two papers.[2] In these, the following facts were established.

1. Phthalic anhydrides containing methoxyl groups can be condensed with cresols and cresol ethers in the presence of anhydrous aluminum chloride and excess of cresol or cresol ether as a solvent, to form substituted benzoyl-benzoic acids which in turn could be converted by means of sulfuric acid to polyhydroxy methylanthraquinones.

2. The structure of the benzoyl-benzoic acids produced in (1) was determined and, as previous authors had found in analogous reactions, the condensation of the phthalic anhydride with the cresols took place *ortho* to the hydroxyl groups and the condensation with the cresol ethers *para* to the methoxyl groups.

3. The general procedure given above was applied to 3,5-dimethoxyphthalic anhydride and *m*-cresol in an attempt to prepare a dimethyl ether of emodin. The anthraquinone obtained had an absorption spectrum which indicated that it was an emodin derivative, thus proving that emodin was 1,6,8-trihydroxy-3-methylanthraquinone. This method of preparation, however, was impractical because the yield was so small.

This paper gives the results of a research on the modification of the process for synthesizing emodin, mentioned above, so that sufficient amounts of emodin derivatives and emodin could be prepared for detailed study.

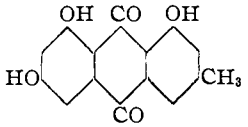
Emodin is the most important of the polyhydroxy methylanthraquinones. It occurs in a large number of natural products such as *Rhamnus frangula*, *R. purshiana*, and rhubarb. Considerable interest has been shown in its structure because of its relation to the purgative action of these plants. The fact that it is a trihydroxy-methylanthraquinone was known as early as 1875, but the exact location of the substituent groups has been a subject of much dispute and careful study. Oesterle,[3] in 1912,

[1] This communication is an abstract of a portion 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] Graves and Adams, THIS JOURNAL, **45**, 2439 (1923). Gardner and Adams, *ibid.*, **45**, 2455 (1923).

[3] Oesterle, *Arch. Pharm.*, **250**, 301 (1912); **253**, 327 (1915).

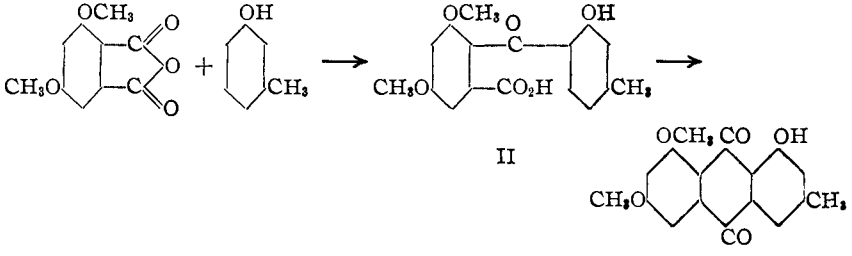
presented satisfactory evidence for assigning to emodin the formula 1,6,8-trihydroxy-3-methylanthraquinone (I).



I

Since the publication, last October, of the first two papers from this Laboratory, a communication by Eder and Widmer[4] has appeared in which the description of a successful synthesis of emodin is given. These authors have included in their paper an excellent historical review of all the papers touching on the chemistry of emodin, as well as a thorough discussion of the reasons for the assumption that Formula I is the correct one for emodin. These data will therefore be omitted from this paper and merely a description of the procedure used in this investigation will be given. The method is considerably different from that described by Eder and Widmer.

The procedure first attempted and mentioned previously was the condensation of 3,5-dimethoxy-phthalic anhydride with *m*-cresol. The formation of 3,5-dimethoxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid (II) proceeded satisfactorily but the condensation of this latter compound with sulfuric acid in order to produce the anthraquinone, which should be a dimethyl ether of emodin, gave too low yields for practical purposes.



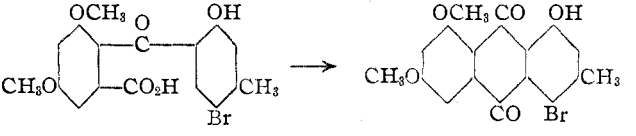
II

It has been pointed out in the previous papers,[2] and also by other investigators that where, in the benzoyl-benzoic acids, there is an *ortho* or *para* directing group *meta* to the position in which condensation to the anthraquinone must take place, the difficulty of forming the anthraquinone is especially pronounced. This is particularly true with phenol derivatives where the tendency to sulfonation prevents the condensation desired. This is the difficulty involved in the formation of a dimethyl ether of emodin from 3,5-dimethoxy-2-(2-hydroxy-4-methylbenzoyl)benzoic acid (II).

A successful conversion of this benzoyl-benzoic acid to an anthraquinone was predicted if the *para* position to the hydroxyl group could be substi-

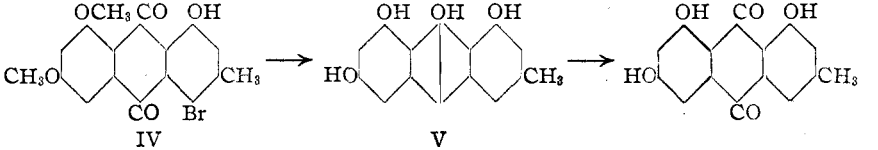
[4] Eder and Widmer, *Helvetica Chim. Acta*, **6**, 966 (1923).

tuted by a group orienting *ortho* and *para*. This would tend not only to prevent sulfonation to a large extent but also would direct toward the position where elimination of water must take place. The benzoyl-benzoic acid was therefore brominated and a monobromo derivative, 3,5-dimethoxy-2-(2-hydroxy-4-methyl-5-bromobenzoyl)benzoic acid (III) was readily obtained. Although the position of the halogen was not determined, the *para* position to the hydroxyl group would be the expected one. The fact that the anthraquinone was readily formed after substitution leaves little doubt that the halogen entered in this position. The condensation of the brominated benzoyl-benzoic acid to an anthraquinone, 1-hydroxy-3-methyl-4-bromo-6,8-dimethoxy-anthraquinone (IV), took place by means of 7% fuming sulfuric acid and boric acid.



III IV

The product is obviously a brominated dimethyl ether of emodin, provided that emodin is 1,6,8-trihydroxy-3-methyl-anthraquinone. By treatment directly with hydriodic acid, a quantitative yield of 1,6,8-trihydroxy-3-methylanthranol (emodin anthranol) (V) was produced, demethylation, elimination of the bromine, and reduction of the ketone groups taking place simultaneously. This anthranol was identical with the anthranol prepared by the reduction of natural emodin and, in addition, gave on oxidation 1,6,8-trihydroxy-3-methylanthraquinone (I) a product melting at 256–257°, identical in every way with natural emodin. The triacetate of the synthetic product was prepared and was found to be identical with that prepared from natural emodin.



IV V

The procedure in this investigation for converting to anthraquinones those benzoyl-benzoic acids in which the groups are so arranged that the reactions take place only with great difficulty or not at all is of some interest. It should have a general application wherever a halogen is readily introduced into the proper position, a condition which would be frequent. The method is, perhaps, not as general as the procedure developed by Bistrzycki and Krauer[5] according to which the benzoyl-benzoic acid is reduced by powdered zinc and hydrochloric acid to a benzyl-benzoic

[5] Bistrzycki and Krauer, *Helvetica Chim. Acta*, **6**, 753 (1923).

acid, condensed to the ring compound, and then reoxidized, but in many instances may prove more convenient.

Although a convenient procedure for showing that 3,5-dimethoxy-phthalic anhydride condensed with the cresols in such a way that the carbonyl adjacent to the methoxyl group became the ketone in the benzoyl-benzoic acid was to be studied experimentally, it was abandoned after the appearance of Eder and Widmer's article. The fact that emodin was produced by this series of reactions proves that the condensation took place as just mentioned. Moreover, condensation in this way would be expected by analogy with the condensation of hemipinic anhydride (3,4-dimethoxy-phthalic anhydride) with phenols.[6]

Experimental Part

3,5-Dimethoxy-phthalic Anhydride.—This was produced according to the procedure described in the first paper by Graves and Adams.[2]

3,5-Dimethoxy-2-(2-hydroxy-4-methyl-benzoyl)benzoic Acid (II).—This substance was described in an earlier paper, but by further experimentation it was found that the yields varied considerably and frequently did not exceed 20% of that calculated. This was on account of the larger proportion of phthalein which formed.

3,5-Dimethoxy-2-(2-hydroxy-4-methyl-5-bromobenzoyl)benzoic Acid (III).—A solution of 4.86 g. of 3,5-dimethoxy-2-(2-hydroxy-4-methyl-benzoyl)benzoic acid in 200 cc. of glacial acetic acid was placed in a bath at 50°. To this was added 2.77 g. of bromine (calculated amount, 2.46 g.) and the solution stirred for two hours. The acetic acid was then removed by evaporation on the steam-bath in a current of air or distillation under diminished pressure. The residue was refluxed for a few minutes with 40 cc. of methyl alcohol and the insoluble portion filtered off. About 2.8 g. of the brominated acid was thus obtained. On evaporation of the methyl alcohol solution, the unchanged benzoyl-benzoic acid was recovered mixed with a small amount of the bromo acid. The benzoyl-benzoic acid thus recovered was again treated with the calculated amount of bromine. In this way, quantitative yields of 3,5-dimethoxy-2-(2-hydroxy-4 methyl-5-bromobenzoyl)benzoic acid were obtained.

The bromo acid crystallized from ethyl alcohol in thick white needles; m. p., 258–259°.

Neutral equivalent: 395. Found: 388.

Analysis. Subs., 0.1220: CO_2, 0.2318; H_2O, 0.0411 g. Calc. for $C_{17}H_{15}O_6Br$: C, 51.65; H, 3.82. Found: C, 51.83; H, 3.77.

1-Hydroxy-3-methyl-4-bromo-6,8-dimethoxy-anthraquinone (IV).—A mixture of 6.25 g. of 3,5-dimethoxy-2-(2-hydroxy-4-methyl-5-bromobenzoyl)benzoic acid, 210 cc. of 7% oleum, and 1.74 g. of boric acid was heated on the steam-bath for three hours. The solution was poured over ice to precipitate the anthraquinone. The product was purified by dissolving it in 10% sodium hydroxide solution, filtering, and saturating the filtrate with carbon dioxide, yielding a precipitate of about 2.36 g. (40%) of anthraquinone. Further purification was effected by recrystallization from glacial acetic acid, giving orange-red needles; m. p., 208–209°.

Only traces of the anthraquinone were obtained when concd. sulfuric acid was used in place of 7% oleum. A 20% oleum was also tried, but the yield of anthraquinone was much smaller than with 7% oleum.

[6] Bistrzycki and Yssel de Schepper, *Ber.*, **31**, 2796 (1898). Adams and Gardner, unpublished results.

Analysis. Subs., 0.1740: CO_2, 0.3464; H_2O, 0.0532. Calc. for $C_{17}H_{13}O_5Br$: C, 54.11; H, 3.47. Found: C, 54.31; H, 3.42.

1,6,8-Trihydroxy-3-methylanthranol (V) (Emodin Anthranol).—A solution of 0.5 g. of 1-hydroxy-3-methyl-4-bromo-6,8-dimethoxy-anthraquinone in 45 cc. of glacial acetic acid was refluxed with 20 cc. of hydriodic acid (d., 1.5) for three hours. This procedure effected demethylation, debromination and reduction to the anthranol. On cooling, the emodin anthranol separated in pale, yellowish-green, rectangular plates or in leaflets in a yield of 0.31 g. (91.4%); it decomposes at 250–258°. Recrystallization from acetic acid did not change the decomposition point.

Analysis. Subs. (dried at 120° for 3 hours), 0.1760: CO_2, 0.4546; H_2O, 0.0730. Calc. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.46; H, 4.64.

Since considerable disagreement among various investigators on the melting or decomposition point of emodin anthranol has appeared in the literature, it may be stated that the value found in this investigation was a decomposition point of 250–258°, which agrees essentially with the value of Tutin and Clewer[7] who reported a decomposition point about 255°. Emodin anthranol produced by the reduction of natural emodin with hydriodic acid gave the same value.

1,6,8-Trihydroxy-3-methylanthraquinone (I) (Emodin).—A solution of 0.78 g. of emodin anthranol in 150 cc. of glacial acetic acid was oxidized at 50° by means of 0.815 g. of chromium trioxide in 20 cc. of 50% acetic acid according to the procedure described by Hesse.[8] A yield of 0.4 g. (50%) of emodin was obtained; m. p., 256–257°. Recrystallization from toluene or glacial acetic acid did not change the melting point.

Analysis. Subs. (dried at 120° for 3 hours), 0.1566: CO_2, 0.3822; H_2O, 0.0504. Calc. for $C_{15}H_{10}O_5$: C, 66.65; H, 3.73. Found: C, 66.58; H, 3.60.

The identity of the synthetic product with natural emodin was shown by a mixed melting point determination; and further by preparing the triacetate; m. p., 193–194°. The absorption spectra curves of the synthetic and natural emodin were identical.

Summary

1. A method is described for the synthesis of 1,6,8-trihydroxy-3-methylanthraquinone which substance proved to be identical with natural emodin.

2. A new procedure has been developed for producing anthraquinones from substituted benzoyl-benzoic acids which resist direct anthraquinone formation.

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[7] Tutin and Clewer, *J. Chem. Soc.*, **101**, 299 (1912).

[8] Hesse, *Ann.* **388**, 80 (1912).