reagent consists in the alkylation of two carbonyls and the loss of one molecule of water, probably with formation of an internal ether. With a tetra-alkylbarbituric acid the same reaction occurs, also an additional reaction of the third carbonyl.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

THE STRUCTURE OF THE CONDENSATION PRODUCTS OF ORTHO-PHTHALALDEHYDIC ACIDS WITH PHENOLS AND PHENOL ETHERS. VIII.[1]

BY M. M. BRUBAKER[2] WITH ROGER ADAMS

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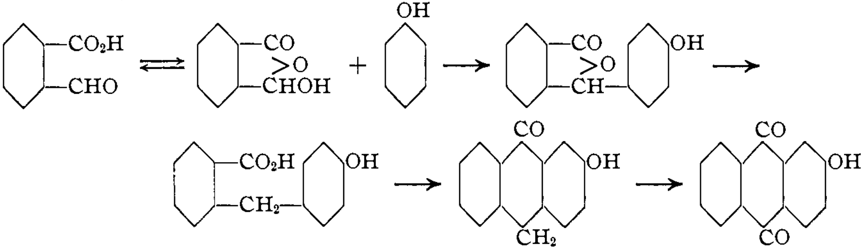
The preparation of substituted phthalides from *ortho*-phthalaldehydic acid by condensation with phenols was discovered by Bistrzycki.[3] He found that the phthalides formed could be reduced to benzyl-benzoic acids and these in turn could be dehydrated and the anthrones oxidized to anthraquinones.



This procedure for preparing certain types of anthraquinones appeared, at first, not to be entirely general, since he was unable to reduce phthalides from opianic acid (2-carboxy-3,4-dimethoxybenzaldehyde) and phenols to the corresponding benzyl-benzoic acids. Jacobson and Adams,[1d] however, found that under the proper conditions these latter phthalides could be reduced, and, although the benzyl-benzoic acids could not in all cases be obtained crystalline and pure, the products served well for the preparation of anthraquinones. In this Laboratory the method has already been applied to the synthesis of morindone,[1e] rufiopin[1g] and

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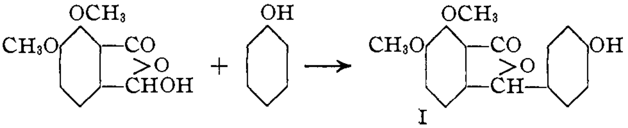
[1] For previous articles in this field see (a) Graves with Adams, THIS JOURNAL, **45**, 2439 (1923); (b) Gardner with Adams, *ibid.*, **45**, 2455 (1923); (c) Jacobson with Adams, *ibid.*, **46**, 1312 (1924); (d) **46**, 2788 (1924); (e) **47**, 283 (1925); (f) **47**, 2011 (1925); (g) Puntambeker with Adams, *ibid.*, **49**, 486 (1927).

[2] This communication is an abstract of a thesis submitted by M. M. Brubaker, Carr Fellow for 1926–1927, in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] (a) Bistrzycki and Oehlert, *Ber.*, **27**, 2632 (1894); (b) Bistrzycki and Yssel de Schepper, *Ber.*, **31**, 2790 (1898); (c) Bistrzycki and Zen-Ruffinen, *Helv. Chim. Acta.*, **3**, 369 (1920); (d) Bistrzycki and Krauer, *ibid.*, **6**, 750 (1923).

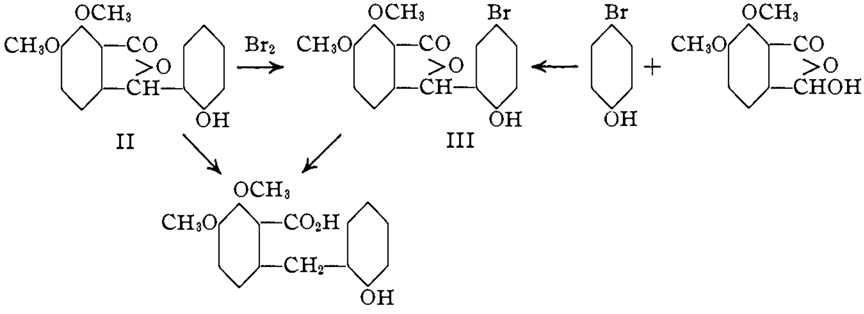
hydroxyanthrarufin. With a certainty of the reduction of the phthalides, the value of this procedure as a means of preparing hydroxyanthraquinones of various known structures depends upon a definite knowledge of the structure of the phthalide. Bistrzycki prepared beta-hydroxyanthraquinone by the series of reactions given above and thus demonstrated without question the structure of the intermediate phthalide; the condensation of the *o*-phthalaldehydic acid takes place *para* to the hydroxyl group of the phenol. He therefore assumed that when opianic acid was used in place of the unsubstituted *o*-phthalaldehydic acid, the condensation with phenol or substituted phenols always proceeded *para* to the hydroxyl. In a series of researches from this Laboratory,[1e,1f,1g] the condensation was directed *ortho* to the hydroxyl group by starting with a *p*-halogenated phenol and the halogen was later removed during reduction to the benzyl-benzoic acid. From time to time in the course of these investigations, it appeared doubtful whether the condensation of opianic acid and phenols with both *ortho* and *para* positions unoccupied always went *para* to the hydroxyl group. Since the success of several problems depended upon a knowledge of this fact, a study was undertaken to determine the structure of the phthalides formed, in other words, the exact position assumed in the condensation of opianic acid with phenols and certain substituted phenols. This paper describes also the results of the condensation of opianic acid with phenol ethers, a continuation of the study of the condensation of *o*-phthalaldehydic acid with certain phenols, the condensation of bromo-opianic acid with phenol, and finally a new class of compounds, the *bis*-phthalidyl phenols or phenol ethers where two molecules of the *o*-phthalaldehydic acid condense with one of phenol or phenol ether.

Bistrzycki[3a,b] condensed opianic acid with phenol and obtained what he considered to be the *para* condensation product (I), though it was obviously impure on account of the melting point reported (160–170° with previous softening).

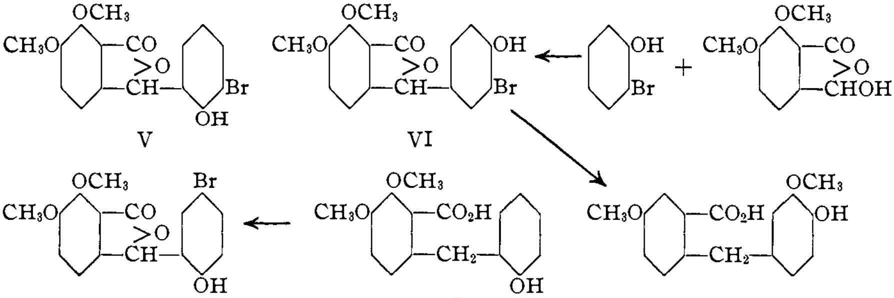


I

He was unable to reduce this compound to the corresponding benzylbenzoic acid. A repetition of this reaction was carried out, and, by a different method of crystallization of the crude product, a pure compound was isolated which melted sharply about 20° higher than the m. p. reported by Bistrzycki. This product was shown without question to be that in which the condensation had taken place in the *ortho* position to the hydroxyl, (II), because on bromination the same monobromo compound (III) resulted as was formed by the condensation of opianic acid with *p*-bromophenol. Moreover, upon reduction of the phthalide, the same benzylbenzoic acid was produced as that formed by the reduction of the phthalide from opianic acid and *p*-bromophenol (III).

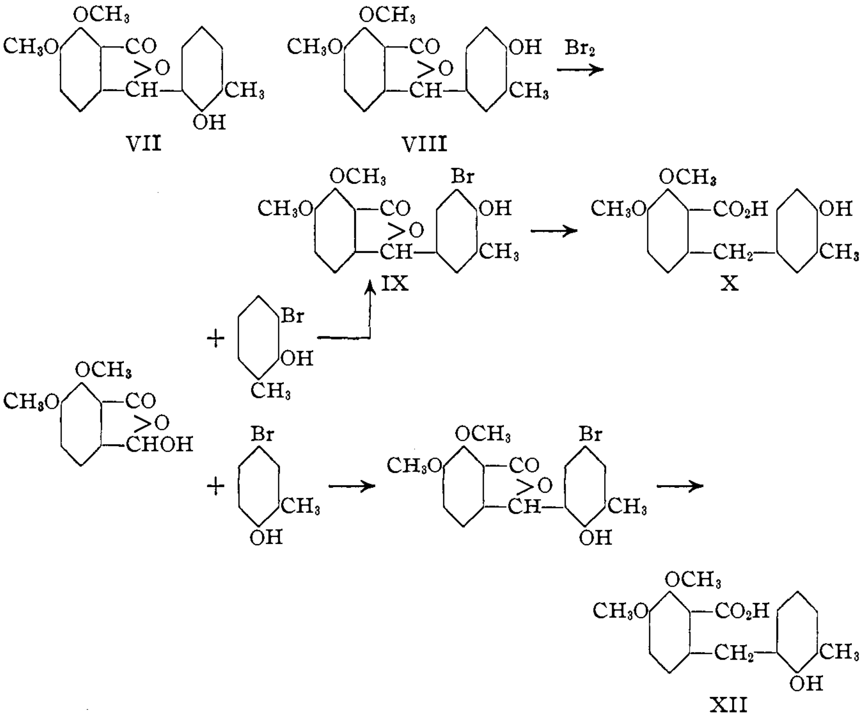

II III IV

This demonstrated that the *ortho* condensation product (II) was formed to a large extent, contrary to what might be expected from Bistrzycki's work with *o*-phthalaldehydic acid. The presence of the *para* condensation product (I) was also demonstrated. It may be stated here that one of the outstanding characteristics of the condensation products from opianic acid and many of the phenols is the slow rate of crystallization. In some instances several days are required for complete crystallization even in the presence of a seed. This is particularly true if isomeric impurities are present and separations by crystallization are frequently rendered difficult, due to the formation of gums. It was discovered early in this work that the bromine derivatives could, in all cases, be crystallized much more readily, and mixtures of these bromo compounds could frequently be separated with comparative ease. Opianic acid was, therefore, condensed with phenol and the crude reaction product brominated in glacial acetic acid. A monobromo compound was readily isolated and purified. If, before bromination, both *ortho* and *para* condensation products were present, there are three possible structures for the brominated compound, (III), (V) and (VI), assuming that the bromine enters only the phenol nucleus.


V VI III II I

The structure of the compound was shown to be that represented by (VI), namely, the monobromo derivative of the phthalide in which the opianic acid was condensed *para* (I) to the hydroxyl group of the phenol. This was demonstrated first by condensation of opianic acid with *o*-bromophenol, which gave the same substance (VI) in excellent yields, thus restricting the structure to (VI) or (V) and eliminating the possibility of bromination in the opianic acid ring. Upon reduction of the bromine compound (VI) a benzyl-benzoic acid resulted which was not identical with the benzyl-benzoic acid formed by reducing either the phthalide isolated from the reaction of opianic acid and phenol or the phthalide from opianic acid and *p*-bromophenol. Since the latter benzyl-benzoic acid must have the linkage *ortho* to the hydroxyl group, the new benzyl-benzoic acid must have the linkage *para*, and formula (V) is thus eliminated. The presence of both *ortho* and *para* compounds in the condensation of opianic acid with phenol is thus substantiated.

A similar plan of attack for the determination of the structure of the opianic acid and *o*-cresol compounds was followed. The probability is that a mixture of isomers, (VII) and (VIII), is also produced here.



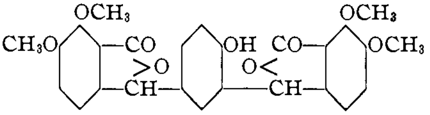
Bistrzycki[3c] isolated a substance which he was unable to reduce to the corresponding benzyl-benzoic acid. Jacobson and Adams repeated the work and obtained apparently the same phthalide, but it melted several degrees higher than reported by Bistrzycki. A successful reduction of the compound to a benzyl-benzoic acid was carried out, though the latter was never obtained in a crystalline state. The phthalide, after isolation in essentially a pure state from the reaction mixture, was brominated and a monobromo product readily produced (IX). This was shown to be identical with the condensation product of opianic acid and *o*-bromo-*o*-cresol, demonstrating that the original reaction must have taken place *para* to the hydroxyl group. The reduction of this brominated product yielded a crystalline benzyl-benzoic acid (X). It is thus obvious that the benzyl-benzoic acids, like the phthalides, readily form gums unless the products are absolutely pure. Since the brominated phthalides are easily purified, it is desirable to use these substances as intermediates if a pure benzyl-benzoic acid is to be readily obtained. When opianic acid is condensed with *p*-bromo-*o*-cresol, the condensation undoubtedly goes *ortho* to the hydroxyl (XI). This was proved with certainty, because upon reduction a benzyl-benzoic acid results (XII) which is different from the one formed from the bromination of the phthalide from opianic acid and *o*-cresol. The isolation of the isomer was not attempted.

From the results with the phenol and *o*-cresol condensations, it is obvious that if the *ortho* and *para* positions to the hydroxyl of the phenol are open both isomeric forms are produced, and the pure compound isolated may be either, depending upon conditions used. An *ortho* condensation will take place if the *para* position to the hydroxyl group is occupied, and a *para* condensation if both the *ortho* positions to the hydroxyl are occupied. If only one position *ortho* to the hydroxyl is filled, probably the chief condensation will take place *para* to the hydroxyl. In the condensations with *o*-bromophenol and *o*-bromo-anisole, the yield of *para* condensation products was practically quantitative. With the *o*-cresol this was not true, and ordinarily it would be necessary to determine the structure of the product with certainty where the compound was to be used as an intermediate for structural work. The same conclusion .in regard to orientation may be drawn about the phenol ethers which are described below.

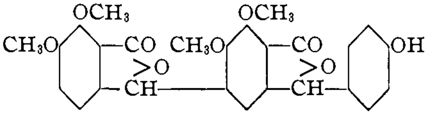
Two products were isolated when opianic acid was condensed with *p*-bromo-*m*-cresol.[1g] Since three isomers are possible from the condensation of opianic acid and *m*-cresol, this reaction was not studied.

In many of the condensations of opianic acid with phenol and phenol derivatives, high-melting by-products were formed in small quantities. Analyses of these compounds revealed the fact that they were not simple phthalides, isomeric with the normal products, but *bis*-phthalidyl compounds formed from two molecules of opianic acid and one molecule of the phenol or phenol derivative. Experiments showed that the amount of by-product formed could be increased from small quantities to good yields by using two molecular proportions of opianic acid to one of the phenol or phenol derivative, and also by increasing the strength of the sulfuric acid used in condensation.

There are two possible structures for these compounds, one in which two molecules of opianic acid condense in the phenol ring, probably in the positions *ortho* and *para* to the hydroxyl (XIII), and the other in which an opianic acid molecule condenses in the opianic nucleus of the primary product (XIV).



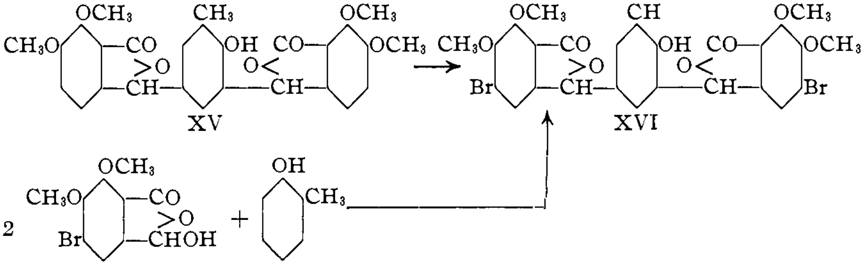
XIII



XIV

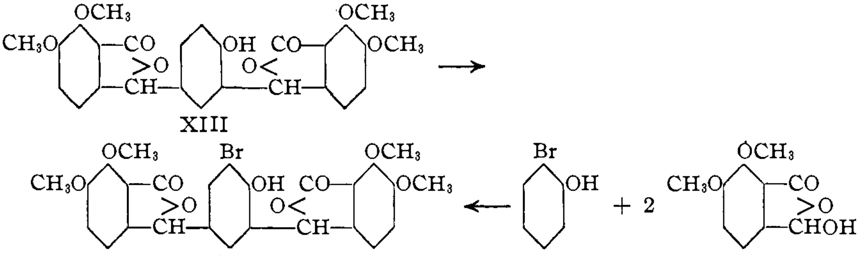
Since the vacant positions in opianic acid are rather difficult to substitute, such a condensation as that represented by formula (XIV) would appear unlikely.

The structure of the *bis*-phthalidyl compound in the case of opianic acid and *o*-cresol was shown definitely to be (XV). If either the *ortho* or *para* position to the hydroxyl in the *o*-cresol nucleus is not occupied, bromination might be expected to take place readily in the cold, similar to the quantitative bromination in the cold of many analogous compounds, (see formulas VIII and IX). The *bis*-phthalidyl *o*-cresol derivative, however, could not be brominated at all in the cold. Upon heating with bromine in glacial acetic acid for two hours, two bromine atoms are introduced. The compound resulting from this bromination (XVI) was found to be identical with the *bis*-phthalidyl compound formed from bromo-opianic acid and *o*-cresol, showing that in the original bromination a bromine atom was introduced into each of the opianic acid nuclei.



This establishes the fact beyond a doubt that the *o*-cresol ring is substituted in two positions and eliminates the possibility of formula (XIV).

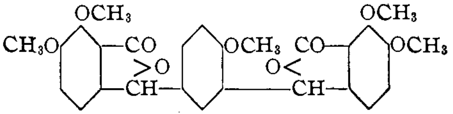
The *bis*-phthalidyl compound from opianic acid and phenol has an *ortho* position to the hydroxyl in the phenol nucleus unfilled (XIII). Bromination might then be expected to take place in the cold with the entrance of a single bromine atom into the phenol nucleus. This actually occurs and a compound (XVII) was produced, identical with the *bis*-phthalidyl compound obtained from the condensation of opianic acid and *o*-bromophenol.



XIII

XVII

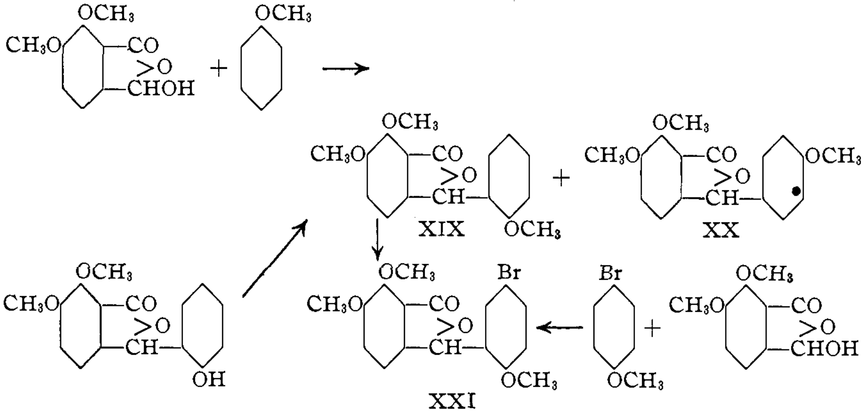
The above experiment also indicates that two opianic acid nuclei have condensed with phenol in the positions *ortho* and *para* to the hydroxyl, rather than in the two *ortho* positions. Methylation of the *bis*-phthalidyl compound from opianic acid and phenol gives a compound identical with the *bis*-phthalidyl derivative from opianic acid and anisole, so its structure may be represented by formula (XVIII).



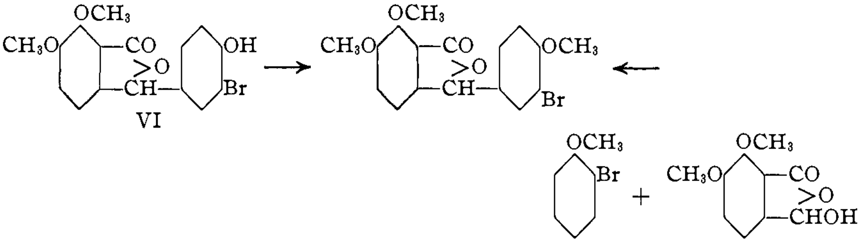
XVIII

Early experiments by Bistrzycki[3a] indicated that *o*-phthalaldehydic acid could not be condensed with phenol ethers, for no product was obtained from *o*-phthalaldehydic acid and phenetole. He was able later,[3c] however, to condense opianic acid and *o*-phthalaldehydic acid, with both *o*-cresol methyl ether and veratrole. It has been shown in this investigation that the condensation of opianic acid and *o*-phthalaldehydic acid with phenol ethers is as general a reaction as that with phenols; *o*-phthalaldehydic acid has been condensed with anisole and *p*-bromo-anisole, and opianic acid has been condensed with anisole, *p*-bromo-anisole, *o*-bromo-anisole and *p*-bromo-*m*-cresol methyl ether.

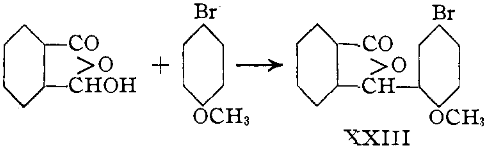
It is very difficult to obtain a pure phthalide from opianic acid and anisole. Considerable *bis*-phthalidyl compound from the condensation of two molecules of opianic acid and one of anisole (XVIII) is formed, due probably to the fact that the anisole is not as soluble as the opianic acid in the 73% sulfuric acid used as a condensing agent, with the result that there is an excess of the opianic acid always present in solution. The gum from the condensation has been shown to contain both isomeric phthalides (XIX) and (XX). By very slow and tedious crystallization, small amounts of the *para* isomer (XX) may be isolated. That the compound was the *para* isomer was concluded from the fact that it was not identical with the *ortho* isomer prepared by the methylation of the *ortho* hydroxyl compound (II), the determination of the structure of which was described earlier in the paper. If the crude product is brominated directly, a bromo derivative (XXI) can be separated, identical with the condensation product of opianic acid and *p*-bromo-anisole, thus indicating that a portion of the condensation product is the *ortho* isomer (XIX).



In contrast to the mixture of isomers and the poor yield which is obtained in the condensation of opianic acid with anisole, a quantitative yield of a pure product is obtained with *o*-bromo-anisole, the structure of which has been shown to be (XXII), for it is identical with the compound obtained by methylation of the phthalide from opianic acid and *o*-bromophenol (VI) and the structure of the latter has already been established.

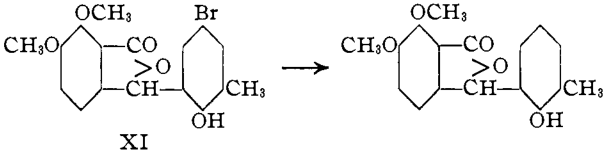


As in the condensation with phenol so with anisole, the simple *o*-phthalaldehydic acid gives more readily crystallizable products, and a fair yield of the *para* isomer with anisole may be isolated. *o*-Phthalaldehydic acid also condenses with *p*-bromo-anisole to give a product which has, undoubtedly, the structure (XXIII).



bis-Phthalidyl compounds from *o*-phthalaldehydic acid were not isolated as by-products in forming the phthalides, and an attempt has not yet been made to modify conditions so as to obtain them.

In determining the structure of the pure phthalides isolated from the condensations of opianic acid with phenol, anisole, *o*-cresol and *m*-cresol, an attempt was made to produce the pure *ortho* phthalides for comparison by catalytic reduction of the halogen from the halogenated phthalides formed by the condensation of opianic acid and *p*-bromophenols. Blocking the position *para* to the hydroxyl directs the condensation to the *ortho* position. Consequently, as, for example, in the case of the phthalide from opianic acid and *p*-bromo-*o*-cresol, if the removal of the halogen from this phthalide (XI) could be effected, a compound would result which would be the phthalide from opianic acid and *o*-cresol, provided the condensation had taken place in the *ortho* position.



XI

Catalytic reduction with platinum-oxide platinum black was not satisfactory for this reaction because after the halogen was replaced by hydrogen in part of the material, further reduction took place in the product before all of the original bromine compound was reduced. This is due, in part at least, to the fact that the bromine compounds used are not very soluble in the alcohol employed as a solvent and have to be reduced in partial suspension. It was not possible in any instance to stop the reduction at the desired point. From two to five moles of hydrogen were usually absorbed before all of the original material was in solution and the products consisted of a mixture of sodium carbonate soluble compounds from which the halogen-free benzyl-benzoic acids were isolated in several experiments in yields varying from a trace to 57% of the calculated amount.

The phthalides from opianic acid with *p*-bromo-*o*-cresol, *p*-bromo-*m*-cresol (condensation *ortho* to the methyl group) and *o*-bromophenol, and from *o*-phthalaldehydic acid with *p*-bromo-anisole, were reduced in this manner and the pure, halogen-free benzyl-benzoic acids isolated. The phthalides from opianic acid with *p*-bromo-*m*-cresol (condensation *para* to the methyl group) and *p*-bromophenol were reduced but only gums isolated. Undoubtedly hydrogenation of the aromatic nuclei also took place to a certain extent in most of the reduction experiments.

Experimental

General Method of Preparation of Phthalides.—The phthalides were prepared by mixing equimolar proportions of opianic acid (or *o*-phthalaldehydic acid) and phenol or phenol ether with sulfuric acid in the proper strength (as given in the table), in the proportion of 50 cc. of sulfuric acid to 0.1 mole of the phthalaldehydic acid. The sulfuric acid was previously cooled in an ice-salt bath to 0° to prevent the reaction from overheating. External cooling was applied if the temperature of the reaction rose above 25–30°, as a higher temperature led to the deepening of the color of the reaction product and to the formation of a certain amount of by-product.

The reactions were probably complete within an hour but were allowed to stand at room temperature overnight. Ice and water were then added to the reaction mixtures, causing the products to separate either as solids or as gums, as, for example, when phenol, anisole, *m*-cresol or *o*-cresol were used. The crude material was then washed with water.

In the condensation of opianic acid with phenol, anisole, *o*-cresol or *m*-cresol, the opianic acid is added in small portions to a mechanically stirred mixture of the phenol or phenol derivative and the condensing acid. This procedure reduces to a minimum the amount of the by-product formed from two molecules of opianic acid and one of phenol or phenol ether. Because of the slight solubility in the condensing acid this order of mixing is particularly desirable in the case of phenol ethers, so that an excess of opianic acid will never be present to make possible the formation of more by-product.

The phthalides from *p*-bromophenol, *p*-bromo-*o*-cresol, *p*-bromo-*m*-cresol, *o*-bromophenol, *p*-bromo-anisole, *o*-bromo-anisole, *o*-bromo-*o*-cresol, *p*-bromo-*m*-cresol methyl ether with opianic acid and from phenol, anisole and *p*-bromo-anisole with *o*-phthalaldehydic acid were very conveniently prepared by adding the condensing acid to an intimate mixture of the phthalaldehydic acid and phenol, or phenol ether, since the formation of by-products was ordinarily not observed if molecular proportions were used. The reaction mixtures often solidified to a hard cake, which prevented mechanical stirring and made it desirable to use as a reaction vessel an evaporating dish and as a stirrer, a pestle. The reaction products were poured into ice and water and then thoroughly washed.

The very small amounts of by-products formed in the phenol and *m*-cresol condensations were eliminated by four or five crystallizations of the crude product from acetic acid. In the anisole and *o*-cresol condensations, the separation of the by-product was more difficult. The by-products are only slightly soluble in hot alcohol, so that the gummy condensation mixtures were dissolved in this solvent. The solid by-product generally separated directly, particularly if the hot solution was allowed to cool in the presence of seed. Even by this procedure it was impossible to obtain a pure *o*-cresol condensation product, due, probably, to the retention of small amounts of by-product.

The crude reaction products are usually very soluble in most organic solvents, whereas after they are once obtained crystalline they are much less soluble. Crystallization of material from solutions of the crude products was almost invariably slow.

Wherever difficulty was encountered in isolation of the pure products, the details for the procedure used are given below. In the table is a list of the most convenient proportions of solvent for crystallization of relatively pure product, and the recovery is almost always 80–90%. The yields referred to in the tables are also of crystalline material, and this is important because practically quantitative yields of crude product are always obtained. The melting points in all cases are corrected.

5,6-Dimethoxy-2-(2-hydroxyphenyl) Phthalide. II.—The reaction product from 21 g. of opianic acid and 9.8 g. of phenol was thoroughly washed and the gum dried. It was dissolved in 125 cc. of hot glacial acetic acid in the presence of a little Norit and then filtered. Upon standing, crystals were slowly deposited, and crystallization was complete in the course of a day or two. The presence of seed assures a more rapid initial crystallization, but for completion essentially the same time is required as mentioned above. In this way 8.2 g. (29%) of crystalline material was obtained. Another small deposit may be obtained from the filtrate but beyond this, evaporation or cooling yields no more crystals. The compound is purified from acetic acid (1 g. in 6 cc.) and forms triangular plates; m. p., 177–178°.

TABLE I

PHTHALIDES (ALL WHITE)

Name	M. p., °C.	Cond. acid, %	Yield, %	Solvent and proportion	Cryst. form
5,6-Dimethoxy-2-( ) Phthalide					
1. (2-hydroxyphenyl)	177–8	73	30	Acetic acid (1:6)	Triangular plates
2. (4-methoxyphenyl)	93–5	73	13	*n*-Butyl ether	Plates
3. (2-methoxyphenyl)	103–4	By methylation	30	Pet. ether and abs. alc.	Prisms
4. (4-hydroxy-3-bromophenyl)	207–8	85	85	Acetic acid (1:14) Alcohol (1:35)	Plates (clusters)
5. (2-methoxy-5-bromophenyl)	157–8	85	40	Alcohol (1:40)	Plates
6. (4-methoxy-3-bromophenyl)	136.5–7[a]	85	97	Alcohol (1:30)	4-Sided plates
7. (4-hydroxy-3-methylphenyl)	185–6	73	42	Alcohol (1:13) Acetic acid (1:9)	Plates
8. (3-methyl-4-hydroxy-5-bromophenyl)	163–4[b]	85	71	Alcohol (1:11)	Thin plates
9. (2-methoxy-4-methyl-5-bromophenyl)	140–0.5	85	83	Alcohol (1:40)	Stout needles
10. (4-hydroxy-2-methylphenyl)	191.5–2.5	73	14	Acetic acid (28%) in toluene (1:25)	Thin plates
11. 2-(4-hydroxyphenyl) Phthalide	155–6	73	79	Acetic acid (28%) in toluene (1:18) Toluene (1:22)	Needles
12. 2-(4-methoxyphenyl) Phthalide	117.5–8.5	73	37	Propyl alc. and water (1:15)	Rectangular plates
13. 2-(2-methoxy-5-bromophenyl) Phthalide	137.5–8.5	85	50	Alcohol (1:28)	Needles

ANALYSES

	Formula	Calcd. C	Calcd. H	Found C	Found H
1.	$C_{16}H_{14}O_5$	67.11	4.93	66.70	5.01
2.	$C_{17}H_{16}O_5$	67.97	5.37	67.61	5.40
3.	$C_{17}H_{16}O_5$	67.97	5.37	67.52	5.35
4.	$C_{16}H_{13}O_5Br$	52.60	3.59	52.45	3.62
5.	$C_{17}H_{15}O_5Br$	Br—21.09%		Br—20.92%	
6.	$C_{17}H_{15}O_5Br$	53.82	3.99	53.92	4.22
7.	Previously prepared by Jacobson with Adams[c]				
8.	$C_{17}H_{15}O_5Br$	53.82	3.99	53.79	4.10
9.	$C_{18}H_{17}O_5Br$	54.96	4.36	55.07	4.75
10.	$C_{17}H_{16}O_5$	67.97	5.37	68.23	5.51
11.	$C_{14}H_{10}O_3$	74.31	4.46	74.16	4.64
12.	$C_{15}H_{12}O_3$	74.97	5.04	74.67	5.05
13.	$C_{15}H_{11}O_3Br$	56.43	3.48	56.79	3.53

[a] Resolidifies and melts at 141°.

[b] Resolidifies and melts at 178–9°.

[c] Ref. 1 f.

5,6-Dimethoxy-2-(2-methoxyphenyl) Phthalide. XIX.—A solution of 2.5 g. of 5,6-dimethoxy-2-(2-hydroxyphenyl) phthalide in 4 cc. of 10% sodium hydroxide solution was diluted with 25 cc. of water and shaken with 2 cc. of dimethyl sulfate. The solution was filtered, acidified and the resulting gum dried and washed. Crystallization from dilute alcohol gave 0.75 g. of solid material. This was crystallized by dissolving in a hot mixture of 10 per cent. absolute alcohol in petroleum ether (70–80°) As the solution cooled, a gum separated which was made just to redissolve by addition of a sufficient amount of absolute alcohol. The resulting solution was allowed to stand for two days and large crystals slowly formed. These were filtered and washed with 10% absolute alcohol in petroleum ether. They melted at 102–103°.

A mixture of this substance with 5,6-dimethoxy-2-(4-methoxyphenyl) phthalide, prepared by the condensation of anisole and opianic acid, showed a melting point of 60–70°, thus indicating that they were not identical.

Bromination in glacial acetic acid gave 5,6-dimethoxy-2-(2-methoxy-5-bromophenyl) phthalide, identical with the compound described later that was produced by condensing opianic acid with *p*-bromo-anisole.

5,6-Dimethoxy-2-(4-methoxyphenyl) Phthalide. XX.—The gummy reaction product from 0.05 mole of opianic acid and anisole was dissolved in about 50 cc. of hot alcohol and cooled. Practically all of the by-product present separated and was filtered. The filtrate was evaporated, and the resulting gum washed with 5% sodium carbonate solution, and then treated with a small amount of ether. In this way 2 g. (13%) of a fairly pure product crystallized. The only procedure found for purification was to dissolve in hot petroleum ether (90–110°), and to allow this solution to cool very slowly in the presence of a seed. A crystalline deposit which formed in the course of a day or longer was filtered and recrystallized from *n*-butyl ether, thus giving microscopic crystals melting at 93–95°.

5,6-Dimethoxy-2-(2-hydroxy-5-bromophenyl) Phthalide. III.—A well-stirred solution of 2.77 g. of 5,6-dimethoxy-2-(2-hydroxyphenyl) phthalide in 50 cc. of glacial acetic acid was treated with 2.5 cc. of a molar solution of bromine in acetic acid. Evaporation of the solution gave a quantitative yield of a monobromo derivative which was identical with the material obtained by condensation of opianic acid with *p*-bromophenol.[1d]

5,6-Dimethoxy-2-(4-hydroxy-3-bromophenyl) Phthalide. VI.—The gummy reaction mixture from 10.5 g. of opianic acid and 4.7 g. of phenol was, without purification, dissolved in chloroform and the solution dried. The cooled solution was then mechanically stirred and 60 cc. of a solution of bromine in chloroform was slowly added. Evaporation of the solvent gave a product which was purified by two crystallizations from alcohol followed by four crystallizations from glacial acetic acid. It was then pure, and melted at 207–208°; it proved to be identical with the compound formed by condensation of opianic acid and *o*-bromophenol.

5,6-Dimethoxy-2-(4-methoxy-3-bromophenyl) Phthalide. XXII.—The crude condensation product from 21 g. of opianic acid and 18.7 g of *o*-bromo-anisole was diluted with 250 cc. of alcohol and cooled without filtering. The resulting crystalline material was filtered and purified by recrystallization from alcohol (1 g. to 30 cc. of alcohol). The product was obtained in practically quantitative yields and melts at 136.5–137°. It resolidified and melted at 141°. If the temperature of the melting-point bath was raised very slowly, crystallization started again before the first melting was complete, so that the compound appeared to soften at 136.5° and to melt at 141°.

Methylation of 5,6-dimethoxy-2-(4-hydroxy-3-bromophenyl) phthalide with dimethyl sulfate and sodium hydroxide gave this same compound and it showed the same phenomenon of melting and resolidification.

***o*-Bromo-*o*-cresol.**—To 108 g. of *o*-cresol, 154 g. (85 cc.) of 95% sulfuric acid was slowly added with cooling. The solution was heated on a steam cone for 8 hours and then poured onto 300 g. of ice in a 2-liter beaker. To the cold reaction solution, 200 g. of powdered barium carbonate was added, in small portions to prevent excessive foaming. The excess of barium carbonate and the barium sulfate formed were filtered on a large filter and the colored filtrate containing the barium salt of *o*-cresol-*p*-sulfonic acid was brominated. The barium salt of *o*-bromo-*o*-cresol-*p*-sulfonic acid is so insoluble that it separated and formed in such bulk as to prevent thorough agitation. It was found best, therefore, to brominate one-fourth of the filtrate at a time. Such a portion was diluted to 600 cc., treated with Norit, filtered and 12.5 g. of bromine in 15 cc. of acetic acid was slowly added to the well-stirred solution. External cooling was applied to prevent the temperature from rising above 20°. Even in this dilution the copious separation of the product made very efficient stirring necessary and the last half of the bromine had to be added slowly. The precipitate was filtered in some runs when half of the bromine had been added and the bromination was completed in the filtrate. The barium salt which separated was sucked as dry as possible and then triturated with 200 cc. of alcohol for each 0.25 mole portion. The insoluble salt was filtered, washed with two more portions of 50 cc. of alcohol and dried. The acid filtrate from the bromination retained some material because of the solvent action of the hydrobromic acid. This was recovered by adding 50 g. of barium chloride and allowing it to stand for a day. This precipitate was washed with alcohol, dried and added to the main portion. In this way 68.0–72.6 g. (81–87%) of dry barium salt was obtained.

A mixture of 115 g. of the barium salt with a solution of 344 cc. of 95% sulfuric acid in 400 cc. of water was heated to boiling, and live steam passed through. The *o*-bromo-*o*-cresol distilled and was separated from the aqueous solution with carbon tetrachloride. The fraction boiling at 210–220° at 745 mm. and weighing 38 g. (60%) was redistilled under reduced pressure, boiling at 71–73° (7 mm.).

The *o*-bromo-*o*-cresol has previously been prepared by the decarboxylation of 3-methyl-4-hydroxy-5-bromo-benzoic acid.[4] It is, however, a very unsatisfactory procedure. An attempt was also made to sulfonate *o*-cresol and brominate the diluted acid solution directly. The difficulty in this procedure, however, consisted in the formation of a certain amount of bromine by the oxidation of the hydrobromic acid by the sulfuric acid. The bromine produced then replaced the sulfonic acid group and the resulting product was, for the most part, dibromo-*o*-cresol. By the isolation of the barium salt of the *o*-bromo-*o*-cresol-*p*-sulfonic acid, no such complication was encountered and a good yield of product resulted.

5,6-Dimethoxy-2-(3-methyl-4-hydroxy-5-bromophenyl) Phthalide. IX.—The crude reaction product from 0.05 mole of opianic acid and *o*-bromo-*o*-cresol was washed with water, then with 100 cc. of cold alcohol and filtered. It was crystallized from 125 cc. of alcohol, giving 13.4 g. of crystalline material. A second crystallization from alcohol gave a pure product, melting at 163–164°, which resolidifies and melts again at 178–179°.

Bromination of the phthalide produced by Jacobson and Adams[1f] from opianic acid and *o*-cresol gives a compound identical with that prepared above.

5,6-Dimethoxy-2-(4-hydroxy-4-methylphenyl) Phthalide.—The crude material from 0.05 mole of opianic acid and *m*-cresol, using 73% sulfuric acid, was dissolved in 50 cc. of glacial acetic acid and allowed to stand for a week. From the viscous solution crystals slowly deposited, which amounted to 2.1 g. when filtered. These were crystallized once from 25 cc. of acetic acid, giving 1 g. of product, and this was further purified by several crystallizations from a constant-boiling mixture of acetic acid and toluene (28% acetic acid). The pure product melts at 191.5–192.5°.

The structure assigned to this compound was merely assumed.

5,6-Dimethoxy-2-(2-methoxy-5-bromophenyl) Phthalide. XXI.—The crude material from 0.05 mole of condensation product of opianic acid and anisole was dissolved in

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[4] Robertson, *J. Chem. Soc.*, 93, 788 (1908).

50 cc. of chloroform and brominated with 45 cc. of a molar solution of bromine in chloroform. The chloroform was evaporated and the gummy reaction product dissolved in 80 cc. of glacial acetic acid. After standing for a day, 3.1 g. (26%) of crystals deposited, which, when purified by recrystallization from acetic acid, melted at 157–158°.

This compound was identical with that obtained by the bromination of 5,6-dimethoxy-2-(2-methoxyphenyl) phthalide in glacial acetic acid or by the condensation of opianic acid with *p*-bromo-anisole.

bis-(Dimethoxyphthalidyl) Phenols and Phenol Ethers

It was mentioned that in the preparation of phthalides from phenol, anisole, *o*-cresol and *m*-cresol, by-products were obtained in small amounts. These by-products, upon further study, proved to be *bis*-phthalidyl derivatives, and could be made practically the main product of reaction in many cases by modification of the amounts of reacting compound and of the conditions. In particular, the concentration of sulfuric acid for condensing was increased and the proportion of opianic acid to phenol or phenol ethers was doubled.

General Method for Preparation of *bis*-Phthalidyl Compounds.—To a mixture of 0.1 mole of opianic acid in 80 cc. of 95% sulfuric acid was added 0.05 mole of phenol or phenol ether, not allowing the temperature to rise above 30°. In the course of three or four hours the reaction mixture was poured into water and the precipitate filtered. The compounds were purified by crystallization from the solvent indicated in the table. The yields ranged from 25–97% and the products were readily purified because of the fact that the mono-phthalidyl compounds were much more soluble in the solvents used.

TABLE II

Bis-PHTHALIDYL DERIVATIVES (ALL WHITE)

	Name	M. p., °C.	Yield, %	Solvent and proportion in g.; cc. solvent	Crystalline form
	4,6-*bis*(5,6-dimethoxyphthalidyl)-				
1.	phenol	204.5–6	34	Alcohol (1:65)	Thin plates
2.	anisole	210–11	46	Alcohol (1:550)	Long needles
3.	2-methylphenol	205–7	50	Acetic acid (1:20) Alcohol (1:46)	Thin, rectangular needles
4.	3-methylphenol	227.5–9.5		Alcohol (1:85)	Needles
5.	2-bromophenol	215–216[a]	97	Acetic acid (1:65)	Thin, rectangular needles
6.	4,6-*bis*(4-bromo-5,6-dimethoxyphthalidyl)-2-methylphenol	266–8 dec.	43	Alcohol (1:700)	Bushy clusters

ANALYSES

	Formula	Calcd. C	Calcd. H	Found C	Found H
1.	$C_{26}H_{22}O_9$	65.25	4.63	65.12	4.74
2.	$C_{27}H_{24}O_9$	65.83	4.92	65.63	4.88
	Sap. equiv.	246		248	
3.	$C_{27}H_{24}O_9$	65.83	4.92	65.50	4.90
4.	$C_{27}H_{24}O_9$	65.83	4.92	65.70	5.08
5.	$C_{26}H_{21}O_9Br$	56.00	3.80	55.92	3.80
6.	$C_{27}H_{22}O_9Br_2$	49.85	3.41	50.38	3.67

[a] Resolidifies and melts again at about 224°.

2,4-*bis*-(5,6-dimethoxyphthalidyl) Anisole. XVIII.—A solution of 1.0 g. of 2,4-*bis*-(5,6-dimethoxyphthalidyl) phenol (XIII) was dissolved in 10% sodium hydroxide solution and shaken and warmed with 1.5 cc. of dimethyl sulfate. The solution remained clear because of the formation of the carboxyl group from the phthalide group by means of the alkali. Upon acidification, a precipitate formed which was filtered and washed with a 5% sodium hydroxide solution. The insoluble material was crystallized from alcohol and melted at 208–210°.

This product proved to be identical with the *bis*-dimethoxyphthalidyl compound obtained by the condensation of 2 moles of opianic acid and 1 mole of anisole.

2-Bromo-4,6-*bis*-(5,6-dimethoxyphthaliydl) Phenol. XVII.—A solution of 2.4 g. of 2,4-*bis*-(5,6-dimethoxyphthalidyl) phenol (XIII) was dissolved in 100 cc. of hot acetic acid, cooled somewhat and treated with 6 cc. of a molar solution of bromine in acetic acid. There thus precipitated 0.92 g. of the monobromo compound, which was purified by two crystallizations from acetic acid.

This substance was identical with that obtained by condensation of 2 moles of opianic acid with 1 mole of *o*-bromophenol.

4,6-*bis*-(4-bromo-5,6-dimethoxyphthalidyl)-2-methyl Phenol. XVI.—A mixture of 1.38 g. of 4,6-*bis*-(5,6-dimethoxy phthalidyl)-2-methyl phenol (XVI) in 50 cc. of acetic acid was refluxed for 2 hours with 7 cc. of a molar solution of bromine in acetic acid. On cooling, there deposited from the solution 0.11 g. of product, and from the filtrate, by evaporation and addition of alcohol, 0.26 g. more was obtained. This was diluted with 20 cc. of alcohol and filtered hot, and the insoluble residue crystallized from 250 cc. of alcohol. In this way 0.12 g. of pure material resulted, melting at 266–268°.

Since the *ortho* and *para* positions in the cresol nucleus were filled, it was assumed that this compound had the formula which has been assigned to it. In other words, the bromines in this case have entered the two opianic acid nuclei. In order to prove this point, 2 moles of bromo-opianic acid were condensed with *o*-cresol, by the general procedure mentioned above, and the same compound was obtained.

Benzyl-Benzoic Acids

The method for the reduction of the substituted phthalides to the corresponding benzyl-benzoic acids was essentially the same as that used by Jacobson and Adams.[1d,e,f]

A mixture of the phthalide (0.05 mole) and 10% sodium hydroxide solution (330 cc. of water and 60 cc. of 50% sodium hydroxide solution) was heated to boiling in a flask fitted with a reflux condenser and a mechanical stirrer. If the phthalide contained no phenolic hydroxyl or was insoluble in the sodium hydroxide solution, the mixture was refluxed until hydrolysis of the inner lactone took place and a clear solution resulted. Zinc dust (60–70 g.) was added to the solution in three or four portions at intervals of an hour. The first portions formed hard balls, but later portions formed a fine suspension of zinc, and the refluxing was continued for 10–20 hours. When the reaction was complete, the zinc was filtered off and the clear, colorless solution was slowly acidified with hydrochloric acid with efficient mechanical stirring. If a pure phthalide had been reduced a crystalline material separated, but it was often difficult to seed the crystallization, and even when seeded it frequently crystallized very slowly and a gum resulted. The gums were best separated with chloroform, the solutions dried and evaporated. The benzyl-benzoic acids from opianic acid were crystallized from toluene, while those from phthalaldehydic acid crystallized best from petroleum ether. The yields given in the table represent those of crystalline material.

During a study of the constitution of various phthalides it was hoped that catalytic reduction could be employed for the replacement of the halogen in the phthalides by hydrogen. This replacement occurred but it was almost impossible to prevent the reduction from going further, with the formation of benzyl-benzoic acids and in some instances partial hydrogenation of the rings. Those reductions from which solid products were isolated are given below.

TABLE III

BENZYL-BENZOIC ACIDS (ALL WHITE)

	Name	M. p., °C.	Yield, %	Solvent and proportion	Crystalline form	Source
	5,6-Dimethoxy-2-					
1.	(4-hydroxybenzyl) benzoic acid	173–4	95	Toluene (1:155)	Needles	Alk. and Cat. red.
2.	(2-hydroxybenzyl) benzoic acid	138.5–40	78	Toluene (1:25)	Microcrystals	Alk. red.
3.	(4-hydroxy-3-methylbenzyl) benzoic acid	140–2	90	Toluene (1:65)	Plates	Alk. red.
4.	(2-hydroxy-3-methylbenzyl) benzoic acid	138.5–9.5	57	Toluene (1:25)	Micro-crystals	Cat. red.
5.	(4-methoxybenzyl) benzoic acid					Alk. red.
6.	(2-methoxy-4-methylbenzyl) benzoic acid	124.5–6.5	85	Toluene (1:10)	Thick, six-sided plates	Alk. red.
7.	(2-hydroxy-6-methylbenzyl) benzoic acid	173.5	21	Toluene (1:130)	Plates	Cat. red.
8.	2-(2-methoxybenzyl) benzoic acid	115–6	46	Pet. ether 90–110° (1:60)	Thin plates	Cat. red.

ANALYSES

	Formula	Calcd.		Found	
		C	H	C	H
1.	$C_{16}H_{16}O_5$	66.64	5.60	66.70	5.78
2.	$C_{16}H_{10}O_5$	Previously prepared by Jacobson with Adams			
3.	$C_{17}H_{18}O_5$	Prepared by Jacobson with Adams—not purified			
		67.52	6.01	67.49	6.12
4.	$C_{17}H_{18}O_5$	67.52	6.01	67.60	6.13
5.	$C_{17}H_{18}O_5$	67.52	6.01		
6.	$C_{18}H_{20}O_5$	68.32	6.38	67.81	6.25
7.	$C_{17}H_{18}O_5$	Previously prepared by Jacobson with Adams			
8.	$C_{15}H_{14}O_3$	74.35	5.92	74.68	5.87

Catalytic Reduction of 5,6-Dimethoxy-2-(4-hydroxy-3-bromophenyl) Phthalide. XI.—A suspension of 2.89 g. of the phthalide in 100 cc. of 95% alcohol was reduced, using 0.1 g. of platinum-oxide catalyst[3] and hydrogen under pressure. When the suspended phthalide was all in solution (3 hr., 45 min.), 3.6 molecular equivalents of hydrogen had been absorbed. The reduction was stopped, the catalyst filtered off and the alcohol removed by evaporation. Sodium carbonate dissolved nearly all of the gum, but a small amount (0.01 g.) remained insoluble. This melted at 156–180° and probably consisted mainly of 5,6-dimethoxy-2-(4-hydroxyphenyl) phthalide, but the small yield prevented further investigation. From the sodium carbonate-soluble gum, by crystallization from toluene, a small amount of material (less than 0.01 g.) melting at 171–172.5° was obtained, and this proved to be 5,6-dimethoxy-2-(4-hydroxybenzyl) benzoic acid. No other pure products were isolated.

Catalytic Reduction of 5,6-Dimethoxy-2-(2-hydroxy-3-methyl-5-bromophenyl) Phthalide. XI.—A suspension of 6.8 g. of the phthalide, prepared as described by Jacobson and Adams,[1d] in 200 cc. of alcohol was reduced catalytically, using 0.1 g. of catalyst. After 2 hours, the phthalide had all gone into solution, and 2.1 molecular proportions of hydrogen had been absorbed. Evaporation of the solvent left a gum which partially crystallized. Crystallization from 50% acetic acid gave 3.07 g. of 5,6-dimethoxy-2-(2-hydroxy-3-methylbenzyl) benzoic acid (57%), which had previously been obtained by Jacobson and Adams[1d] using zinc and 10% sodium hydroxide as a reducing agent.

Catalytic Reduction of 5,6-Dimethoxy-2-(2-hydroxy-5-bromo-6-methylphenyl) Phthalide.—A suspension of 1.0 g. of the phthalide in 100 cc. of alcohol was reduced, using 0.1 g. of catalyst. The phthalide was all in solution at the end of 2 hours and the reduction was stopped. Evaporation of the alcohol and crystallization of the resulting gum from 10 cc. of toluene gave 0.17 g. (21%) of 5,6-dimethoxy-2-(2-hydroxy-6-methylbenzyl) benzoic acid (melting at 169–171°), which had previously been prepared by Jacobson and Adams.[1f]

Catalytic Reduction of 2-(2-Methoxy-5-bromophenyl) Phthalide. XXIII.—A suspension of 4.0 g. of the pure phthalide in 100 cc. of alcohol was reduced, using 0.1 g. of catalyst. At the end of 1.75 hours, the material had all dissolved and 2.7 molecular proportions of hydrogen had been absorbed. Partial evaporation of the solvent and addition of water gave 1.4 g. (46%) of crystalline material, which was purified by recrystallization from petroleum ether (90–110°) and proved to be 2-(2-methoxybenzyl) benzoic acid. The pure material melted at 117–118° and was quickly soluble in 5% sodium carbonate solution.

Catalytic Reduction of 5,6-Dimethoxy-2-(2-hydroxy-4-methyl-5-bromophenyl) Phthalide and of 5,6-Dimethoxy-2-(2-hydroxyphenyl) Phthalide gave products from which no solid materials were isolated.

Summary

1. Opianic acid and *o*-phthalaldehydic acid condense with phenol and phenol derivatives to form substituted phthalides which may be converted to anthraquinone derivatives by reduction to substituted benzylbenzoic acids, ring closure and oxidation. This is an important method of synthesizing anthraquinone derivatives of definite structure, if the structure of the substituted phthalides is known with certainty. A study has, therefore, been made of the condensation of opianic acid and *o*-phthalaldehydic acid with phenol and phenol derivatives, and the structure of the resulting products has been demonstrated.

2. The condensation of opianic acid with phenol, anisole, *m*-cresol and *o*-cresol gives mixtures of *o*- and *p*-isomers and the isolation of a pure compound is difficult.

3. The use of bromine to block certain positions in the phenol or phenol derivative restricts or prevents the formation of isomers, and the resulting bromophthalides are also easier to crystallize. If a bromine atom was in the position *ortho* to the hydroxyl or methoxyl, the condensation was directed almost entirely to the *para* position in two cases studied (*o*-bromophenol and *o*-bromo-anisole). If a bromine atom was *para* to the hydroxyl or methoxyl, the condensation took place in the *ortho* position.

4. Attempts were made to remove the bromine from bromophthalides by catalytic reduction. The reductions, however, could not be stopped

at this stage, and as a result the corresponding benzyl-benzoic acids were the only compounds isolated and identified.

5. *o*-Phthalaldehydic acid was condensed with phenol, anisole and *p*-bromo-anisole to give the corresponding substituted phthalides.

6. In the condensation of opianic acid with phenol, anisole, *o*-cresol and *m*-cresol, by-products were formed. These were found to be derivatives of *bis*-phthalidyl phenol, formed by the condensation of two molecules of opianic acid with one of the phenol or phenol derivatives. By varying the conditions these could frequently be made the main product of reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

A STUDY OF THE SYSTEM: ACETANILIDE-PROPIONANILIDE

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Incidental to a study of ketenes, Hurd[1] reports that fractional crystallization of mixtures of acetanilide and propionanilide yields a crystalline material melting sharply at 79.0–79.5°, but states that it is not a definite compound. The behavior would seem to indicate either that the material is a compound or a solid solution, and it was thought by the writers that a study of the freezing-point curves of mixtures of the two substances might furnish additional confirmation of his conclusions.

Experimental

Materials.—Propionanilide was prepared by refluxing redistilled aniline with propionic acid (Eastman Kodak Company). It was recrystallized from alcohol and carbon tetrachloride and melted at 105.0° (corr.).

The acetanilide (Merck) was recrystallized from alcohol, acetone and carbon tetrachloride and froze at 113.6° (corr.).

It was found early in the investigation that very small traces of water had a large effect on the freezing point, though not so much on the customary capillary tube melting point, so the materials were preserved at all times in a vacuum desiccator over sulfuric acid.

Manipulation.—Mixtures of approximately 10 g. each were made up by weight in a large stoppered test-tube, fused and then placed in a Dewar flask filled with hot water. A stirrer and an accurately calibrated thermometer were inserted and the temperature noted while the system cooled. The points at which the first solid phase separated out were obtained with ease and accuracy as there was always a small amount of supercooling, with the resultant rise of temperature. Where the per cent. of either component was large, the system was almost solid at the tem-

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[1] Hurd, THIS JOURNAL, **45**, 3095 (1923).