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

POLYHYDROXY AND POLYHYDROXYMETHYL ANTHRAQUINONES. VI. SYNTHESES FROM OPIANIC ACID AND PHENOLS OR CRESOLS

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

RECEIVED APRIL 24, 1925 PUBLISHED JULY 3, 1925

It has been known for several years that opianic acid (3,4-dimethoxy-2-carboxy-benzaldehyde) readily condenses with phenols or phenol ethers in the presence of sulfuric acid to give phthalides.[2] In all cases the para position to the hydroxyl or methoxyl groups in the phenols or phenol ethers was unoccupied and the condensation took place in the *para* position. In recent articles of this series,[1d,1e] it was shown that when the *para* position to the hydroxyl is occupied, the condensation takes place *ortho* to the hydroxyl.

Bistrzycki[2a] was unable to reduce his opianic-acid phenol or phenol ether condensation products to benzyl-benzoic acids, and as a consequence the synthesis of anthraquinones through these intermediates was impossible. In a previous paper the reduction of the phthalides from opianic acid and certain *para* substituted phenols[1d] was described. Simultaneous elimination of the halogen present occurred and the benzyl-benzoic acids were obtained in excellent yields. The syntheses of many new types of anthraquinones were thus rendered possible and incidentally the preparation of morindone was completed. The reduction of Bistrzycki's phthalides was predicted, if proper conditions were used.

This research has been undertaken to prove the following: (1) the condensation of opianic acid (and therefore probably of any substituted *o*-aldehyde-benzoic acid) with *para* substituted phenols to give phthalides is a general reaction and the position taken is that *ortho* to the hydroxyl group; (2) the phthalides formed in (1) can be reduced to benzyl-benzoic acids; if a halogen is present *ortho* or *para* to the hydroxyl group it is removed at the same time; (3) the benzyl-benzoic acids formed in (2) can be condensed to anthrones, then oxidized to anthraquinones and finally demethylated to give polyhydroxy- and polyhydroxymethyl-anthraquinones; (4) the phthalides of Bistrzycki obtained by condensing opianic

---

[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.

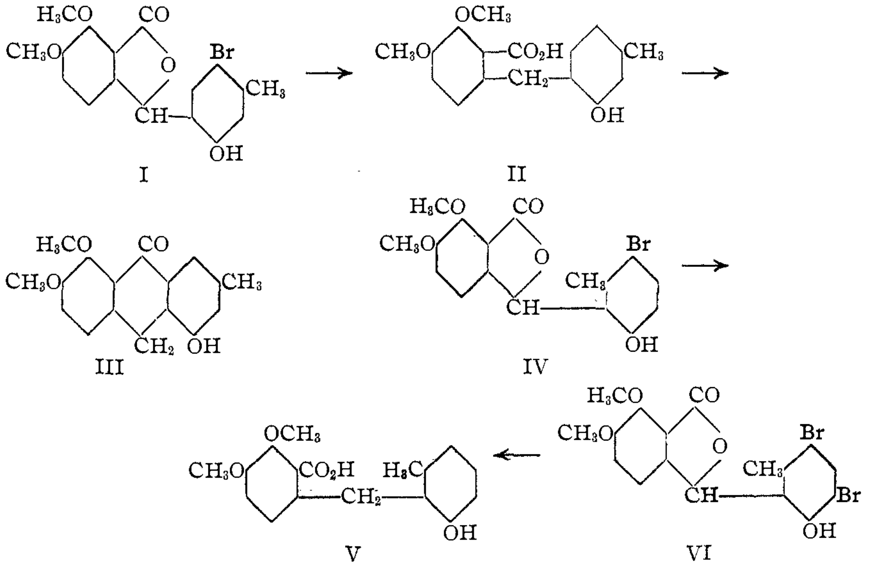
Previous papers in this field are (a) Graves with Adams, THIS JOURNAL, **45,** 2439 (1923); (b) Gardner with Adams, *ibid.*, **45,** 2455 (1923); (c) Jacobson with Adams, *ibid.*, **46,** 1312, (d) 2788 (1924); (e) **47,** 283 (1925).

[2] (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).

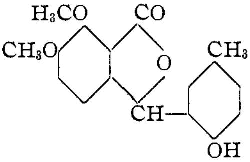
acid with various phenols and phenol ethers, the *para* positions of which are not occupied, may be reduced under proper conditions to benzyl-benzoic acids; the benzyl-benzoic acids can in turn be converted to anthrones and the anthrones to anthraquinones.

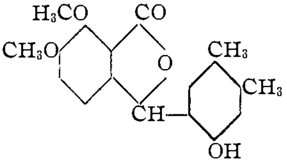
All these have been accomplished; the reactions have been shown to be general and as a consequence synthesis of a wide variety of anthraquinones is made possible.

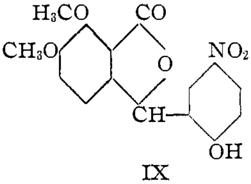
Opianic acid[1d] has already been condensed with *p*-bromophenol and *p*-bromo-*o*-cresol. In this investigation it was condensed first with *p*-bromo-*m*-cresol. By this condensation two compounds were isolated which undoubtedly have Formulas I and IV, respectively. The two were distinguished from each other by the fact that after reduction of each to the corresponding benzyl-benzoic acid, only that formed from I could be condensed to an anthrone. That the constitution of IV is correct was proved by condensing opianic acid with *o*,*p*-dibromo-*m*-cresol VI, under which conditions the union of the two molecules must take place between the methyl and hydroxyl groups. This product upon reduction gave the same benzyl-benzoic acid V as formed by reduction of IV. In all the reductions, the halogens were quantitatively removed.



Opianic acid was also condensed with *p*-cresol giving VII, *o*,*p*-xylenol giving VIII and *p*-nitrophenol giving IX, indicating that a halogen *para* to the hydroxyl group is not necessary, but that probably any group in that position will be satisfactory to cause the condensation to go *ortho* to the hydroxyl. The fact that the condensation takes place between the hydroxyl

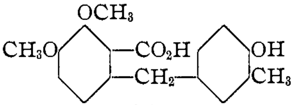

VII

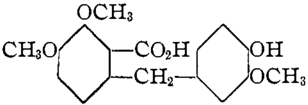

VIII

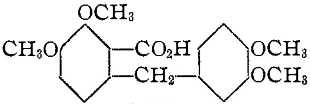

IX

and methyl groups, IV and VI, indicates the ease with which the reaction occurs.

Bistrzycki reports his failure to reduce the phthalides from opianic acid and *o*-cresol, guaiacol and veratrole. Under the conditions employed in this investigation no difficulty was encountered and the expected benzyl-benzoic acids were obtained, X, XI, XII.


X


XI


XII

The reductions of all the phthalides discussed were carried out by means of zinc dust (commercial) and alkali with good mechanical stirring. Some phthalides required longer treatment than others but all gave good yields of the products. The benzyl-benzoic acids were obtained from the reaction mixtures by acidification and were purified first by solution in sodium carbonate and reprecipitation with acid. The material thus obtained was invariably a thick sirup, but in general solidified on standing.

The anthrones could be produced in most instances by the action of 95% sulfuric acid on the benzyl-benzoic acid. In some instances, it was desirable to use somewhat more dilute acid (85%) depending on the character of the substituting groups in the benzyl-benzoic acids. The yields with one exception were satisfactory; treatment of II with 85% sulfuric acid resulted in only 14% yields of the anthrone. This may be due to the influence of the *ortho*- and *para*-directing methyl group in the position *meta* to that in which condensation must occur. A similar difficulty was encountered in the preparation of emodin.[1a,1c] In many cases the crude anthrone could not be purified and under these conditions was oxidized in crude form to the anthraquinone which in all cases could be crystallized.

The oxidation of the anthrones to anthraquinones took place in yields varying from 42 to 85% with the exception of 1,2-dimethoxy-5-hydroxy-7-methyl-9,10-dihydro-9-keto-anthracene which on oxidation gave only

28% yield of product. The anthrone having only methoxyl groups gave the best yield of anthraquinone.

The demethylation of the methoxy-anthraquinones was accomplished by means of hydrobromic acid in glacial acetic acid and gave good yields of hydroxy-anthraquinones. The reactions usually have to be carried out with small amounts of methoxy-anthraquinones, due to the insolubility of these substances. The final products are very high melting and were acetylated in order to characterize them.

Experimental Part

Substituted Phthalides, Table I.—Equimolecular quantities of opianic acid and the substituted phenol are intimately mixed in a mortar. Sulfuric acid of the proper strength (73%, 85% or 95%) is slowly added, in

Table I

Substituted Phthalides

No.	Phthalides 5,6-Dimethoxy-2-	Compound condensed with opianic acid	Solvent for crystallization	Form white	M. p. (corr.) °C.
1	(2-Hydroxy-5-methylphenyl)	*p*-Cresol (73% H_2SO_4)	Toluene	Needles	181.5–183
2	(2-Hydroxy-3,5-dimethylphenyl)	4-Hydroxy-1,3-dimethylbenzene (73% H_2SO_4)	Methyl alcohol	Needles	170–171
3	(2-Hydroxy-5-nitrophenyl)	*p*-Nitrophenol (95% H_2SO_4)	Acetic acid	Needles	269–270
4	(3,4-Dimethoxyphenyl)	Veratrole (73% H_2SO_4)	Alcohol	Plates	122–123 (lit. 120.5–121.5)
5	(3-Methoxy-4-hydroxyphenyl)	Guaiacol (73% H_2SO_4)	Alcohol	Needles	171–172 (lit. 164–166)
6	(3-Methyl-4-hydroxyphenyl)	*o*-Cresol (73% H_2SO_4)	Alcohol	Plates	185–186 (lit. 181)
7	(2-Hydroxy-4-methyl-5-bromophenyl)	*p*-Bromo-*m*-cresol (85% H_2SO_4)	Acetic acid	Plates or needles	180–181
8	(2-Hydroxy-5-bromo-6-methylphenyl)	*p*-Bromo-*m*-cresol (85% H_2SO_4)	Acetic acid	Plates	270–271 Begins to sinter at 265
9	(2-Hydroxy-3,5-dibromo-6-methylphenyl)	*o*-*p*-Dibromo-*m*-cresol (85% H_2SO_4)	Acetic acid Alcohol	Plates	205–205.5

	Analysis				
	Formula	Subs. G.	G. CO_2 H_2O	Calcd. % C H	Found % C H
1	$C_{17}H_{16}O_5$	0.1732	0.4303 .0807	67.98 5.37	67.77 5.21
2	$C_{18}H_{18}O_5$	.1919	.4812 .0952	68.77 5.77	68.41 5.55
3	$C_{16}H_{13}O_7N$	.1893	.4045 .0725	57.99 3.95	58.29 4.28
4	Previously prepared				
5	Previously prepared				
6	Previously prepared				

	Formula	Subs.	AgBr	Calcd. Br	Found
7	$C_{17}H_{15}O_5Br$	.3650	.1833	21.08	21.37
8	$C_{17}H_{15}O_5Br$	.2425	.1193	21.08	20.93
9	$C_{17}H_{14}O_5Br_2$	.1810	.1474	34.89	34.65

the ratio of 65 cc. of acid to 25 g. of opianic acid. The nature of the substituting groups in the phenol determines the strength of the sulfuric acid to be used. For the simple cresols, 73% sulfuric acid is the best condensing agent, while for the bromo derivatives, a stronger acid (85%) is necessary. The mixture is liquid at first but usually becomes solid or very thick on standing. An exception to this is the reaction mixture of opianic acid and *p*-nitrophenol which remains liquid. Water is then added, the granular solid filtered and washed free from sulfuric acid.

The yield of crude material is almost quantitative. Purification is effected by crystallization from alcohol, methyl alcohol or acetic acid. In a few instances, the yield of purified phthalide is poor. In most cases, the yield of phthalide after one or two crystallizations amounts to 50–70%.

Substituted Benzyl-benzoic Acids, Table II.—A solution of 25 g. of the substituted phthalide in 500 cc. of boiling 10% sodium hydroxide solution is made and 75 g. of zinc dust (commercial) is added. The mixture is boiled gently and stirred for 15 hours. Unless efficient stirring is provided, the zinc dust soon forms a layer or cake in the bottom of the flask and reduction is retarded. Usually reduction is complete in 15 hours, but occasionally a longer time is necessary. In the latter case, a further addition of zinc dust at the end of the 15-hour period is desirable. The zinc is filtered off, washed and the filtrate and washings are acidified with hydrochloric acid. The substituted benzyl-benzoic acid is precipitated as a sirup which on cooling collects on the bottom of the beaker and in some cases solidifies. The thick sirup of solid is dissolved in 10% sodium car-

Table II

Benzyl-benzoic Acids

No.	Acid 5,6-Dimethoxy-2-	Phthalide reduced No.	Yield (from Na_2CO_3) %	Solvent for crystallization	Form
1	(2-Hydroxy-5-methylbenzyl)benzoic	1	79	Toluene	White plates
2	(3,4-Dimethoxybenzyl)benzoic	4	71	....	Very thick sirup forming a plastic solid on standing
3	(2-Hydroxy-6-methylbenzyl)benzoic	8 9	62 82	Toluene	White plates
4	(3-Methyl-4-hydroxybenzyl)benzoic	6	76	....	Thick sirup finally becoming solid on standing
5	(2-Hydroxy-4-methylbenzyl)benzoic	7	83	....	Very thick sirup forming a plastic solid on standing
6	(3-Methoxy-4-hydroxybenzyl)benzoic	5	79	Water	White plates

			Analysis						
	M. p. (corr.) °C.	Formula	Subs. G.	CO_2 G.	H_2O G.	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
1	125–126	$C_{17}H_{18}O_5$	0.1828	0.4511	0.0950	67.52	6.00	67.32	5.81
2	.....	.....	....	....	....	...	..	...	..
3	173–175	$C_{17}H_{18}O_5$	0.1940	0.4823	0.1020	67.52	6.00	67.82	5.88
4	.....	.....	....	....	....	...	..	...	..
5	.....	.....	....	....	....	...	..	...	..
6	105–106	$C_{17}H_{18}O_6.H_2O$	0.1661	0.3685	0.0846	60.59	5.99	60.52	5.70
				H_2O	1 H_2O calcd.	Found			
Moisture detn. shows 1 H_2O			0.3362	[0.0184	5.35	5.47]			

bonate solution, the solution filtered from small amounts of insoluble impurities and acidified with hydrochloric acid. The reprecipitated benzyl-benzoic acid is washed free from hydrochloric acid and dried. By this procedure it is obtained as a granular solid or a very thick, sticky liquid in approximately 75% yields. Some of the acids do not crystallize readily from the ordinary organic solvents, but are sufficiently pure for direct conversion into the corresponding anthrones.

Anthrones, Table III.—The benzyl-benzoic acid is suspended in concd. sulfuric acid in the ratio of 1 g. of acid to 10 cc. of sulfuric acid and the mixture allowed to stand until solution is complete. If sulfonation takes place, the concentrated acid is substituted by 85% sulfuric acid. The solution is poured on ice to precipitate the anthrone. This is at first obtained as a granular, yellow precipitate which, however, often becomes sticky upon being washed with water. Unchanged benzyl-benzoic acid is removed by washing with 10% sodium carbonate solution. The crude anthrone is oxidized directly to the anthraquinone, since crystallization is usually somewhat difficult. It reacts in the enolic form with acetic anhydride in the presence of sodium acetate to give the acetate of the anthranol which crystallizes from alcohol or acetic acid.

TABLE III

ANTHRONES

	Anthrone	Strength of H_2SO_4 %	Yield of crude product %	Solvent for crystallization	Form
1	1,2,6,7-Tetramethoxy-9,10-dihydro-9-keto-anthracene	95	80	Dil. acetic acid	Yellow needles
2	1,2,6-Trimethoxy-7-hydroxy-9,10-dihydro-9-keto-anthracene	95	95	....	....
3	1,2-Dimethoxy-6-methyl-7-hydroxy-9,10-dihydro-9-keto-anthracene	95	52	....	....
4	1,2-Dimethoxy-5-hydroxy-7-methyl-9,10-dihydro-9-keto-anthracene	85	14	....	....
5	1,2-Dimethoxy-5-hydroxy-8-methyl-9,10-dihydro-9-keto-anthracene	85	95	....	....
	Acetyl derivative				
6	1,2-Dimethoxy-5-acetoxy-8-methyl-9-acetylanthranol	..	..	Acetic acid	Greenish-yellow hexagonal plates

	M. p. (corr.) °C.	Formula	Subs. G.	CO_2 G.	H_2O G.	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
1	153–154	$C_{18}H_{18}O_5$	0.1853	0.4657	0.0906	68.77	5.77	68.56	5.47
6	188.5–189	$C_{21}H_{20}O_6$	.1794	.4480	.0835	68.45	5.47	68.12	5.21

Oxidation of Anthrone to Anthraquinone, Table IV.—The anthrone is dissolved in a small volume of acetic acid and to this solution is added the calculated amount of chromium trioxide dissolved in a few cubic centimeters of water. The molecular ratio of anthrone to chromium trioxide is 1:1.33. Oxidation begins at once as indicated by a change of color of the solution from greenish-yellow to violet, and by the generation of heat. Yellow needles are deposited from the solution on cooling. Acetic acid and ethyl acetate are good solvents for crystallization.

Some difficulty was at first experienced in the oxidation of 1,2-dimethoxy-5-hydroxy-8-methyl-9,10-dihydro-9-keto-anthracene. Oxidation at room temperature resulted in the formation of a compound of chromium, presumably with the anthraquinone. The nature of this compound was not investigated, but it separated from the solution as a bright red precipitate, insoluble in organic solvents except acetic acid, and infusible on ignition. The formation of this chromium complex was avoided by conducting the oxidation at 50°.

Table IV

Anthraquinones

All formed yellow needles

Anthraquinone	Yield (pure) based on anthrone %	Solvent for crystn.	M. p. (corr.) °C.	Analysis				
				Formula	Subs.	G. CO_2 H_2O	Calcd. C H	Found C H
1,2-Dimethoxy-5-hydroxy-8-methyl	42	Ethyl acetate	168–169	$C_{17}H_{14}O_5$	0.1068	0.2668 .0473	68.44 4.73	68.15 4.95
1,2-Dimethoxy-5-acetoxy-8-methyl	. .	Alcohol	173–174	$C_{19}H_{16}O_6$	.1645	.4060 .0707	67.04 4.74	67.33 4.80
1,2-Dimethoxy-5-hydroxy-7-methyl	28	Ethyl acetate	231.5–232.5	$C_{17}H_{14}O_5$	.0784	.1968 .0350	68.44 4.73	68.48 4.99
1,2,6-Trimethoxy-7-hydroxy	55	Acetic acid	269–270	$C_{17}H_{14}O_6$	.1611	.3838 .0628	64.95 4.49	64.99 4.36
1,2-Dimethoxy-6-methyl-7-hydroxy	55	Acetic acid	About 310 (not sharp)[a]	$C_{17}H_{14}O_5$	.1588	.3962 .0651	68.44 4.73	68.06 4.58
1,2,6,7-Tetramethoxy	85	Acetic acid	244–245 (lit. 239)	Previously prepared				

[a] Starts darkening at 285°.

Demethylation, Table V.—A solution of 0.5 g. of the methoxy-anthraquinone in glacial acetic acid is boiled under a reflux condenser with 25 cc. of concd. aqueous hydrobromic acid (d., 1.48) for 12 hours. Sufficient acetic acid to maintain a clear solution during the boiling is necessary, otherwise partially demethylated products separate. On account of the large volume of solvent required, only small amounts at a time are conveniently demethylated in this manner. The clear solution on cooling deposits crystals (needles) of the completely demethylated anthraquinone. Small amounts may be recrystallized by the use of large volumes of acetic acid or nitrobenzene.

Acetylation, Table V.—The anthraquinone (1 g.) is heated with 15 cc. of acetic anhydride and 1 g. of fused sodium acetate for a few minutes, the solution cooled and poured into water. The acetate separates as an oil that becomes crystalline on standing for a few minutes. The acetate is readily purified by crystallization from alcohol or acetic acid.

TABLE V

ACETYL DERIVATIVES

Anthraquinone	Yield on demethylation %	Solvent for crystallization	Color[b] and m. p. (corr.)	Analysis				
				Formula	Subs.	G. CO_2 H_2O	Calcd. C H	Found C H
1,2,5-Trihydroxy-8-methyl	85	Acetic acid	Red 301 Decomp. at 290	$C_{15}H_{10}O_5$	0.1600	0.3913 .0558	66.65 3.73	66.72 3.90
1,2,5-Acetoxy-8-methyl	..	Alcohol	Light yellow 204–205	$C_{21}H_{16}O_8$	.1285	.2997 .0480	63.62 4.07	63.63 4.18
1,2,6,7-Tetrahydroxy[a]	69	Nitrobenzene	Orange above 330	$C_{14}H_8O_6$	.1569	.3568 .0403	61.76 2.96	62.04 2.87
1,2,6,7-Tetraacetoxy	..	Acetic acid	Light yellow 239–241	$C_{22}H_{16}O_{10}$	.1603	.3520 .0521	59.99 3.66	59.90 3.64
1,2,7-Trihydroxy-6-methyl	70	Nitrobenzene	Orange-red above 330	$C_{15}H_{10}O_5$	.1710	.4189 .0620	66.65 3.73	66.83 4.05
1,2,7-Triacetoxy-6-methyl	..	Alcohol	Light yellow 232–233	$C_{21}H_{16}O_8$	.1513	.3530 .0553	63.62 4.07	63.65 4.09

[a] Prepared by Bistrzycki, Ref. 2 c.

[b] All formed needles.

Summary

1. The condensation of opianic acid with *para* substituted phenols to give substituted phthalides has been shown to be a general reaction.
2. The phthalides thus formed and the phthalides prepared by the condensation of opianic acid with *o*-cresol, guaiacol and veratrole have been reduced to the benzyl-benzoic acids.
3. The benzyl-benzoic acids have been converted to anthrones and the latter to anthraquinones.
4. A number of new anthraquinones formerly difficult of synthesis have been prepared by the general methods described.

URBANA, ILLINOIS

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

QUINOLINE AND THE CENTROID STRUCTURE

BY REYNOLD C. FUSON

RECEIVED APRIL 27, 1925 PUBLISHED JULY 3, 1925

In a recent article[1] the writer presented the results of an attempt to test Huggins'[2] centroid model for naphthalene. From the experimental data given there, it was concluded that naphthalene cannot have the centroid structure and, by inference at least, this structure for benzene is made doubtful. The present paper sets forth the results of a similar attempt to apply the centroid structure to quinoline and some of its derivatives.[3]

---

[1] Fuson, THIS JOURNAL, **46,** 2779 (1924).

[2] Huggins, *ibid.*, **44,** 1607 (1922).

[3] The idea of using quinoline for the purpose of testing the validity of the centroid structure was suggested to the author by Dr. M. L. Huggins.