

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

THE PREPARATION OF SEVERAL SUBSTITUTED ANTHRONES<sup>1</sup>

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RECEIVED AUGUST 22, 1931

PUBLISHED APRIL 6, 1932

In view of the fact that 9-hydroxy-9-phenylanthrone-10 (phenyl-oxanthranol)<sup>2</sup> and 9,9-diphenylanthrone-10<sup>2b,3</sup> have been isolated as reaction products from the interaction of phthalyl chloride and benzene, it seemed not improbable that corresponding hydroxy compounds, namely, 3,9-dihydroxy-9-(4'-hydroxyphenyl)-anthrone-10 (I), 3-hydroxy-9,9-di-(4'-hydroxyphenyl)-anthrone-10 (II) and possibly, in addition, 3-hydroxy-9,9,10-tri-(4'-hydroxyphenyl)-9,10-dihydroanthrol-10 (III) might be formed as by-products from the condensation of phthalic anhydride with phenol. Since the cathartic action of yellow phenolphthalein may be due to the presence of these compounds, we wished to prepare them in order that they might be tested for laxative action.

Although Baeyer<sup>4</sup> stated that he had obtained compound I, called by him "dihydroxyphenylanthranol," from phenolphthalein it has been shown<sup>5</sup> that Baeyer's compound is, in reality, 2-(4''-hydroxybenzoyl)-4'-hydroxy-benzophenone.

We have not been able, as yet, to obtain the first three substances mentioned above but the methyl ethers of the corresponding 2-hydroxy compounds XI, XV and XVI as well as several other anthraquinone derivatives have been prepared. Upon demethylation of the methoxy derivatives highly colored, gummy or resinous products were obtained, undoubtedly fuchsones, which proved to be very difficult to purify.

It was found that interaction of 4-methoxyphenylmagnesium iodide with anthraquinone and with 2-methoxyanthraquinone yields 9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (IV) and 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (XI), respectively. In the case of the latter compound it was necessary to prove that the Grignard reagent had reacted with carbonyl 9 in the methoxyanthraquinone and not with carbonyl 10; therefore the substance was synthesized according to the scheme shown.

2-Methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 (XV) and 2-methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10 (XVI) were obtained by means of the reactions indicated.

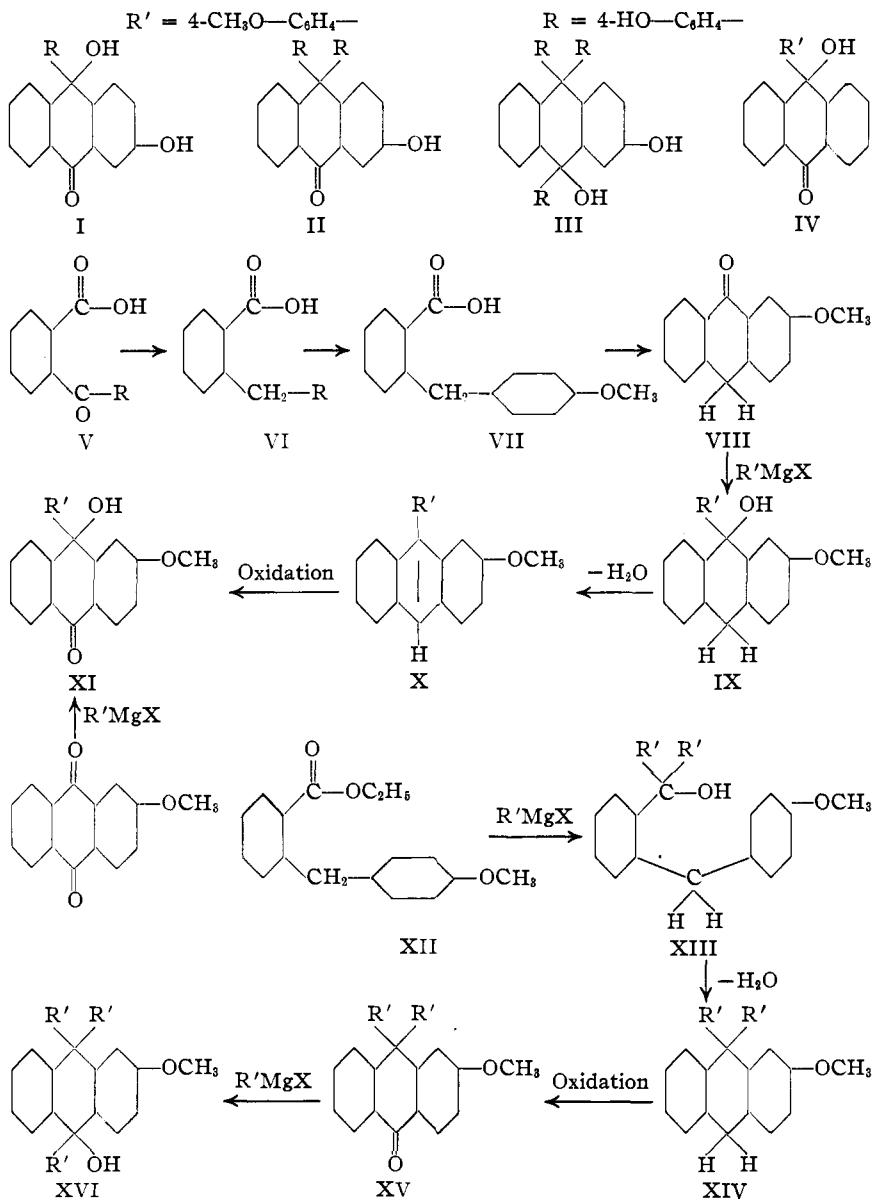
<sup>1</sup> This paper represents the third part of a dissertation submitted to the Graduate School by O. J. Weinkauff in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. O. J. Weinkauff was awarded The Upjohn Company Fellowship, 1928-1931.

<sup>2</sup> (a) Copisarow, *J. Chem. Soc.*, 111, 10 (1917); (b) 117, 209 (1920).

<sup>3</sup> Haller and Guyot, *Bull. soc. chim.*, [3] 17, 873 (1897).

<sup>4</sup> Baeyer, *Ann.*, 202, 100 (1880).

<sup>5</sup> Blicke and Weinkauff, *THIS JOURNAL*, 54, 1446 (1932).



**Experimental Part**

9-Hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (IV).—4-Methoxyphenylmagnesium iodide was prepared from 23.4 g. of 4-iodoanisole, 2.4 g. of magnesium and 60 cc. of ether. Forty grams of dry anthraquinone, suspended in 200 cc. of ether, was added to the Grignard reagent while the latter was stirred vigorously. The mixture was heated for two hours on a steam-bath and then decomposed with ice and ammonium chloride.

The ether-benzene solution was separated, filtered, dried and the solvents removed. The solid residue, after recrystallization from alcohol, melted at 206–207°. The material dissolved in concd. sulfuric acid with the formation of a dark green solution.

*Anal.* Calcd. for  $C_{21}H_{16}O_3$ : mol. wt., 316; C, 79.74; H, 5.06;  $OCH_3$ , 8.8. Found: mol. wt. (benzene),<sup>8</sup> 314; C, 79.41; H, 5.00;  $OCH_3$ , 9.8.<sup>7</sup>

**2-(4'-Hydroxybenzyl)-benzoic Acid (VI).**—The following method is a modification of that reported by Bistrzycki and Yssel de Schepper.<sup>8</sup> A solution prepared from 150 g. of 2-(4'-hydroxybenzoyl)-benzoic acid and 2.5 liters of 10% aqueous sodium hydroxide was heated on a steam-bath and stirred rapidly. One hundred and fifty grams of zinc dust was added and the mixture was heated for twenty hours. After filtration the filtrate was acidified and the product recrystallized from alcohol; m. p. 153–154°;<sup>9</sup> yield, 114 g.

**2-Hydroxyanthraquinone from 2-Hydroxyanthrone-9.**—Thirty grams of 2-hydroxyanthrone-9,<sup>8</sup> prepared from 2-(4'-hydroxybenzyl)-benzoic acid, was suspended in 150 cc. of acetic acid and treated with 32 g. of sodium dichromate, dissolved in 15 cc. of hot water, in a flask fitted with a reflux condenser. The mixture soon began to boil. After some time the flask was heated on a steam-bath for about ten minutes, cooled, the crystalline reaction product filtered, washed with acetic acid and then with water. The material weighed 30 g. and melted at 303–304°.<sup>10</sup>

**2-Methoxyanthrone-9 (VIII).**—Since difficulties were encountered in the methylation of 2-hydroxyanthraquinone, the methyl ether of the latter substance was prepared by an indirect method.

The methyl ester of 2-(4'-methoxybenzyl)-benzoic acid (VII) was obtained from 45.6 g. of 2-(4'-hydroxybenzyl)-benzoic acid, 160 cc. of 10% sodium hydroxide solution and 40 cc. of dimethyl sulfate. The ester separated as an oil. In order to hydrolyze the ester, 25 g. of sodium hydroxide was added to the reaction mixture and the latter was refluxed for several hours. The clear, cold solution was acidified. After recrystallization from alcohol the 2-(4'-methoxybenzyl)-benzoic acid melted at 116–117°;<sup>11</sup> yield, 94% of the calculated amount.

Forty-eight and four-tenths grams of finely powdered 2-(4'-methoxybenzyl)-benzoic acid was dissolved in 250 cc. of concd. sulfuric acid which had been cooled to 5°. At the end of three minutes the temperature of the mixture had risen to 25°. The solution was poured immediately into 1.5 liters of ice water. The product was filtered, washed with water and recrystallized from methyl alcohol; m. p. 94–95°; yield of pure product, 30 g.

*Anal.* Calcd. for  $C_{15}H_{12}O_2$ : C, 80.32; H, 5.40;  $OCH_3$ , 13.7. Found: C, 80.11; H, 5.23;  $OCH_3$ , 13.8.<sup>12</sup>

<sup>6</sup> Menzies method.

<sup>7</sup> Phenol was used as a solvent [Weishut, *Monatsh.*, **33**, 1165 (1912)]. In this instance, as well as when acetic anhydride was used as a solvent, the apparatus used (Gattermann-Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter, Berlin and Leipzig, 1928, p. 71) was modified to the extent that a 5-cc. dropping funnel was fused to the carbon dioxide inlet tube. The sample and phenol were placed in the apparatus and the hydriodic acid added through the dropping funnel.

<sup>8</sup> Bistrzycki and Yssel de Schepper, *Ber.*, **31**, 2792 (1898).

<sup>9</sup> Bistrzycki and Yssel de Schepper<sup>8</sup> recorded the melting point as 145–146°.

<sup>10</sup> Liebermann [*Ann.*, **212**, 25 (1882)] recorded the melting point as 302°.

<sup>11</sup> The melting point reported by Nourrisson [*Bull. soc. chim.*, [2] **46**, 206 (1886)] is 110–111°.

<sup>12</sup> Phenol was used as a solvent.

The structure of the methoxyanthrone was proved by its conversion into 2-methoxy-anthraquinone by oxidation. Eleven and two-tenths grams of the methoxyanthrone, suspended in 80 cc. of acetic acid, was treated with 11 g. of sodium dichromate, dissolved in 10 cc. of hot water. The mixture soon began to boil. After it had been heated for one hour on a steam-bath it was cooled and the crystalline reaction product recrystallized from acetic acid. Nine and seven-tenths grams of pale yellow 2-methoxyanthraquinone was obtained; m. p. 194–195°. <sup>13</sup>

When 2-hydroxyanthrone was oxidized in the manner described above, 2-hydroxy-anthraquinone was formed; m. p. 303–304°.

**2-Methoxy-9-(4'-methoxyphenyl)-anthracene (X).**—4-Methoxyphenylmagnesium iodide was prepared from 23.4 g. of 4-iodoanisole, 2.4 g. of magnesium, 45 cc. of dry benzene and 45 cc. of ether. Nine and four-tenths grams of 2-methoxyanthrone-9, suspended in 50 cc. of benzene, was added to the Grignard reagent and the mixture heated for four hours. After decomposition of the reaction mixture with ice and ammonium chloride, removal of the solvents and steam distillation, 5.2 g. of the anthracene was obtained. After recrystallization from acetic acid and then from benzene-petroleum ether (30–60°) it melted at 175–176°. The compound is very soluble in benzene, slightly soluble in ether and alcohol. The solutions all exhibit a blue fluorescence.

*Anal.* Calcd. for  $C_{22}H_{18}O_2$ : mol. wt., 314; C, 84.05; H, 5.77;  $OCH_3$ , 18.5. Found: mol. wt. (benzene), 313; C, 83.72; H, 5.63;  $OCH_3$ , 19.7. <sup>14</sup>

Because of its instability no attempt was made to isolate the primary product of the reaction, 2-methoxy-9-(4'-methoxyphenyl)-9,10-dihydroanthrol-9 (IX).

**2-Methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 (XI).**—Five grams of the above-mentioned anthracene, suspended in 25 cc. of acetic acid, was treated with 3.5 g. of sodium dichromate dissolved in 3 cc. of hot water. The mixture soon began to boil. After the reaction had subsided the mixture was heated on a steam-bath for five minutes, cooled and the crystalline product removed by filtration. The yield was 4.7 g. After recrystallization from acetic acid the anthrone melted at 199–201°. The material is slightly soluble in benzene and insoluble in alcohol and ether.

*Anal.* Calcd. for  $C_{22}H_{18}O_4$ : mol. wt., 346; C, 76.29; H, 5.24;  $OCH_3$ , 17.7. Found: mol. wt. (benzene), 362; C, 76.23; H, 5.24;  $OCH_3$ , 17.9. <sup>15</sup>

The anthrone was also obtained from 2-methoxyanthraquinone and 4-methoxyphenylmagnesium iodide. To the Grignard reagent prepared from 5.8 g. of 4-iodoanisole, 0.6 g. of magnesium and 15 cc. of ether there was added 4.7 g. of 2-methoxyanthraquinone, dissolved in 100 cc. of benzene. The mixture was heated for four hours, decomposed and the reaction product subjected to steam distillation. The gummy residue was dissolved in 10 cc. of hot acetic acid. The solution was allowed to cool, whereupon 1.4 g. of unchanged methoxyanthraquinone separated. This was removed immediately by filtration. After some time 2.3 g. of 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10 precipitated from the filtrate. After several recrystallizations from acetic acid the compound melted at 199–200°. The mixed melting point with the substance obtained by oxidation of 2-methoxy-9-(4'-methoxyphenyl)-anthracene was 199–201°.

**2-Methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 (XV).**—The ethyl ester of 2-(4'-methoxybenzyl)-benzoic acid (XII) was prepared from the methoxybenzylbenzoic

<sup>13</sup> Graebe and Bernhart [*Ann.*, **349**, 222 (1906)] reported the melting point to be 186.5° while Kaufler [*Ber.*, **37**, 65 (1904)] reported 195–196°.

<sup>14</sup> Acetic anhydride was used as a solvent [Herzig, *Monatsh.*, **9**, 544 (1888)].

<sup>15</sup> Acetic anhydride was used as a solvent.

acid, alcohol and hydrogen chloride. The ester boiled at 214–216° under approximately 10 mm. pressure. Twenty-seven grams of the ester, dissolved in 60 cc. of ether, was added in small portions to the Grignard reagent obtained from 93.6 g. of 4-iodoanisole, 9.6 g. of magnesium and 200 cc. of ether. After the mixture had been heated for four hours, it was decomposed with ice and ammonium chloride. A crystalline by-product, insoluble in the ether layer,<sup>16</sup> was removed by filtration. The ether layer was subjected to steam distillation for some time and the oily product, 2-(4'-methoxybenzyl)-4'',4'''-dimethoxytriphenylcarbinol (XIII), converted into 2-methoxy-9,9-di-(4-methoxyphenyl)-9,10-dihydroanthracene (XIV) in the following manner. The carbinol was dissolved in 150 cc. of acetic acid which had been partially saturated with hydrogen chloride. The deep red solution was heated for two hours on a steam-bath. Most of the solvent was removed from the solution, which had now become brown in color, and the residue was poured into water. The gummy anthracene (XIV), which we could not obtain in solid form, was oxidized to the anthrone. The anthracene, dissolved in 180 cc. of acetic acid, was heated for four hours with 24 g. of sodium dichromate dissolved in 12 cc. of hot water. The greater part of the acetic acid was removed and water was added to the residue. The solid product obtained was recrystallized several times from acetic acid. The yield of the anthrone was 12 g.; m. p. 183–184°.

*Anal.* Calcd. for  $C_{29}H_{24}O_4$ : C, 79.78; H, 5.54;  $OCH_3$ , 21.0. Found: C, 79.66; H, 5.38;  $OCH_3$ , 21.3.<sup>17</sup>

**2-Methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10 (XVI).**—To 4-methoxyphenylmagnesium iodide, prepared from 4.7 g. of 4-iodoanisole, 0.48 g. of magnesium and 15 cc. of ether, there was added 2.18 g. of 2-methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10 suspended in 50 cc. of benzene. The mixture was heated for four hours, decomposed and the ether-benzene layer subjected to steam distillation. The gummy product, which soon became solid, was recrystallized from alcohol and then from acetic acid; m. p. 193–194°.

*Anal.* Calcd. for  $C_{36}H_{30}O_5$ : C, 79.37; H, 5.93. Found: C, 78.78; H, 5.86.

### Summary

The preparation of the following compounds has been described: 9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10, 2-hydroxyanthraquinone, 2-methoxyanthrone-9, 2-methoxy-9-(4'-methoxyphenyl)-anthracene, 2-methoxy-9-hydroxy-9-(4'-methoxyphenyl)-anthrone-10, 2-methoxy-9,9-di-(4'-methoxyphenyl)-anthrone-10, 2-methoxy-9,9,10-tri-(4'-methoxyphenyl)-9,10-dihydroanthrol-10.

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<sup>16</sup> Barnett, Cook and Nixon [*J. Chem. Soc.*, 505 (1927)] obtained a by-product, insoluble in ether, from the interaction of phenylmagnesium bromide and ethyl 2-benzylbenzoate and suggested that the compound might be a pinacol.

<sup>17</sup> Acetic anhydride was used as a solvent.