357. *Hydroxy- and Chloro-derivatives of 2-Methylanthraquinone.*

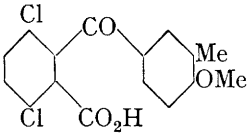
By G. J. Marriott and Robert Robinson.

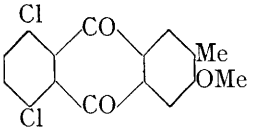
This investigation was initiated in the hope of obtaining synthetically, and in relatively large amounts, some close analogue of helminthosporin (Charles, Raistrick, Robinson, and Todd, *Biochem. J.*, 1933, **27**, 499) so that the derivatives of this trihydroxymethylanthraquinone might be studied by proxy at least in a preliminary exploratory manner. This work is still in progress and we now report some matters of interest that have arisen incidentally.

The substance which we desired to obtain was 1 : 5 : 8-trihydroxy-2-methylanthraquinone, which has been described by Graves and Adams (*J. Amer. Chem. Soc.*, 1923, **45**, 2439) but not characterised very closely, for example, by means of its triacetate or other derivative. Graves and Adams started from 3 : 6-dimethoxyphthalic acid and we sought to utilise the more readily accessible 3 : 6-dichlorophthalic acid.

The condensation of 3 : 6-dichlorophthalic anhydride with *o*-tolyl methyl ether in the presence of aluminium chloride was described by Walsh and Weizmann (J., 1910, **97**, 691), but these authors considered that demethylation occurred in the process. We have obtained the same substances (substituted benzoylbenzoic acid and anthraquinone) and find that demethylation does not occur, and indeed the analytical results of Walsh and Weizmann are in better agreement with this view than with that which was adopted. Demethylation or partial demethylation certainly occurred in the corresponding reaction with *p*-tolyl methyl ether, and this is another instance of the protective effect of an *o*-situated methyl group. It is also probable that the constitutions for their products proposed by Walsh and Weizmann are incorrect, because the original condensation should give the acid (I) by attack of the *p*-position to the methoxyl (compare Graves and Adams, *loc. cit.*) and this might yield the anthraquinone (II) or (III). This view receives strong confirmation from the formation of the anthraquinone (II) or (III) (demethylated) from *o*-cresol-3 : 6-dichlorophthalein in which the hydroxyl group is certainly in the *p*-position to the

phthalic residue. The substance (II) or (III) has m. p. 246—247° (Walsh and Weizmann, 249°) and the related dichlorohydroxymethylanthraquinone has m. p. 298°. The latter


(I.)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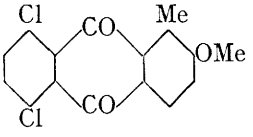
(III.)

is therefore different from 5 : 8-*dichloro*-1-*hydroxy*-2-*methylanthraquinone* (IV), m. p. 196—197°, which we have obtained by a two-stage condensation of 3 : 6-dichlorophthalic anhydride with *o*-cresol. Unfortunately the replacement of the chlorine atoms by hydroxy-, alkyloxy-, or aryloxy-groups proved to be a troublesome operation, although 1 : 5 : 8-

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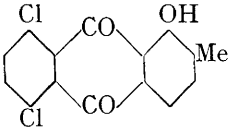

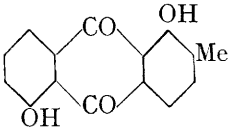
(V.)

trihydroxy-2-methylanthraquinone was obtained. When sodium methoxide in methyl-alcoholic solution at 100° was used, the main product was a dihydroxymethylanthraquinone which from its spectrographic and other properties is certainly 2-*methylanthrarufin* (V). The chlorine atom in position 8 in (IV) suffers reduction rather than hydrolysis. A comparison of the absorption of sulphuric acid solutions of 1 : 5 : 8-trihydroxy-2-methylanthraquinone (VI) and catenarin (VII ?) (compare Raistrick, Robinson, and Todd, *Biochem. J.*, **1934**, **28**, 559) in the visible region is of interest in relation to the constitution of the latter substance and confirms the feasibility of suggestions already made (*loc. cit.*).

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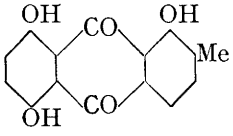
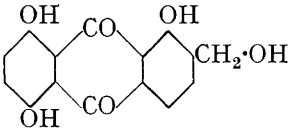
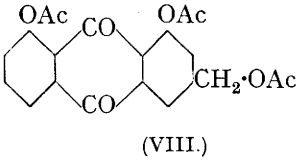
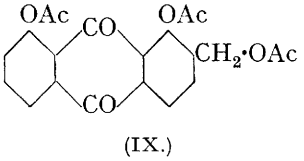



(VII.)

An attempt to reduce catenarin to an anthrone which might give (VI) on oxidation was made in view of the recent work of McDonnell and Gardner (*J. Amer. Chem. Soc.*, **1934**, **56**, 1246). These authors reduced aloe-emodin-9-anthrone to chrysophanic acid-9-anthrone ($\cdot CH_2OH \longrightarrow CH_3$) by means of stannous chloride and hydrochloric acid. Catenarin is changed under these conditions and affords a substance $C_{15}H_{12}O_4$, which after acetylation and oxidation yields a *triacetoxymethylanthraquinone*. Very little of this substance was available, but its solution in sulphuric acid had absorption bands in the visible region closely resembling those of chrysazin and unlike those of any known trihydroxyanthraquinone, or anthrarufin, or quinizarin. As catenarin is certainly a derivative of 1 : 4 : 5-trihydroxyanthraquinone, it is clear that the product of its reduction and oxidation is a chrysazin derivative and it follows that the side-chain hydroxyl remains unchanged. Once again the protective effect of the *o*-situated group is in evidence. The new triacetoxymethylanthraquinone differs from aloe-emodin triacetate (VIII) and, as it is derived from a member of the 2-methylanthracene series (R., R., and T., *loc. cit.*), it must be (IX).


(VIII.)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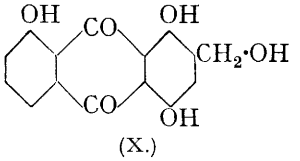

(X.)

This evidence leaves, as the alternatives for catenarin, the formulæ (VII) and (X).

Experimental.

3 : 6-*Dichloro*-2-(4′-*methoxy*-3′-*methylbenzoyl*)*benzoic Acid and Anthraquinone Derivatives therefrom.*—The method of Walsh and Weizmann (*loc. cit.*) was employed and gave the acid, m. p. 182—183° (W. and W., m. p. 183°), in 50% yield. No coloration was developed with alcoholic ferric chloride, and this shows that no phenolic hydroxyl is present in the *o*-position to a carbonyl group. The closure of the ring was effected in 10 minutes by the action of 10% oleum at 130° on the acid mixed with an equal weight of boric acid. The yellow needles, m. p. 245—246° (W. and W., m. p. 249°), were identical with one of the products of the following experiment.

Dichloromethoxymethylbenzoylbenzoic acid (1·5 g.) and boric acid (1·5 g.) were heated with concentrated sulphuric acid (20 c.c.) at 140—150° for 15 minutes. The resulting mixture of anthraquinones was extracted with boiling aqueous sodium carbonate, about a half passing into solution. The insoluble portion, also washed with boiling aqueous sodium hydroxide, crystallised from acetic acid and then from pyridine as a brownish-yellow powder (0·25 g.), m. p. 246—247° (Found : MeO, 9·7. $C_{16}H_{10}O_3Cl_2$ requires 1MeO, 9·6%). **5 : 8-*Dichloro*-2-*methoxy*-1** (or **3**)-*methylanthraquinone* (II or III) is insoluble in alkaline solutions and its red solution in sulphuric acid is unchanged on the addition of boric acid.

5 : 8-*Dichloro*-2-*hydroxy*-1 (or **3**)-*methylanthraquinone.*—(A) The alkaline solution from the experiment last described was acidified; the precipitate obtained crystallised from pyridine and from acetic acid in yellow needles, m. p. *ca.* 298° (Found : C, 58·8; H, 2·9; Cl, 23·0. $C_{15}H_8O_3Cl_2$ requires C, 58·7; H, 2·6; Cl, 23·1%). The substance sublimes below its m. p. in yellow needles; it is soluble in aqueous alkalis to a reddish-purple solution and in sulphuric acid to a carmine-red solution, unchanged on the addition of boric acid.

(B) A substance with identical properties was obtained in small yield by heating *o*-cresoldichlorophthalein (1·0 g.) and **3 : 6**-dichlorophthalic acid (0·5 g.) at 110—115° in sulphuric acid (20 c.c.) for 40 hours.

3 : 6-*Dichloro*-2-(2′-*hydroxy*-3′-*methylbenzoyl*)*benzoic Acid.*—(A) Powdered anhydrous aluminium chloride (52 g.) was added to a vigorously stirred mixture of **3 : 6**-dichlorophthalic anhydride (60 g.) and *o*-cresol (240 g.), and the temperature raised to 40°. Vigorous evolution of hydrogen chloride occurred and the temperature rose to 68°; more aluminium chloride (100 g.) was then added, and the temperature kept at 70—75° for 18 hours. The product (217 g. of the red viscous mass were worked up) was treated with dilute hydrochloric acid and steam-distilled, and the residue thrice extracted with aqueous sodium carbonate. This dissolved the benzoylbenzoic acid derivative together with a phthalein and these were later separated by boiling with an aqueous suspension of calcium carbonate. Thereby the calcium salt of the acid passed into solution; the acid itself crystallised from acetic acid in pale yellow prisms, m. p. 197° (yield, 54%) (Found : C, 55·6; H, 3·2; Cl, 21·8. $C_{15}H_{10}O_4Cl_2$ requires C, 55·4; H, 3·1; Cl, 21·8%). An alcoholic solution develops a reddish-brown coloration on the addition of ferric chloride. The calcium carbonate–phthalein mixture was treated with dilute hydrochloric acid; the phthalein (2·1 g.) crystallised from acetic acid as a nearly colourless powder, m. p. 268° (Found : C, 63·6; H, 3·7; Cl, 17·9. $C_{22}H_{16}O_4Cl_2$ requires C, 63·6; H, 3·9; Cl, 17·1%). *o-Cresol*-**3 : 6**-*dichlorophthalein* dissolves in alkalis to purple solutions; its solution in sulphuric acid is red by transmitted and purple by reflected light.

(B) A stirred mixture of **3 : 6**-dichlorophthalic anhydride (15·0 g.), *o*-cresol (12 g.), and boric acid (20 g.) was heated at 160—170° for 4 hours. The mixture was boiled with water in an open flask for 2 hours and filtered hot; the residue crystallised from acetic acid in pale yellow prisms, m. p. 197° (yield, 12%), identical with the product under (A).

5 : 8-*Dichloro*-1-*hydroxy*-2-*methylanthraquinone* (IV).—As the result of 25 trials of conditions the best yield in the ring closure of the foregoing substituted benzoylbenzoic acid was 40% and the unconverted acid could not be recovered but was sulphonated or destroyed.

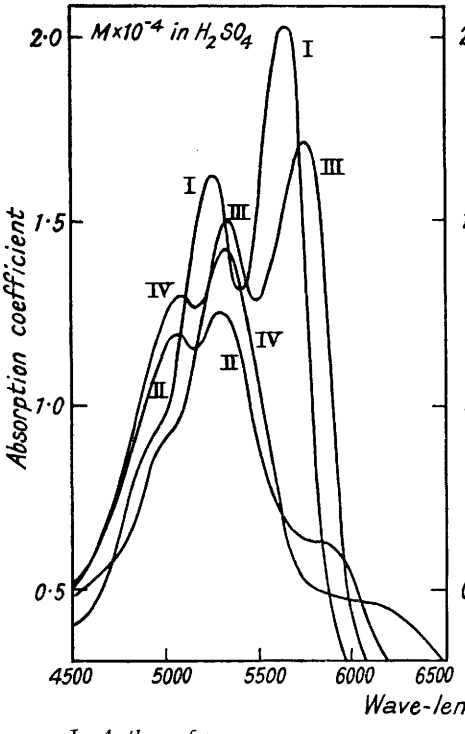
Oleum (31 c.c. of 20%) was added to an intimate mixture of dichlorohydroxymethylbenzoylbenzoic acid (4 g.) and boric acid (4 g.); the temperature rose spontaneously to 97° and was maintained for 2 minutes without external heating. The deep purple solution was allowed to cool and added to ice and water; the orange precipitate was coagulated by boiling the solution, collected, and boiled with aqueous sodium carbonate (100 c.c. of 5%), and the insoluble part collected and dried (1·5 g.). The substance crystallised from acetic acid in orange needles, m. p. 196—197°. The analysed specimen was obtained by hydrolysis of the acetate (Found : C, 58·5; H, 2·8; Cl, 23·1. $C_{15}H_8O_3Cl_2$ requires C, 58·6; H, 2·6; Cl, 23·1%). This *dichlorohydroxymethylanthraquinone* is rather easily soluble in boiling acetic acid to yellow non-

fluorescent solutions. Its solution in sulphuric acid is reddish-orange (yellowish-orange on addition of a nitrite) and if sufficiently concentrated a purple colour is developed on the addition of boric acid. The *acetate* crystallises from acetic acid in yellow needles, m. p. 191° (Found : C, 59·0; H, 3·0; Cl, 19·2. $C_{17}H_{10}O_4Cl_2$ requires C, 58·4; H, 2·8; Cl, 20·3%).

1 : 5-*Dihydroxy*-2-*methylanthraquinone* (V) *and* 1 : 5 : 8-*Triacetoxy*-2-*methylanthraquinone*.—The replacement of the chlorine atoms of the foregoing dichlorohydroxymethylanthraquinone by hydroxyl does not proceed smoothly under any conditions. Calcium hydroxide was tried 8 times at temperatures varying from 210° to 260°, but only traces of the trihydroxy-compound were indicated; baryta gave worse results. Some success followed the use of sodium methoxide in methyl alcohol, but the hydrolysis was accompanied by reduction.

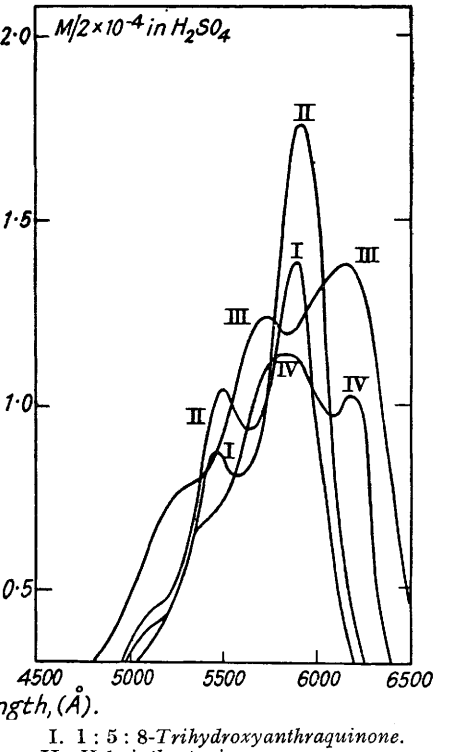
(A) Methyl alcohol (20 c.c.) containing sodium methoxide (1·5 g. of sodium) was made into a paste with dichlorohydroxymethylanthraquinone (0·9 g.) and copper-bronze (0·1 g.), and the

FIG. 1.



I. *Anthrarufin.*
II. *Chrysazin.*
III. 2-*Methylanthrarufin.*
IV. 2-*Hydroxymethylchrysazin triacetate.*

FIG. 2.



I. 1 : 5 : 8-*Trihydroxyanthraquinone.*
II. *Helminthosporin.*
III. *Catenarin.*
IV. 1 : 5 : 8-*Trihydroxy*-2-*methylanthraquinone triacetate.*

mixture heated in a sealed tube at 100—105° for 5½ hours. The violet mass was extracted with boiling water, and hydrochloric acid added to the filtrate; the yellow precipitate became reddish-orange on boiling and it was then collected and refluxed for 6 hours with acetic acid (20 c.c.) and hydrobromic acid (20 c.c., *d* 1·7). The reddish-orange solid was dissolved in hot 2% aqueous sodium hydroxide, recovered by acidification, and crystallised from acetic acid. The product was acetylated and then crystallised from acetic anhydride in yellow needles, m. p. 220°, chlorine-free (Found : C, 67·3; H, 4·4. $C_{19}H_{14}O_6$ requires C, 67·4; H, 4·1%). The absorption spectrum in sulphuric acid solution was practically identical with that of the *dihydroxymethylanthraquinone* obtained on hydrolysis by means of 10% aqueous sodium hydroxide. The latter crystallised from acetic acid in well-formed orange-brown needles, m. p. 187° (Found : C, 70·7; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%). The alkaline solution is red and not sufficiently blue-toned for a methylquinizarin; in addition the yellow solution in acetic acid is not fluorescent and all quinizarins of comparable constitution show this property

(green fluorescence). The absorption spectrum of a sulphuric acid solution (Fig. 1) showed two peaks, one at 5350 Å. and another at 5750 Å., with indications of a third peak at 5000 Å. The colour is a little bluer and less persistent than that due to anthrarufin, but is very different from that of chrysazin under similar conditions.

(B) Sodium (4 g.) was dissolved in methyl alcohol (80 c.c.), the solution made into a paste with dichlorohydroxymethylanthraquinone (4 g.), and the mixture heated in sealed tubes at 135—140° for 6 hours. The quasi-acidic fraction was demethylated and later acetylated, and the product fractionated from acetic acid. The first crops were identified as 2-methylanthrarufin diacetate and also contained chloro-derivatives. The later crops contained a very small proportion of a triacetoxymethylanthraquinone along with chloro-derivatives.

A specimen consisting of yellow prisms, m. p. *ca.* 211° (Found : C, 62·8; Cl, 1·7%), was twice recrystallised; slender yellow needles, m. p. 210° (Found : C, 63·5; H, 3·9. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%). The purple solution in sulphuric acid is blue in thin layers and exhibits a strong red fluorescence, augmented on the addition of boric acid. The absorption in the visible region showed peaks at 5800 Å. and 6170 Å. (Fig. 2). As compared with 1 : 4 : 5-trihydroxyanthraquinone, we observe the blueing and weakening effect of the methyl group. Comparison with helminthosporin (R., R., and T., *loc. cit.*) shows that the *o*-situated methyl group weakens the colour much more than that in the *m*-position. Comparison with catenarin indicates a significant general resemblance.

2-*Hydroxymethylchrysazin Triacetate* (IX).—Catenarin (1 g.), dissolved in glacial acetic acid (70 c.c.), was mixed with a hot solution of crystallised stannous chloride (32 g.) in concentrated hydrochloric acid (60 c.c.). After boiling for an hour, granulated tin (10 g.) was added, followed by concentrated hydrochloric acid (40 c.c.), added to the boiling solution in small portions during 3½ hours. Further quantities of tin (3 g.) and acid (10 c.c.) were then added and the boiling was continued for 2 hours more. On cooling, yellow plates (0·57 g.) separated and after recrystallisation from acetic acid the substance decomposed at 230° (Found : C, 69·8; H, 4·7. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

The *anthrone* gives in sulphuric acid a pale yellow colour, rapidly turning green. It dissolves in aqueous sodium hydroxide to a purple solution. On the addition of borax to an alcoholic solution and boiling, the colour changes from pale yellow to light brown and on keeping develops a port-wine colour. The addition of aqueous chromic acid to a solution in glacial acetic acid gives immediately a scarlet coloration, which becomes brownish-violet on warming, and no anthraquinone could be detected in the tarry residue formed on pouring into water.

On acetylation with acetic anhydride and a trace of sulphuric acid a brown amorphous mass was obtained (0·45 g.); this was dissolved in acetic acid (30 c.c.), and an aqueous solution of chromic acid (0·22 g.) added. The clear brown, warm solution became black and opaque and was heated on the steam-bath for 1 hour. The yellow precipitate formed on pouring into water became tarry on boiling; it was hydrolysed by means of sodium hydroxide and the product was sublimed at 14 mm. The yield of a red anthraquinone derivative was small and there was a black residue. The product was acetylated, and the derivative twice crystallised from alcohol and again from acetic acid, forming bright yellow needles (*ca.* 6 mg.), m. p. 182° (largely depressed on admixture with aloe-emodin triacetate) (Found : C, 63·9; H, 4·5. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·1%). This substance dissolves in sulphuric acid to a bright purple solution, bluer than that of chrysazin and aloe-emodin, and without the red fluorescence of 1 : 5 : 8-trihydroxy-2-methylanthraquinone. The absorption spectrum of the solution in sulphuric acid was very similar to that of chrysazin, to which the compound is obviously related (Fig. 1). The paucity of the yield prevented an extension of the investigation.

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