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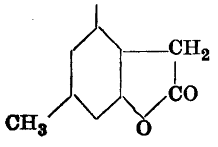
Indigoid Oxidation Products of some *Iso*coumaranone Derivatives

ERLING BERNATEK and ENDRE BERNER

Universitetets Kjemiske Institutt, Blindern — Oslo, Norway

In the course of an investigation of the reaction between maleic anhydride and acetylacetone, one of us[1] prepared the hitherto unknown 6-methyl*iso*coumaranone-4-carboxylic acid (I). This compound may also be regarded as the lactone of an *o*-hydroxyphenylacetic acid and accordingly on dissolution in sodium hydroxide the lactone ring is opened. When such an alkaline solution was treated with potassium permanganate the methyl group was oxidized to a carboxyl group, and a tricarboxylic acid could be isolated. If, however, substance I was dissolved in a dilute solution of sodium carbonate, no opening of the lactone ring took place, and oxidation with potassium permanganate in the cold in this case gave a blood-red solution from which an intensely red powder, containing only carbon, hydrogen and oxygen, separated on the addition of sulphuric acid. This result seemed so remarkable that the present authors took up the question of the constitution of the red oxidation product.

The red oxidation product (hereafter designated as R) was at first isolated in an amorphous and hygroscopic state. No accurate analysis could therefore be obtained, and the substance was used only for some preliminary experiments. The question naturally arose as to how far the structure of the starting material (I) had been affected by the oxidation. As R was found to be very labile in the presence of alkali it was assumed that the lactone ring was still present after the oxidation. This would also seem to be in accordance with the titrations, as seen from the following:



I

If R was dissolved in cold 0.1 *N* sodium hydroxide and the solution titrated immediately, the following highly varying figures for the equivalent weight were obtained:

$E = 130.4$, 134.1, 166.0. Calc. for I as a monobasic acid 192.2.

If, however, the solution of R in the alkali was left for some 50 hours at 40° before the titration the values were:

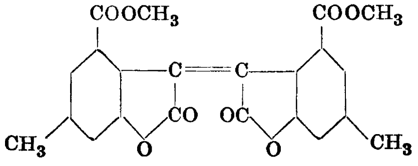
$E = 93.0$, 92.1, 93.4. Calc. for I as a dibasic acid 96.1.

Another red substance, similar to R, was obtained by oxidation of the methyl ester of I. As the ester was insoluble in aqueous solutions the oxidation had to be carried out in acetone. This new red substance, abbreviated R-Me, could be brought into crystalline form and consequently could be purified sufficiently for analysis. The empirical formula was $C_{11}H_8O_4$ as compared with the formula $C_{11}H_{10}O_4$ for the starting material, the methyl ester of I. The result of the oxidation was therefore that two atoms of hydrogen were removed for each molecule of I. This is also in accordance with the fact that a maximum yield of R-Me (about 60 per cent) was obtained when oxidizing the ester of I with a quantity of potassium permanganate corresponding to the taking up of two redox-equivalents.

Cryoscopic measurements in benzene showed that R-Me had the molecular formula $C_{22}H_{16}O_8$. The molecule of R-Me must therefore be built up of two molecules of the ester of I from which, in all, four atoms of hydrogen had been removed. The following additional facts should also be considered in setting up a structural formula.

1. The carboxyl group is not involved in the coupling.
2. The lactone —O—CO-grouping is present in the oxidation product.
3. The deep red colour of R and R-Me indicates that the new linking contributes to the formation of a chromophoric group.
4. The new linking between the two halves of the molecule is most probably of an unsaturated character, since, by catalytic hydrogenation or by reduction with nascent hydrogen, R-Me took up one molecule of hydrogen giving a colourless substance $C_{22}H_{18}O_8$.

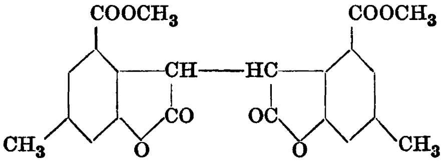
Accordingly formula II is suggested for R-Me. The corresponding free dicarboxylic acid should then most likely represent the original red substance R. It ought to be mentioned that, as in the case of indigo, the formula could as well be written in a *trans*-form.



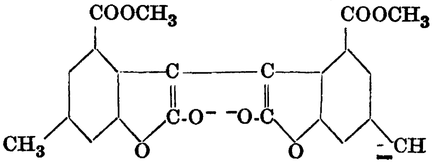
II

The skeleton of this formula is isomeric with that of oxindigo. The two red substances R and R-Me could therefore be designated as 4,4′-dicarboxy-6,6′-dimethyl*iso*oxindigo and 4,4′-dicarbmethoxy-6,6′-dimethyl*iso*oxindigo respectively. According to a proposal by P. Jacobson, referred to by Friedländer [2], such substances could be named as derivatives of bis-(coumaran-3)-indigo.

As mentioned in point 4, R-Me on hydrogenation took up one molecule of hydrogen. The hydrogenated substance would therefore have formula III. When a little sodium hydroxide was added to a solution of III in alcohol or acetone the solution immediately turned brownish-red, the colour disappearing again on acidifying. The reason for this was obviously that a double enolisation took place in alkaline solution as shown in formula IV.

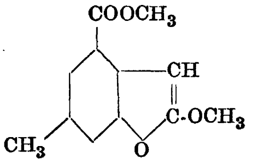


III



IV

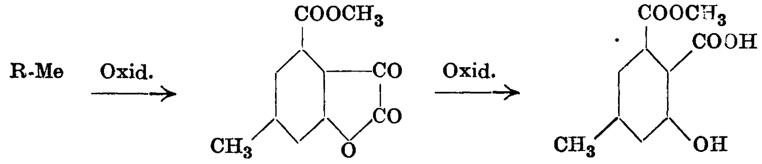
If the brownish-red solution was allowed to stand for a short time the colour turned yellow, probably due to an opening of the enolised lactone rings by the prolonged action of the alkali. The hydrogenated substance itself was partly oxidised again when exposed to the air giving R-Me which was relatively stable in the presence of mineral acid.



V

By the action of diazomethane on the methyl ester of I in the presence of some methanol, the methyl enol ether V was prepared. In this substance the enol grouping is fixed and there should be no possibility of the formation of a double bond between two such molecules. Accordingly no red oxidation product could be obtained from V.

Further oxidation of R-Me gave a substance $C_{10}H_{10}O_5$ which was evidently a derivative of phtalic acid having the formula VII. The coumarandione derivative VI may be expected as an intermediate product of the oxidation, but attempts to isolate it were unsuccessful.



VI

VII

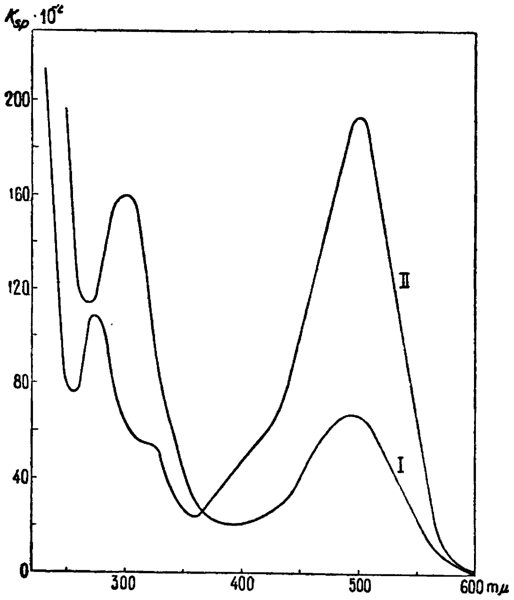
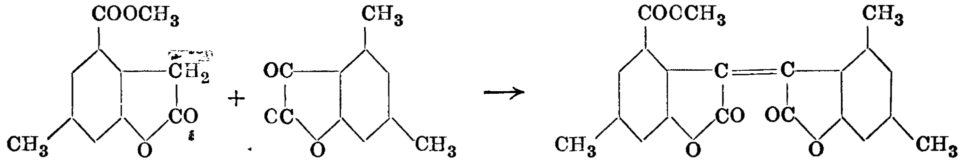


Fig. 1. Light absorption in ethanol.

I 4,4'-Dicarboxy-6,6'-dimethylisooxindigo (R)
II 4,4'-Dicarbmethoxy-6,6'-dimethylisooxindigo (R-Me)

The free acid corresponding to VII had a m. p. of 223°, and on sublimation in a vacuum easily split off water giving an anhydride of m. p. 206°. Both these substances gave a strong fluorescein reaction when heated with resorcinol and sulphuric acid. According to the literature[3] 4-methyl-6-hydroxyphtalic acid and its anhydride have m. p. 226—228° and 209° respectively.

The synthesis of a red compound analogous to R-Me was accomplished in the manner used by Stollé and Knebel[4] in their synthesis of tetramethyloxindirubin. The methyl 6-methyl*iso*coumaranone-4-carboxylate (VIII) was condensed by means of sulphuric acid with 4,6-dimethylcoumarandione (IX) prepared according to Stollé and Knebel. The condensation product (X), which had the composition $C_{21}H_{16}O_6$, resembled R-Me in colour and behaviour. The light absorption curves of the two substances will be found in Fig. 2.



VIII IX X

This synthesis could lead one to the opinion that the oxidation of the methyl ester of I proceeded in such a way that some molecules were first

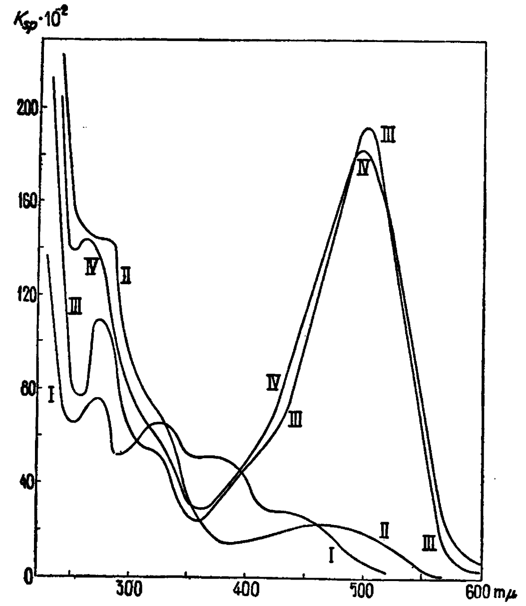


Fig. 2. Light absorption in ethanol.

I Isooxindigo
II 4,4'-Dimethyl isooxindigo
III 4,4'-Dicarbmethoxy-6,6'-dimethyl-isooxindigo (R-Me)
IV 4-Carbmethoxy-6,4',6'-trimethyl-isooxindigo

oxidized to a coumarandione derivative which then condensed with other non-oxidised molecules. This interpretation is opposed by two facts:

1. The bad yield of the condensation (5—6 per cent) as compared to that of the oxidation (60 per cent).

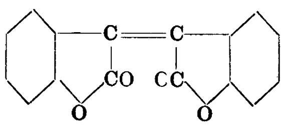
2. The solution in which the oxidation was carried out was not free from water, and it became alkaline during the oxidation. A coumarandione derivative would certainly, under these conditions, be very rapidly hydrolysed and withdrawn from further reaction.

In this connection it ought to be mentioned that the methyl ester of I could be dehydrogenated directly to R-Me. Thus R-Me was obtained in excellent yield when the methyl ester was heated with selenium in a nitrogen atmosphere.

In the foregoing a complete analogy in the structures of the two oxidation products R and R-Me has been assumed, although R was at first obtained only in an amorphous state. Later, however, after experience had been gained in the work with R-Me, even R could be brought into a crystalline form which was no longer hygroscopic. It could therefore easily be purified and analysed. The analysis gave the formula $(C_{10}H_6O_4)_n$, but as the solubility of the substance was very small no determination of the molecular weight by cryoscopic or ebullioscopic methods could be carried out. On reduction of R with nascent hydrogen a colourless, crystalline substance $(C_{10}H_7O_4)_n$ was obtained. It therefore seems justified in the case of R also to accept $n = 2$. A comparison of the light absorption of R and R-Me will be found in Fig. 1. The great increase in absorption in the visible part of the spectrum when the carboxyl groups are esterified is very remarkable.

Substances similar to R and R-Me were obtained by the oxidation of other *iso*coumaranone derivatives. They are mentioned in the experimental part.

By treatment of *iso*coumaranone with S_2Cl_2 Chovin[5] prepared a yellow-orange substance $C_{16}H_8O_4$ which he assumed to be *iso*oxindigo (XI).



XI

We have repeated his experiments and were able to verify them. As our red oxidation products may be regarded as derivatives of *iso*oxindigo it was of interest to compare the light absorption of them with that of *iso*oxindigo. The results of our measurements will be found in Fig. 2. As can be seen, the introduction of methyl groups in the benzene nuclei affects mainly the absorption in ultraviolet. The introduction of one esterified carboxyl group, however, very markedly increases the absorption in the visible part of the spectrum. This absorption is not increased appreciably by the introduction of further esterified carboxyl groups.

EXPERIMENTAL PART

Preparation of substance R

6-Methyl*iso*coumaranone-4-carboxylic acid (3 g), prepared according to Berner[1], was dissolved in 2 *N* sodium carbonate (20 ml) and diluted to 500 ml. Keeping the solution at about + 1° and stirring vigorously, 70 ml of a 2.5 per cent solution of potassium permanganate were slowly added. After the manganese dioxide had been filtered off a clear blood-red solution was obtained from which R was precipitated as a very fine red powder by the addition of sulphuric acid. This was left over night in a refrigerator after which it could easily be filtered by suction. After washing with distilled water until the filtrate gave no reaction for sulphuric acid, the red powder was dried in a vacuum desiccator. Yield 0.7 g.

The precipitated form of R was amorphous and very hygroscopic. Leaving it in an atmosphere of 50 per cent humidity the weight increased 1.8 per cent in 7 hours. The samples used for the titration experiments already mentioned, were dried directly in small weighing tubes which were fitted with stoppers.

Crystallisation: Amorphous R (1 g) was dissolved in acetone (50 ml), filtered, and water (10 ml) added. When the acetone was allowed to evaporate slowly, a red powder separated which seen under the microscope was found to consist of small but well developed crystals. After recrystallisation in the same manner, the powder was dried at 80°. It had no definite melting point.

$C_{20}H_{12}O_8$ Calc. C 63.25 H 3.18
Found » 63.18, 63.06 » 3.28, 3.30

Reduction of substance R

Crystallized R (0.5 g) was dissolved in ethanol (50 ml) and zinc dust (2.5 g) and a little 2 *N* sulphuric acid were added. The reaction vessel was closed with a stopper and shaken for 17—18 minutes when the solution still had a light red colour. After filtration some more zinc dust and acid were therefore added. In a couple of minutes the red colour disappeared completely and only a light brownish-yellow colour remained. The solution was again filtered, and, after adding water, the ethanol was evaporated by blowing a current of air on the surface. A colourless crystalline substance began to separate, but the solution gradually became red, obviously due to oxidation by the air. In order to obtain quite colourless crystals, the substance was recrystallized from acetone-water leading a current of nitrogen through the solution. The crystals had no definite m. p., but on heating turned into a red substance which was decomposed.

$(C_{10}H_7O_4)_n$ Calc. C 62.82 H 3.69
Found » 62.71, 62.65 » 3.85, 3.79

Preparation of substance R-Me

6-Methyl*iso*coumaranone-4-carboxylic acid was esterified in the usual way by means of an ethereal solution of diazomethane. The optimum conditions for the oxidation of the ester to R-Me were found to be the following: The methyl ester (1 g) was dissolved in acetone (100 ml) and potassium permanganate (0.5 g) in acetone (100 ml) was added slowly. The solution was stirred mechanically and the temperature kept below 10°. The manganese dioxide was filtered off and washed twice with acetone as it easily adsorbed the red oxidation product. Having added a sufficient quantity of 2 *N* sulphuric acid, the filtrate was evaporated on the water-bath to half volume and cooled. Water was now added until the solution became slightly opaque, and the solution afterwards heated until it was clear again. On standing, small red crystals began to separate. They were filtered off and the filtrate left in an open beaker where the acetone gradually evaporated and more crystals of R-Me were obtained. The yield was about 60 per cent of theory. The substance was recrystallized twice from acetone-water and, after drying, had the unsharp m. p. 205—210°.

$C_{22}H_{16}O_8$ (408.4) Calc. C 64.71 H 3.92
Found » 64.85, 64.60 » 4.07, 3.96
0.0970, 0.1009 g subst. in 22.8, 20.6 g benzene, Δ 0.053, 0.062° Mol. wt. 411, 405.

This red oxidation product was so insoluble in water that it remained unchanged after boiling for half an hour with 2 *N* sodium hydroxide. If, however, a few drops of alkali were added to a solution of R-Me in ethanol, the red colour disappeared momentarily, and the solution became yellow with a strong fluorescence in green.

Hydrogenation of R-Me

With gaseous hydrogen: A solution of R-Me (4 g) in glacial acetic acid (200 ml), to which platinum oxide (0.4 g) had been added, took up 165 ml hydrogen (1200 mm Hg, 20°) in 5 hours; calc. for one mole hydrogen 152 ml. During the hydrogenation the red colour disappeared and at the end the solution became quite colourless. However, upon evaporating the main part of the glacial acetic acid on the waterbath, the solution again took on a red colour; and after the remaining acetic acid had been removed in a vacuum desiccator over potassium hydroxide the hydrogenated substance was obtained as light red crystals. After being recrystallised twice from acetone, the substance became colourless. When heated, the crystals took on a red colour at about 200°, and they melted at 230—232° giving a dark red liquid. For analysis see below, sample a.

With nascent hydrogen: After shaking a solution of R-Me (0.5 g) in ethanol (50 ml) to which zinc dust (3 g) and 2 *N* sulphuric acid (3 ml) had been added, the red colour disappeared in half a minute. After the filtered solution had been diluted with water small colourless crystals separated. They were recrystallised from acetone-water and had the same m. p. as above. Sample b.

$C_{22}H_{18}O_8$ (410.4)	Calc.	C	64.40	H	4.43
Sample a	Found	»	64.30, 64.27	»	4.56, 4.50
» b	»	»	64.37, 64.45	»	4.42, 4.25

0.0830, 0.0919 g subst. in 21.3, 20.8 g benzene, Δ 0.048, 0.054° Mol. wt. 416, 419.

The hydrogenated substance was entirely insoluble in water. Dissolved in chloroform it did not add bromine. When 2 *N* sodium hydroxide (2 ml) was added to a solution of the hydrogenated substance (0.05 g) in acetone (50 ml), the solution turned brownish-red. A small part of this solution was set aside and in a short time the colour became yellow. The rest of the solution was acidified with sulphuric acid. After some time a red substance congregated on the surface, whereas colourless crystals were formed on the walls and bottom of the beaker. The two substances could therefore be isolated separately.

The red substance on purification gave crystals of the same form as found for R-Me and the m. p. was the same (205—210°), alone and in admixture. The colourless substance was identical with the hydrogenated R-Me. M. p. 229°, alone and in admixture.

Enol-ether of methyl 6-methyl*iso*coumaranone-4-carboxylate

Finely powdered methyl 6-methyl*iso*coumaranone-4-carboxylate (1 g) was added to an ethereal solution of diazomethane (from 4 g of methylnitrosourea) which contained 1 ml methanol. After standing for 12 hours in a refrigerator and 4 days at room temperature, most of the ester had dissolved. The solution was still strongly yellow, but it contained no more diazomethane. On evaporating the ether some unchanged ester gradually separated and was removed. When all the solvent had been evaporated, a yellow viscous residue remained. This was extracted with a small quantity of ether and a small residue of the unchanged ester was left. After evaporation, the new residue was subjected to a second extraction process. Finally the enol-ether was obtained in a quite pure form as a yellow highly viscous syrup. The last traces of solvent were removed by leaving the syrup for 4 days in a vacuum desiccator (1 mm Hg) above conc. sulphuric acid. The enol-ether rapidly added bromine and simultaneously split off hydrogen bromide.

0.1150, 0.1083 g subst. gave 0.2395, 0.2240 g AgI
$C_{10}H_6O_2(OCH_3)_2$ Calc. CH_3O 28.18 Found 27.50, 27.31

When the enol-ether (1.3 g) dissolved in acetone (50 ml) was oxidized with a 2.5 per cent solution of potassium permanganate in acetone no formation of a red oxidation product took place.

Further oxidation of R-Me

To a solution of methyl 6-methyl*iso*coumaranone-4-carboxylate (0.5 g) in acetone (100 ml) a 2.5 per cent solution of potassium permanganate in acetone was added until the permanganate colour remained. In all 40 ml of the latter were needed. The red colour of the R-Me first formed disappeared with prolonged oxidation. During the last stage of the oxidation the temperature was kept at 45°. Having destroyed the excess of permanganate, the filtered solution was acidified with sulphuric acid, and the acetone evaporated on the water-bath. The remaining aqueous solution was left for a couple of days in a cool place when a small quantity of a brown material separated and was removed by filtration. Upon extraction of the filtered solution with ether a crystalline substance was obtained which after recrystallising twice from benzene-gasoline had m. p. 128—129°. The substance gave a violet colour with ferric chloride.

$C_{10}H_{10}O_5$	Calc.	C	57.15	H	4.81
	Found	»	57.03, 57.10	»	4.86, 4.95

A solution of this substance (0.1 g) in 2 *N* sodium hydroxide (5 ml) was boiled for 10 minutes. After acidifying with sulphuric acid the solution was shaken three times with ether. On evaporation of the dried ethereal solution a crystalline substance was obtained which obviously was the 4-methyl-6-hydroxyphtalic acid. It had m. p. 223° and when sublimated in a high vacuum gave a yellowish anhydride with m. p. 206°. Both substances on heating with resorcinol and conc. sulphuric acid gave the fluorescein reaction. According to Schleussner and Voswinckel[3] 4-methyl-6-hydroxyphtalic acid and its anhydride have m. p. 226—228° and 209° respectively.

Condensation of coumarandione and *iso*coumaranone derivatives

4,6-Dimethylcoumarandione (0.33 g), prepared according to Stollé and Knebel[4] and methyl 6-methyl*iso*coumaranone-4-carboxylate (0.33 g) were mixed and glacial acetic acid (1 ml) added. The mixture was cooled to about — 20° and conc. sulphuric acid (5 ml) added cautiously. After keeping the mixture for 20 hours in a refrigerator it was poured into water and a precipitate was obtained consisting of a red component mixed with some of the starting material. Boiling the dried precipitate with ligroin dissolved the red component and some of the starting material, but upon cooling most of the dimethylcoumarandione separated again and was filtered off. When the filtrate was concentrated the red component congregated along the walls of the glass vessel, whereas some more of the unchanged starting material crystallized on the bottom and could easily be removed. The red substance was dissolved in acetone and water added until the solution became opaque. After the solution had been heated till it became clear again it was left for crystallisation. At first a little dimethylcoumarandione separated and was removed by filtration, and then the red substance crystallized. It was recrystallized from acetone-water and dried in a vacuum. M. p. 190—200°. Yield 5—6 per cent of theory.

$C_{21}H_{16}O_6$	Calc.	C	69.21	H	4.43
	Found	»	69.08, 69.16	»	4.58, 4.60

Dehydrogenation with selenium

Methyl 6-methyl*iso*coumaranone-4-carboxylate (1 g) and selenium (0.5 g) were ground together thoroughly in a mortar and then heated in a sealed tube in a nitrogen atmosphere to 180° for 10 hours. When the tube was opened a considerable amount of hydrogen selenide effused. The reaction product was extracted with acetone and a strongly red-coloured solution was obtained. A red crystalline substance was gained from this solution in the same way as described for R-Me. M. p. 205—210°.

$C_{22}H_{16}O_8$	Calc.	C	64.71	H	3.95
	Found	»	64.60, 64.65	»	4.03, 4.15

Oxidation of other *iso*coumaranones

The oxidation was carried out as described for the preparation of R-Me. Therefore only the analytical results are given here.

Methyl *iso*coumaranone-4,6-dicarboxylate, prepared from the corresponding acid[1] by means of diazomethane, gave a red crystalline substance which had no definite melting point.

$C_{22}H_{10}O_{10}(OCH_3)_2$	Calc.	C	58.05	H	3.25	CH_3O	25.00
	Found	»	57.80, 58.10	»	3.40, 3.44	»	24.60

4-Methyl*iso*coumaranone, prepared by stud.mag.scient. E. Augdahl (unpubl.), gave a red crystalline substance which melted from 210 to 245°.

$C_{18}H_{12}O_4$	Calc.	C	73.98	H	4.14
	Found	»	73.86, 73.80	»	4.25, 4.28

Methyl *iso*coumaranone-7-carboxylate, prepared by stud.mag.scient. O. Aubert (unpubl.), gave a red crystalline substance which was extremely labile in the presence of alkali.

$C_{20}H_{12}O_8$	Calc.	C	63.17	H	3.18
	Found	»	63.00, 62.88	»	3.25, 3.30

SUMMARY

The red substance obtained by the oxidation of 6-methyl*iso*coumaranone-4-carboxylic acid with potassium permanganate in sodium carbonate solution was found to be a derivative of *iso*oxindigo. Similar red substances, all crystalline, could be obtained by the oxidation in acetone solution of other *iso*coumaranones or by the condensation of an *iso*coumaranone with a coumarandione. Dehydrogenation with selenium could be used instead of oxidation with permanganate. The light absorption of the *iso*oxindigo derivatives dissolved in ethanol was measured.

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