

Anthraquinone & Anthrone Series: Part XXVI— A New Synthesis of Chrysophanol, Rhein, Islandicin, Emodin & Physcion*

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A new general method for the synthesis of chrysophanol, rhein, islandicin, emodin and physcion, starting from common dye intermediates such as 1-amino-5-chloroanthraquinone and 2-methylanthraquinone, is described. Though a number of stages such as halogenation, deamination, replacement of halogen by hydroxyl, methoxylation and demethylation are involved in the synthesis, the reactions proceed without difficulty and good yields are obtained.

THE known methods¹⁻⁴ of synthesis of chrysophanol (chrysophanic acid) (I), emodin (IV) and other naturally occurring hydroxyanthraquinones, which are based on the condensation of nitro- and methoxyphthalic anhydrides with phenols or their ethers, require relatively inaccessible intermediate derivatives, and moreover, the constitution of the intermediate derivatives has not been proved. A new approach to the unambiguous synthesis of chrysophanol and emodin starting from the common anthraquinone dye intermediates is now described. With appropriate modifications the present method can be used for the synthesis of other naturally occurring polyhydroxy-2-methylanthraquinones⁵. Halogenation of aminoanthraquinones, deamination via the diazonium salts, and the replacement of halogen by hydroxyl or methoxyl followed by demethylation has been explored earlier as a general method for the synthesis of hydroxyanthraquinones^{6,7}.

In the method described here for the synthesis of chrysophanol (Chart I) the dye intermediate 1-amino-5-chloroanthraquinone (an intermediate for the dye Indanthrene Golden Orange 3G) was used as the starting material.

Marschalk⁸ prepared 1-amino-5-chloro-2-methylanthraquinone (VI) from 1-amino-5-chloroanthraquinone by the action of formaldehyde bisulphite solution in the presence of sodium hydrosulphite. Bromination of (VI) with bromine in glacial acetic acid at 20° gave 1-amino-4-bromo-5-chloro-2-methylanthraquinone (VII). Diazotization followed by deamination in boiling ethanol gave 4-bromo-5-chloro-

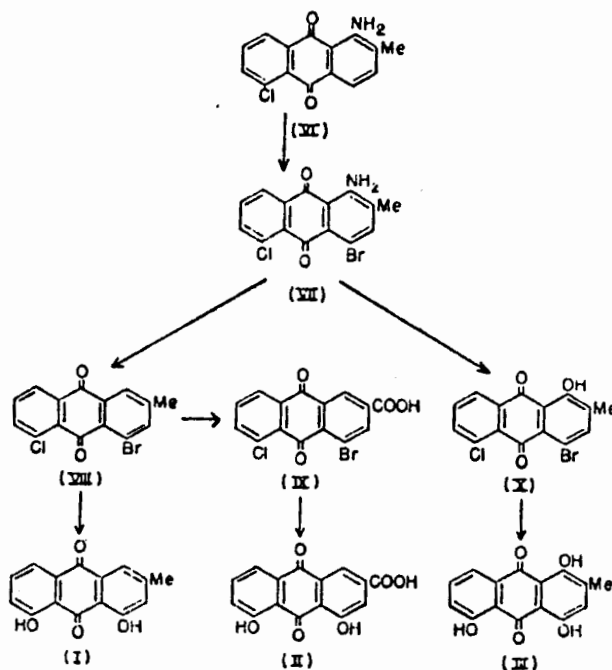


Chart I

2-methylanthraquinone (VIII), while the conversion of the diazonium group to hydroxyl by boiling with 50 per cent sulphuric acid gave 4-bromo-5-chloro-1-hydroxy-2-methylanthraquinone (X). Oxidation of (VIII) with chromic acid gave 4-bromo-5-chloroanthraquinone-2-carboxylic acid (IX). Replacement of halogens by hydroxyl groups in (VIII), (IX) and (X) by heating with slaked lime in presence of copper bronze at 200° in an autoclave yielded chrysophanol (I), rhein (II) and islandicin (III) respectively. The synthesis of (III), a red colouring

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matter present in *Penicillium islandicum* Sopp⁹, was reported earlier by Joshi *et al.*¹⁰, and more recently by Neelakantan *et al.*¹¹.

2-Methylanthraquinone served as a more satisfactory intermediate for the synthesis of chrysophanol (I), emodin (IV) and other related naturally occurring hydroxyanthraquinones. Nitration of 2-methylanthraquinone to the dinitro stage gave a mixture of 1,5-dinitro- and 1,8-dinitro-2-methylanthraquinones (XI) and (XII) which could be separated easily on account of their different solubilities in conc. sulphuric acid and organic solvents such as acetone and acetic acid¹². A series of subsequent reactions gave chrysophanol (I) and emodin (IV); in general the reactions proceeded smoothly and good yields were obtained (Chart II).

For the synthesis of chrysophanol (I), 1,5-dinitro-2-methylanthraquinone (XI) was the suitable starting material. Partial reduction of (XI) by short boiling with dimethylaniline (a reaction applied earlier to the partial reductions of 1,5- and 1,8-dinitroanthraquinones¹³) gave 1-nitro-2-methyl-5-aminoanthraquinone (XIII) in 60-65 per cent yield; the monoamine (XIII) separating from the dimethylaniline solution was crystalline and required no further purification before proceeding to the next stage. The constitution of (XIII) was confirmed by deamination to 1-nitro-2-methylanthraquinone. Diazotization of (XIII) and hydrolysis with boiling 40 per cent sulphuric acid gave 1-nitro-2-methyl-5-hydroxyanthraquinone (XIV). Reduction of (XIV) with sodium sulphide gave 1-amino-2-methyl-5-hydroxyanthraquinone (XV). When (XV) was treated with bromine in glacial acetic acid at 20°, the hydroxylated ring was unaffected and the sole product was the 4-bromo compound (XVI), which was deaminated to 2-methyl-4-bromo-5-hydroxyanthraquinone (XVII) by boiling the diazonium salt solution with ethanol; (XVI) could also serve as a useful intermediate for the synthesis of islandicin (III). Chrysophanol (I) was obtained as before by the replacement of the halogen atom in (XVII) by hydroxyl, by heating with aqueous lime and copper bronze in an autoclave at 200° for 24 hr.

1,8-Diamino-2-methylanthraquinone (XVIII) was used as the starting material for the synthesis of emodin (IV) and physcion (V). Bromination of (XVIII) with excess of bromine in glacial acetic acid at 100° gave the tribromo compound (XIX), which was deaminated through the diazonium salt to give 4,5,7-tribromo-2-methylanthraquinone (XX). Prolonged refluxing of (XX) with sodium methoxide and methanol in presence of copper oxide gave emodin trimethyl ether (XXI) in about 60 per cent yield; methoxylation could also be effected by heating in

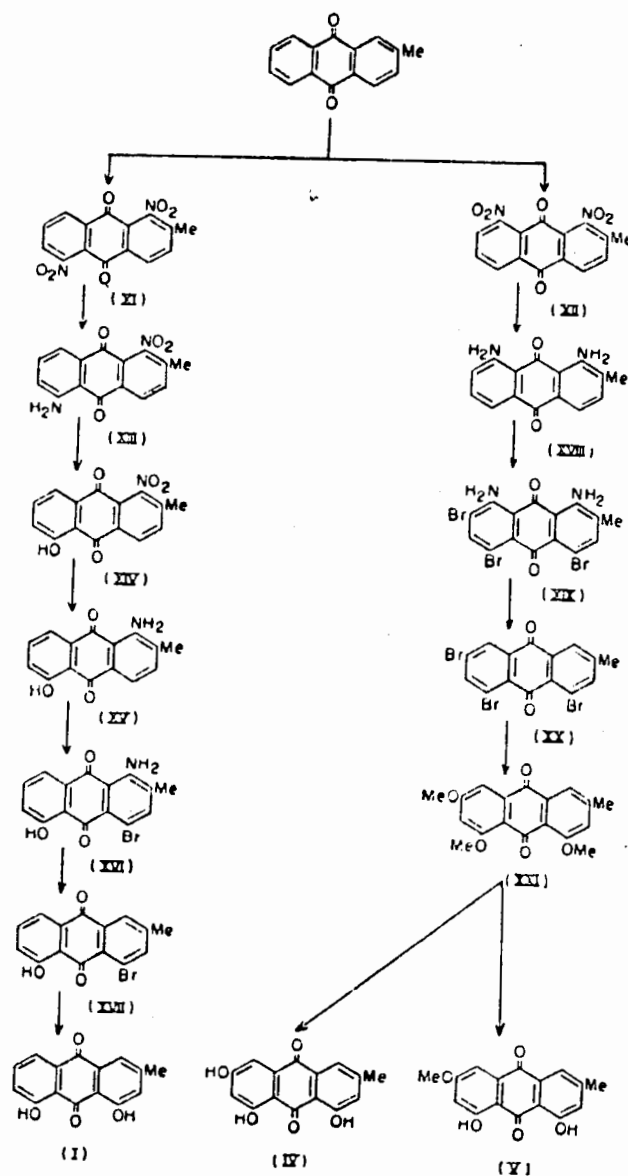


Chart II

a sealed tube at 160-70° for 6-12 hr, but the yield was somewhat lower. Complete demethylation of emodin trimethyl ether (XXI) to emodin (IV) was best effected by treatment for a few minutes with a melt of aluminium chloride-sodium chloride at 140-50°. Selective demethylation of the α -methoxyl groups in (XXI) by refluxing with hydrobromic and glacial acetic acids for 1 hr yielded physcion (V). Physcion was synthesized earlier by the partial methylation of emodin (IV) with methyl iodide and sodium methoxide in methanol or with potassium acetate and dimethyl sulphate^{14,15}.

Experimental procedure

1-Amino-2-methyl-5-chloroanthraquinone (VI) was prepared from 1-amino-5-chloroanthraquinone by the method⁶ described by Marschalk. Purification

of the crude reaction product (m.p. 175-80°) was effected by percolation of a toluene solution through a short column of alumina, followed by crystallization from toluene. The 1-amino-2-methyl-5-chloroanthraquinone (VI), obtained as red needles in 35-40 per cent yield, had m.p. 207° (Marschalk *et al.*⁴ quote a m.p. 213° after several crystallizations from nitrobenzene or pyridine). (Found: C, 66.4; H, 3.5; Cl, 12.6. $C_{15}H_{10}ClNO_2$ requires C, 66.3; H, 3.7; Cl, 13.1%.)

1-Amino-2-methyl-4-bromo-5-chloroanthraquinone (VII) — A suspension of (VI) (10 g.) in glacial acetic acid (140 ml.) was stirred with bromine (3.5 ml.) at 15-20° for 8 hr, and left overnight. The scarlet product was collected, washed with 5 per cent sodium bisulphite solution and water, and dried (11.6 g.). Crystallization from glacial acetic acid gave scarlet needles, m.p. 260° (decomp.). (Found: C, 51.1; H, 2.2; N, 4.5. $C_{15}H_9BrClNO_2$ requires C, 51.4; H, 2.6; N, 4.0%.)

2-Methyl-4-bromo-5-chloroanthraquinone (VIII) — A solution of (VII) (10 g.) in conc. sulphuric acid (150 ml.) was cooled in an ice bath to 5° and diazotized with sodium nitrite (2.5 g.) dissolved in conc. sulphuric acid (20 ml.). After 1 hr glacial acetic acid (20 ml.) was added and after 15 min. the mixture was poured over crushed ice (1 kg.). The solution of the diazonium salt was added to an equal volume of 95 per cent ethanol, and the mixture was gradually heated to boil and then refluxed for 30 min. The pale yellow crystalline product was collected, washed free of acid and dried. Crystallization from glacial acetic acid gave yellowish brown needles (7 g.), m.p. 226°. (Found: C, 53.3; H, 2.1; Br, 24.1; Cl, 10.3. $C_{15}H_8BrClO_2$ requires C, 53.7; H, 2.4; Br, 23.8; Cl, 10.4%.)

1-Hydroxy-2-methyl-4-bromo-5-chloroanthraquinone (X) — The diazonium solution prepared as above from (VII) (5 g.) was gradually added to a boiling 50 per cent sulphuric acid solution (300 ml.), and the mixture heated at 140° for 30 min. The brownish yellow product, obtained by dilution, was collected, washed free of acid and dried (3.5 g.). Crystallization from glacial acetic acid gave brownish yellow needles, m.p. 220°. (Found: C, 51.0; H, 2.2; Cl, 9.9; Br, 22.4. $C_{15}H_8BrClO_3$ requires C, 51.3; H, 2.2; Cl, 10.0; Br, 22.5%.)

4-Bromo-5-chloroanthraquinone-2-carboxylic acid (IX) — A mixture of (VIII) (5 g.), glacial acetic acid (125 ml.) and acetic anhydride (125 ml.) was stirred and treated with a solution of chromic acid (10 g.) in glacial acetic acid (100 ml.) during 30 min. at 60-65°. After stirring for 3 hr at 65-70°, the green solution was poured in hot water (1 litre) and left overnight. The lemon-yellow crystalline product

was collected, washed thoroughly and dried (4 g.). Crystallization from glacial acetic acid gave lemon-yellow plates, m.p. 296-8°. (Found: C, 48.8; H, 2.1; Cl, 9.5; Br, 22.5. $C_{15}H_6BrClO_4$ requires C, 49.1; H, 1.7; Cl, 9.8; Br, 21.9%.)

Chrysophanic acid (I) — To a thin slurry made from slaked lime (50 g.) in water (200 ml.), (VIII) (10 g.) and copper bronze (4 g.) were added. The mixture was heated in an autoclave at 200° for 24 hr. The red reaction mixture was acidified with hydrochloric acid and filtered. The crude product was dissolved in 5 per cent sodium hydroxide solution (200 ml.) and filtered. The filtrate was acidified and the brownish yellow precipitate collected, washed free of acid and dried (4.5 g.). Purification was effected by Soxhlet extraction with hexane and crystallization from alcohol to give yellow needles, m.p. 196° (literature¹⁻³, 196°). (Found: C, 70.9; H, 4.2. $C_{16}H_{10}O_4$ requires C, 70.9; H, 3.9%.)

The acetyl derivative crystallized from alcohol in yellow needles, m.p. 208°. (Found: C, 67.4; H, 4.1. $C_{18}H_{14}O_6$ requires C, 67.4; H, 4.1%.)

Rhein (II) — Treatment of (IX) (3 g.) with slaked lime (15 g.) and copper bronze (1.2 g.) as above and purification by sublimation at 180°/5 mm. gave a product (1.5 g.) which crystallized from glacial acetic acid in orange-yellow needles, m.p. 310-12° (rapid heating), undepressed when mixed with a natural sample. Melting points of 310° (Kofler hot plate) to 321° have been quoted for rhein. (Found: C, 63.1; H, 3.1. $C_{15}H_8O_8$ requires C, 63.4; H, 2.8%.)

The acetyl derivative was crystallized from glacial acetic acid as pale yellow needles, m.p. 247°.

Islandicin (III) — Treatment of (X) (2 g.) with slaked lime (10 g.) and copper bronze (0.8 g.) in a sealed tube at 200° for 24 hr yielded a product (0.85 g.) which crystallized from chloroform in bronze-red plates, m.p. 218°, undepressed when mixed with the natural sample and had all the properties described by Howard and Raistrick⁹ for islandicin. (Found: C, 66.7; H, 3.9. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%.) The substance is insoluble in aqueous sodium carbonate and ammonia, but goes into solution in aqueous sodium hydroxide giving a violet colour and in glacial acetic acid with orange colour having greenish fluorescence. It dissolves in conc. sulphuric acid with bright red colour, appearing bluish red with red fluorescence in thin layers.

1,5-Dinitro-2-methylanthraquinone (XI) (m.p. 346°; yield 30-35 per cent) and **1,8-dinitro-2-methylanthraquinone (XII)** (m.p. 293°; yield 10-12 per cent) were prepared by nitrating 2-methylanthraquinone and separating the two isomers¹².

1-Nitro-2-methyl-5-aminoanthraquinone (XIII) — A mixture of 1,5-dinitro-2-methylanthraquinone

(5 g.) and freshly distilled dimethylaniline (50 ml.) was stirred in a round bottom flask fitted with a reflux condenser. The mixture was heated gently with vigorous stirring to the boiling point. The suspension of the nitro compound went into solution with a red colour. The reaction was continued for 20 min. from the start and left overnight. The separated crystalline product was collected, washed with ether and dried (2.8 g.). Crystallization from chlorobenzene gave garnet-red needles, m.p. 300°. (Found: C, 63.7; H, 3.6; N, 9.9. $C_{15}H_{10}N_2O_4$ requires C, 63.8; H, 3.5; N, 9.9%.)

1-Nitro-2-methylanthraquinone --- 1-Nitro-2-methyl-5-aminoanthraquinone (XIII) (0.75 g.) was dissolved in conc. H_2SO_4 (20 ml.), cooled in ice bath to 5°, and diazotized with sodium nitrite (0.7 g.) in conc. H_2SO_4 (10 ml.) for 1 hr. Glacial acetic acid (2 ml.) was added and after 15 min. the mixture was poured over crushed ice (30 g.). The diazonium salt solution was added to ethanol (75 ml.) and the mixture was gradually heated to boil, and then refluxed for 30 min. The yellow product was collected, washed free of acid and dried (0.7 g.). Crystallization from glacial acetic acid gave yellow needles, m.p. 270-1°, undepressed when mixed with an authentic sample of 1-nitro-2-methylanthraquinone.

1-Nitro-2-methyl-5-hydroxyanthraquinone (XIV) — 1-Nitro-2-methyl-5-aminoanthraquinone (XIII) (5 g.) in conc. H_2SO_4 (100 ml.) was cooled to 5° and diazotized with a mixture of sodium nitrite (5 g.) and conc. H_2SO_4 (25 ml.). The diazonium solution was poured over crushed ice (150 g.) and then added to 50 per cent H_2SO_4 solution (300 ml.) at the boil. The mixture was heated at 140° for 1 hr and diluted with water (300 ml.). The crystalline yellow product was collected, washed and dried (4.6 g.). Crystallization from glacial acetic acid gave yellow needles, m.p. 275°. (Found: C, 63.7; H, 2.7; N, 4.8. $C_{15}H_9NO_5$ requires C, 63.6; H, 3.2; N, 4.9%.)

1-Amino-2-methyl-5-hydroxyanthraquinone (XV) — 1-Nitro-2-methyl-5-hydroxyanthraquinone (4 g.) was made into a paste in a round bottom flask with sodium sulphide (15 g.). The mixture was diluted with water (90 ml.) and heated gradually on a water bath at 100° with vigorous stirring for 1 hr. The red crystalline mass was collected, washed and dried (3.5 g.). Crystallization from toluene gave red needles, m.p. 192°. (Found: C, 71.4; H, 4.3; N, 5.3. $C_{15}H_{11}NO_3$ requires C, 71.2; H, 4.3; N, 5.5%.)

1-Amino-2-methyl-4-bromo-5-hydroxyanthraquinone (XVI) — A suspension of 1-amino-2-methyl-5-hydroxyanthraquinone (XV) (3 g.) in glacial acetic acid (50 ml.) was stirred with bromine (1.1 ml.) at 15-20° for 8 hr and left overnight. The scarlet product was collected, washed with 5 per cent sodium

bisulphite solution and with water and dried (3.78 g.). Crystallization from toluene gave brownish red needles, m.p. 242°. (Found: C, 53.7; H, 3.2; N, 4.3; Br, 24.2. $C_{15}H_9BrNO_3$ requires C, 54.2; H, 3.2; N, 4.2; Br, 24.1%.)

2-Methyl-4-bromo-5-hydroxyanthraquinone (XVII) — A solution of 1-amino-2-methyl-4-bromo-5-hydroxyanthraquinone (XVI) (3.3 g.) in conc. H_2SO_4 (50 ml.) was cooled in an ice bath to 5°, and diazotized with sodium nitrite (2 g.) dissolved in conc. H_2SO_4 (20 ml.). After an hour glacial acetic acid (20 ml.) was added, and after 15 min. the mixture was poured over crushed ice (80 g.). The solution of the diazonium salt was added to ethanol (150 ml.), and the mixture was gradually heated to boil and then refluxed for 30 min. The yellow crystalline product (3 g.) was collected, washed free of acid and dried. Crystallization from glacial acetic acid gave yellow needles, m.p. 203°. (Found: C, 56.9; H, 3.2. $C_{15}H_9BrO_3$ requires C, 56.8; H, 2.8%.)

Chrysophanic acid (1) — To a thin slurry made from slaked lime (12.5 g.) in water (50 ml.), 2-methyl-4-bromo-5-hydroxyanthraquinone (XVII) (2.5 g.) and copper bronze (1 g.) were added. The mixture was heated in an autoclave at 200° for 24 hr. The red reaction mixture was acidified and the yellow precipitate collected, washed free of acid and dried (1.9 g.). Crystallization from alcohol gave yellow needles, m.p. 196°. (Found: C, 70.8; H, 4.2. $C_{15}H_{10}O_4$ requires C, 70.9; H, 3.9%.)

The acetyl derivative crystallized from alcohol as yellow needles, m.p. 208°.

1,8-Diamino-2-methylanthraquinone (XII), m.p. 206°, was prepared by the reduction of 1,8-dinitro-2-methylanthraquinone¹⁰ with sodium sulphide.

1,8-Diamino-4,5,7-tribromo-2-methylanthraquinone (XIX) — A mechanically agitated solution of 1,8-diamino-2-methylanthraquinone (17.5 g.) in glacial acetic acid (1750 ml.) was treated at 100° with bromine in glacial acetic acid (20 ml. in 250 ml.) for 8 hr. After cooling to room temperature overnight, the crystalline product was collected, washed with sodium bisulphite solution, water, and dried (25 g.). Crystallization from chlorobenzene or glacial acetic acid gave dark red needles, m.p. 246°. (Found: C, 37.1; H, 1.8; N, 6.0; Br, 48.6. $C_{15}H_9Br_3N_2O_4$ requires C, 36.8; H, 1.8; N, 5.7; Br, 49.0%.)

4,5,7-Tribromo-2-methylanthraquinone (XX) — A solution of 1,8-diamino-4,5,7-tribromo-2-methylanthraquinone (XIX) (10 g.) in conc. H_2SO_4 (300 ml.), cooled to 5°, was diazotized with sodium nitrite (5 g.) in conc. H_2SO_4 (40 ml.) for 1 hr. Glacial acetic acid (40 ml.) was added and the mixture was poured over crushed ice (2 kg.). The diazonium solution thus obtained was refluxed with ethanol (1.5 litres)

for 1 hr. On cooling, the product was collected, washed and dried (9 g.). Crystallization from glacial acetic acid gave pale brownish yellow needles, m.p. 200°. (Found: C, 39.5; H, 1.9; Br, 51.9. $C_{12}H_7Br_3O_2$ requires C, 39.3; H, 1.5; Br, 52.3%.)

Emodin trimethyl ether (XXI) — Sodium metal (12.5 g.) was dissolved in absolute methanol (250 ml.). 4,5,7-Tribromo-2-methylanthraquinone (XX) (5 g.) and copper oxide (2 g.) were added, and the mixture refluxed for 72 hr under anhydrous conditions. Dilution with water (1 litre) gave a product, which was collected, washed, dried and dissolved in benzene. The solution was passed through a short column of alumina, the percolate evaporated and the residue, which gave a negative test for halogen (1.77 g.), was crystallized from alcohol in yellow plates, m.p. 226° (Oesterle and Tisza¹⁶, 225°). (Found: C, 68.9; H, 5.1; OMe, 29.3. $C_{18}H_{16}O_6$ requires C, 69.2; H, 5.1; OMe, 29.8%.)

Emodin (IV) — To a melt prepared from anhydrous aluminium chloride (7.5 g.) and dry sodium chloride (1.5 g.), emodin trimethyl ether (1.5 g.) was added and the mixture stirred at 140° for 5 min. On cooling and adding 2 per cent HCl (150 ml.), the orange-yellow product was collected, dissolved in 5 per cent aqueous sodium carbonate (75 ml.), filtered and the filtrate acidified. The precipitate (1.1 g.) crystallized from alcohol in orange needles, m.p. 256° (literature¹ 255°). (Found: C, 66.5; H, 3.9. $C_{12}H_{10}O_5$ requires C, 66.7; H, 3.7%.) The substance gives a cherry-red colour with aqueous alkali, sodium carbonate and ammonia, and a red colour with conc. H_2SO_4 . In the ultraviolet and visible region (IV) exhibits the following maxima: 254, 287 and 445 m μ ; log ϵ max. 4.42, 4.38 and 4.13 respectively.

The diacetyl derivative crystallized from ethanol as yellow needles, m.p. 197°.

Physcion (V) — Emodin trimethyl ether (0.5 g.) was refluxed with 48 per cent hydrobromic acid (12 ml.) and glacial acetic acid (80 ml.) for 1 hr. The

yellow crystalline product which separated on cooling crystallized from glacial acetic acid in golden yellow leaflets (0.3 g.), m.p. 207°. (Found: C, 67.2; H, 4.4. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.2%.) The product gives a red colour in conc. H_2SO_4 and cherry-red colour in aqueous sodium hydroxide. It is insoluble in cold aqueous sodium carbonate or ammonia. The properties agree with those described for natural physcion.

The diacetyl derivative was crystallized from alcohol in greenish yellow needles, m.p. 189°. (Found: C, 65.0; H, 4.3. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%.)

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