121. *A Synthesis of Helminthosporin.*

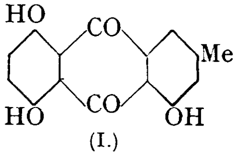
By Harold Raistrick, Robert Robinson, and Alexander R. Todd.

A metabolic product of *Helminthosporium gramineum*, Rabenhorst, grown on Czapek–Dox solution containing 5% of glucose has been identified by analytical methods as 4 : 5 : 8-trihydroxy-2-methylanthraquinone (I) (contemporaneous publication in the *Biochem. J.*). The present communication deals with the synthesis of the substance.

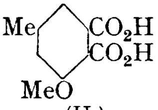
The starting point was the methyl ether of γ-coccinic acid (II) and we first attempted the preparation of this substance by the method of Schleussner and Voswinckel (*Annalen*, 1921, **422**, 111) which depends on an initial condensation of chloral with *m*-cresotinic acid. The intermediates of these authors could be obtained without difficulty, but their statement that γ-coccinic acid methyl ether is accessible by this route is erroneous. The final product was always α-coccinic acid or a derivative and we therefore confirm the work of Shah and Alimchandani (*J. Indian Chem. Soc.*, 1931, **8**, 261), who have already submitted a criticism of the conclusions of Schleussner and Voswinckel.

The method of Meldrum (J., 1911, **99**, 1712) was then adopted with some modifications for the preparation of (II).

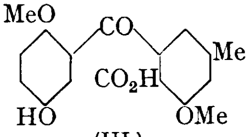
The anhydride of the acid was condensed with quinol dimethyl ether with the help of aluminium chloride in carbon disulphide solution, and the *product*, probably (III) from analogies, yielded helminthosporin, identical with the natural product, on treatment with hot sulphuric acid.



(I.)



(II.)



(III.)

Experimental.

3-*Methoxy*-5-*methylphthalide*.—Instead of using the ester (Meldrum, *loc. cit.*), we mixed 5-methoxy-*m*-toluic acid (10 g.) with chloral hydrate (10 g.) and conc. H_2SO_4 (50 c.c.); after 24 hr. at room temp. the product was isolated and recrystallised from MeOH (yield, 15 g. of m. p. 117°).

This material (20 g.), which is a mixture, was added to boiling EtOH (30 c.c.), and the hot paste mixed with NaOH (20 g.) in H_2O (100 c.c.); the temp. was kept at 50—60° and the mass shaken frequently. When the solid had passed into solution the mixture was kept at room temp. for 4 hr. The clear liquid was rendered faintly alkaline, the EtOH evaporated, and the gummy solid pptd. by HCl dissolved in hot AcOH. On ccoling, 3-methoxy-5-methylphthalide-2-carboxylic acid separated in small colourless prisms; it was recrystallised from AcOH (yield, 6 g., m. p. 190°). The mother-liquors slowly deposited 4 g. of cryst. material; recryst. from AcOH, this furnished 5-methoxy-3-methylphthalide-2-carboxylic acid, m. p. 169—170°.

3-Methoxy-5-methylphthalide-2-carboxylic acid (4 g.) and copper chromite (0·4 g.) were heated with quinoline (12 c.c.) (paraffin bath at 150—160°). Rapid evolution of CO_2 occurred and decarboxylation was complete in about 10 min. The mixture was cooled and poured into dil. HCl. The ppt., recryst. from EtOH, formed small, faintly yellow, oblique plates (1·7 g.), m. p. 134—135°.

3-Methoxy-5-methylphthalide (2·4 g.), oxidised by the method of Meldrum (*loc. cit.*), gave 3-methoxy-5-methylphthalic acid (2·2 g.), m. p. *ca.* 200° (efferv.). The anhydride was prepared by carefully heating the acid; recryst. from C_6H_6, it had m. p. 166—167°.

Hydroxymethoxybenzoylmethoxytoluic Acid (probably III).—Powdered $AlCl_3$ (2 g.) was added in 3 portions to a mixture of 3-methoxy-5-methylphthalic anhydride (1 g.) and quinol dimethyl ether (2 g.) in CS_2 (25 c.c.). The slow reaction was completed by heating under reflux on a steam-bath for 24 hr., the CS_2 then decanted, and the brownish semi-solid mass decomposed with dil. HCl and distilled in steam. A cream-coloured solid (1·1 g.) remained and after recrystn. from AcOH was obtained as small, colourless, rod-shaped crystals, m. p. 222—225° (Found: C, 64·0; H, 5·2; MeO, 19·6. $C_{17}H_{16}O_6$ requires, C, 64·5; H, 5·0; 2MeO, 19·6%). The EtOH solution becomes only faintly greenish-yellow on the addition of $FeCl_3$ and therefore we assume that no hydroxyl group is in the *o*-position to carbonyl or carboxyl; hence the suggested constitution (III).

4 : 5 : 8-*Trihydroxy-2-methylanthraquinone* (*Helminthosporin*) (I).—The crude benzoyltoluic acid (0·65 g.) obtained as above was heated at 150° during 30 min. with conc. H_2SO_4 (3 c.c.), the magenta-coloured solution poured into H_2O, and the reddish-brown ppt. collected. Recryst. from pyridine, 4 : 5 : 8-*trihydroxy-2-methylanthraquinone* was obtained as flat maroon-coloured needles with a bronze lustre, m. p. 226—227°. Mixed m. p. with helminthosporin (m. p. 225—226°) 226° (Found: C, 66·7; H, 3·8. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

The substance had all the properties of helminthosporin—the colour and fluorescence of the solutions in conc. H_2SO_4 and org. solvents being identical; the alkali-colour reactions were also found to exhibit no divergences. On acetylation the synthetic product gave an acetate, m. p. 225°, whose appearance was identical with that of triacetylhelminthosporin (m. p. 223—224°); the m.p. of a mixture with the latter substance was 224—225°.

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