383. *The Pigments of " Dragon's Blood " Resin. Part II. A Synthesis of Dracorhodin.*

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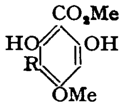
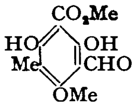
The constitution (V) assigned to dracorhodin by Brockmann and Junge has been confirmed by a synthesis of the compound starting from acetophenone and 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (III) which has been prepared by a novel route.

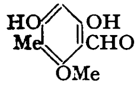
From the alkaline liquor left on the decomposition of crude dracorubin picrate with aqueous sodium hydroxide Brockmann and Junge (*Ber.*, 1943, **76**, 751) isolated dracorhodin, a minor pigment of " dragon's blood " resin which they recognised to be an anhydropyranol base. On hydrolytic fission this compound gave rise to 2-methylphloroglucinol 3-methyl ether along with acetophenone and was isomeric with the anhydro-base from synthetical 5-hydroxy-7-methoxy-8-methyl- and from 5-hydroxy-7-methoxy-6-methyl-flavylium chloride. These results and studies on the anhydro-bases derived from 5- and 7-hydroxyflavylium salts (cf. subsequent work of Brockmann, Junge, and Eckhardt, *Ber.*, 1944, **77**, 347) led the authors to conclude that dracorhodin had formula (V). By the condensation of 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde and acetophenone according to the standard procedure Brockmann and Junge (*loc. cit.*) obtained a product in insufficient quantity for purification and analysis but from an examination of its ultra-violet absorption spectrum within a restricted range of wave-lengths they concluded that their synthetical material contained dracorhodin. The aldehydic component, m. p. 163—164°, employed by these authors in this synthesis, was obtained as a by-product in the preparation of 2 : 6-dihydroxy-4-methoxy-3-methylbenzaldehyde from 2-methylphloroglucinol 3-methyl ether by the method of Gattermann and appears to have been impure. Accordingly, in view of its possible relation to dracorubin, the main pigment of " dragon's blood " resin, it seemed desirable to confirm the structure of dracorhodin by an unequivocal synthesis. Small specimens of dracorhodin were isolated from " dragon's blood " resin in these laboratories during 1944 by Dr. F. Haworth (unpublished work; see also Part I, preceding paper) and had properties identical with those described by the German authors.



(I.)



(II.)



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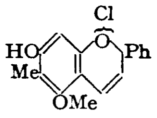
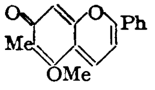
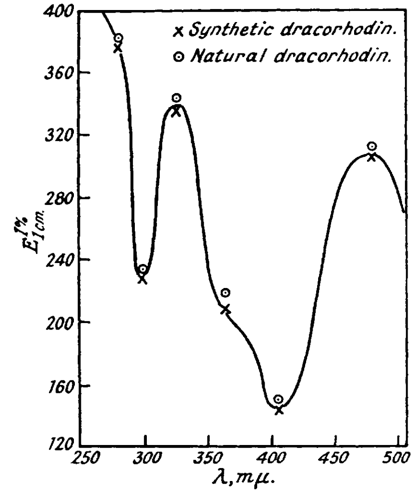


(IV.)



(V.)



In a prolonged search for a satisfactory route to the intermediate 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (III) required for the synthesis of dracorhodin it was ultimately discovered that this aldehyde could be obtained in good yield by the hydrolysis of the anil of methyl 2 : 6-dihydroxy-4-methoxy-3-formyl-5-methylbenzoate (II) with simultaneous decarboxylation of the resulting acid. All attempts to hydrolyse the parent formyl derivative (II) to (III) were unsuccessful. The intermediate ester (I; R = Me) required for the preparation of (II) has been obtained in good yield by the Clemmensen reduction of (I; R = CHO) in methanol, a route which is superior to that described by Herzig and Wenzel (*Monatsh.*, 1902, **23**, 113).

The condensation of the aldehyde (III) and acetophenone with hydrogen chloride to give (IV) did not proceed smoothly and the results depend greatly on the solvent employed. In methanol the main product appears to be a red substance which may be a xanthylium salt and this is formed, to a small extent, even in acetic acid which was found to be the most satisfactory medium. Thus prepared, 7-hydroxy-5-methoxy-6-methylflavylium chloride (IV) was identical with the hydrochloride of natural dracorhodin and on treatment with aqueous sodium acetate or sodium carbonate gave the anhydro-base (V), identical with the natural compound. The identity of natural and synthetical dracorhodin was confirmed by examination of their absorption spectra and by comparison of their respective picrates and perchlorates. The absorption curves for synthetical and natural dracorhodin were coincidental within the limits of experimental error, and the curve for the natural base only is reproduced (see figure).

Dracorhodin.		Minima.		Inflexions.		Maxima.	
Natural	λ, mμ.	298·0	402·0	283·0	367·0	324·5	480·0
	$E^{1\%}_{1\,\text{cm.}}$	227	154	374	222·2	349	317·5
Synthetic	λ, mμ.	298·0	401·0	282	368·5	325·0	479·0
	$E^{1\%}_{1\,\text{cm.}}$	230	150	379	210	335	310

EXPERIMENTAL.

Methyl 2 : 6-*Dihydroxy*-4-*methoxy*-3-*methylbenzoate* (I ; R = Me).—Methyl 2 : 6-dihydroxy-4-methoxy-3-formylbenzoate (I ; R = CHO), m. p. 177·5°, was prepared by the following modification of the method described by Clarke, Glaser, and Robertson (*J.*, 1948, 2260). A solution of methyl 2 : 6-dihydroxy-4-methoxybenzoate (I ; R = H) (6·2 g.) and hydrogen cyanide (15 ml.) in ether (225 ml.) was saturated at 0° with hydrogen chloride and 24 hours later the copious, colourless precipitate was washed with ether and heated with water to 100°. The solid dissolved and was replaced by the formyl derivative which separated almost quantitatively when the hydrolysate was cooled. The crude compound (5·6 g.) had m. p. 176°.

A solution of the foregoing formyl derivative (I ; R = CHO) (6·5 g.) in methanol (250 ml.) was added during 20 minutes to concentrated hydrochloric acid (80 ml.) and water (20 ml.) containing amalgamated zinc (80 g.), and the reaction completed by heating the mixture under reflux for 10 minutes. The hot liquid was then decanted, the residual amalgam was washed with hot methanol (100 ml.), and the combined liquor and washings were diluted with water (300 ml.). On cooling, the mixture deposited methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (I ; R = Me) in colourless needles (5·2 g.), m. p. 132—133°, unchanged on recrystallisation from aqueous methanol from which it separated in colourless rectangular plates (cf. Herzig and Wenzel, *loc. cit.*).

2 : 4-*Dihydroxy*-6-*methoxy*-5-*methylbenzaldehyde* (III).—The interaction of methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (3. g.) (I ; R = Me) with hydrogen cyanide (5 ml.) and zinc cyanide (5 g.) in ether saturated at 0° with hydrogen chloride gave a colourless crystalline solid together with a small amount of an oil. This product was isolated 24 hours later, washed with ether, and dissolved in water (150 ml.). The solution was rapidly heated to boiling and, on cooling, deposited *methyl* 2 : 6-*dihydroxy*-4-*methoxy*-3-*formyl*-5-*methylbenzoate* (II) in almost colourless plates (1·5 g.). Recrystallised from light petroleum or methanol, this compound formed long, slender, colourless needles, m. p. 122°, which in contact with the mother-liquor changed into stout colourless prisms, m. p. 122° (Found : C, 55·3 ; H, 5·2. $C_{11}H_{12}O_6$ requires C, 55·0 ; H, 5·0%), having a red-brown ferric reaction in alcohol. The aldehydo-ester, which is readily soluble in acetone, moderately soluble in alcohol, and sparingly soluble in light petroleum, sublimes at 120°/0·1 mm., forming clusters of stout needles.

When the ethereal mother-liquors from the aldimine derivative were mixed with more hydrogen cyanide (5 ml.) and zinc cyanide (3 g.) and again saturated with hydrogen chloride, a further quantity of the aldimine complex was obtained which gave the aldehyde (0·7 g.).

Prepared by heating a mixture of the aldehydo-ester (II) (5 g.) and aniline (2·5 g.) in methanol (100 ml.) on the steam-bath for 5 minutes, the *anil* crystallised from methanol in clusters of lemon-yellow needles (5·5 g.), m. p. 162° (Found : N, 4·6. $C_{17}H_{17}O_5N$ requires N, 4·4%). When a solution of this anil (1 g.) in 10% aqueous sodium hydroxide (25 ml.) was heated under reflux in an atmosphere of nitrogen for 2 hours, cooled, and acidified with concentrated hydrochloric acid, 4 : 6-*dihydroxy*-2-*methoxy*-3-*methylbenzaldehyde* (III) separated as a pale fawn-coloured crystalline solid, m. p. 170—172°, which, on recrystallisation from benzene–light petroleum or aqueous methanol, formed slender colourless prisms (0·4 g.), m. p. 175° (Found : C, 59·5 ; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3 ; H, 5·5%) (cf. Brockmann and Junge, *loc. cit.*, who gave m. p. 163—164°). The aldehyde, which has a red-brown ferric reaction in alcohol, is readily soluble in alcohol, acetone, or benzene and sparingly soluble in light petroleum. The *anil* separated from aqueous methanol in clusters of orange needles, m. p. 160° (decomp.) (Found : N, 5·4. $C_{15}H_{15}O_3N$ requires N, 5·4%), and the 2 : 4-*dinitrophenylhydrazone* formed tiny, deep-scarlet, shining prisms, m. p. 294—295° (decomp.), from ethyl acetate (Found : N, 15·2. $C_{15}H_{14}O_7N_4$ requires N, 15·5%) (cf. Brockmann and Junge, *loc. cit.*, who give m. p. 245—247°).

Dracorhodin (V).—A stream of hydrogen chloride was led into a solution of 4 : 6-dihydroxy-2-methoxy-3-methylbenzaldehyde (0·5 g.) and acetophenone (1·3 g.) in acetic acid (5 ml.) for 1 hour, and 24 hours later the golden-orange crystalline product was collected, washed with ether, and crystallised from 2N-hydrochloric acid, giving 7-hydroxy-5-methoxy-6-methylflavylium chloride (IV) as a *hydrate* in golden-brown needles, m. p. 205° (decomp.) after darkening at about 180° (Found : C, 63·3 ; H, 5·9 ; Cl, 10·8. $C_{17}H_{15}O_3Cl,H_2O$ requires C, 63·7 ; H, 5·3 ; Cl, 11·1%). Obtained from (IV) by means of aqueous sodium acetate or sodium hydrogen carbonate, dracorhodin separated from aqueous methanol in rosettes of deep-red prisms having a green reflex, m. p. 169° (decomp.), undepressed on admixture with a natural specimen (Found : C, 77·0 ; H, 5·5. Calc. for $C_{17}H_{14}O_3$: C, 76·6 ; H, 5·3%). The picrate crystallised from methanol containing a little picric acid in slender golden-brown needles, m. p. 217—220° (decomp.), alone or admixed with a specimen prepared from natural dracorhodin (Found : C, 55·6 ; H, 3·6 ; N, 8·7. Calc. for $C_{23}H_{17}O_{10}N_3$: C, 55·8 ; H, 3·4 ; N, 8·4%). Crystallised from methanol containing a trace of perchloric acid, 7-hydroxy-5-methoxy-6-methylflavylium perchlorate formed irregular golden-brown prisms, m. p. 227—230° (decomp.), the properties of which are identical with those of the natural derivative (Found : C, 55·5 ; H, 4·3 ; Cl, 10·4. Calc. for $C_{17}H_{15}O_7Cl$: C, 55·7 ; H, 4·1 ; Cl, 9·7%) [cf. Brockmann and Junge, *loc. cit.*, who give m. p. 233—236° (decomp.)].

Natural dracorhodin was isolated from the requisite fraction obtained during the isolation of dracorubin and converted into the picrate which on repeated recrystallisation from methanol containing a little picric acid had m. p. 217—220° (decomp.) (Found : C, 55·9; H, 3·6; N, 8·2%). Regenerated from the picrate, dracorhodin separated from aqueous methanol in rosettes of deep-crimson prisms, m. p. 169° (decomp.), having a green reflex.

The ultra-violet absorption spectra were determined with a Beckman quartz spectrophotometer in benzene solution by the courtesy of Professor R. A. Morton of the Biochemistry Department to whom we express our thanks.

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