

606. *The Pigments of "Dragon's Blood" Resins. Part III.*
The Constitution of Dracorubin.

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By degradation and synthesis dracoic acid $C_{16}H_{13}O_4 \cdot OMe$, an oxidation product of dracorubin formed along with draconol $C_{23}H_{17}O_5 \cdot OMe$, has been shown to be (-)-7-hydroxy-5-methoxyflavan-8-carboxylic acid (IV; R = H). Their salt-forming properties and their behaviour with boroacetic anhydride indicated that the dihydric phenol draconol and its ether contained a γ -pyrone system of the 1-hydroxyxanthone type, and consequently, since dracoic acid is formed by the oxidation of draconol, the latter phenol and its methyl ether are chromonoflavans having formula (III; R = H) and (III; R = Me) respectively in which the C-methyl group may be in the 2- or the 4-position of the xanthone system. Dracorubin is represented by formula (I) and its salts by formulæ of the type (II; R = H).

Synthesised from 5 : 7-dihydroxyflavanone by way of 7-benzyloxy-5-hydroxy-, 7-benzyloxy-5-methoxy-, and 7-hydroxy-5-methoxy-flavanone, 7-hydroxy-5-methoxyflavan has been converted into 8-formyl-7-hydroxy-5-methoxyflavan (XIII; R = H) the orientation of which is shown by reduction to 7-hydroxy-5-methoxy-8-methylflavan, synthesised unequivocally from 2 : 4-dihydroxy-6-methoxy-3-methylacetophenone. Oxidation of the acetate (XIII; R = Ac) followed by deacetylation of the product gave (\pm)-7-hydroxy-5-methoxyflavan-8-carboxylic acid, resolved to give the (-)-isomeride, identical with dracoic acid. The syntheses of 5 : 7-dihydroxyflavan-6-carboxylic acid and the dimethyl ether of its ester are described.

Attention is directed to the fact that the natural flavanone alpinetin is 7-hydroxy-5-methoxyflavanone.

In Part I (J., 1950, 1876) dracorubin was shown to be an anhydro-benzopyranol base $C_{31}H_{21}O_4 \cdot OMe$ and to give on oxidation a dihydric phenol draconol, the monomethyl ether of which was identical with a monohydric phenol obtained by the degradation of *O*-methyl-dracorubanol (cf. Brockmann *et al.*, *Ber.*, 1944, 77, 279). Along with draconol there is formed an optically active monobasic acid, dracoic acid, which Brockmann *et al.* (*loc. cit.*) claimed to be a keto-acid $C_{16}H_{14}O_5$ represented by a structure of the type (VII) in agreement with a partial structure derived for dracorubin.

In continuation of the studies on dracorubin described in Part I (*loc. cit.*) we have examined dracoic acid which we have found to be formed by the oxidation of draconol and to have the empirical formula $C_{15}H_{12}O_2(OMe) \cdot CO_2H$ in accordance with that of its methyl ester. Further, dracoic acid, which is devoid of a carbonyl or C-methyl group (contrast Brockmann *et al.*, *loc. cit.*), contains a hydroxyl group in the *o*-position to the carboxyl group, thus accounting for the intense ferric reaction exhibited by the acid and its ester. On decarboxylation the acid furnished a lævoratory, saturated, monohydric phenol $Ph \cdot C_9H_7O(OMe) \cdot OH$ in which the undefined oxygen atom appeared to be present in an ether system. From a comparison of the properties of this phenol with those of a number of hydroxychromans and hydroxycoumarans (see, e.g., Robertson *et al.*, J., 1936, 212; 1937, 1530, 1535; 1939, 921, 925) it seemed reasonably certain that the compound had a structure of the type (V) or (VI) *—the presence of the phloroglucinol rather than a hydroxyquinol or pyrogallol residue was suspected by analogy with dracorhodin (Part II, J., 1950, 1882) and the natural anthocyanidins and because on fusion with alkali draconol gave a small amount of a product considered to be impure phloroglucinol.

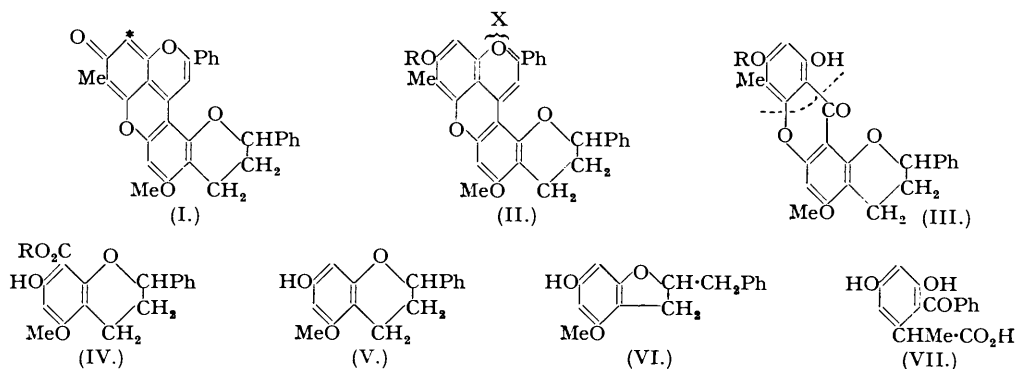
Since only small amounts of the phenol from dracoic acid were available and because of the difficulty of effecting a stepwise gradation of compounds of the type (V) and (VI), the (\pm)-7-hydroxy-5-methoxyflavan (V) was synthesised and from a comparison of its properties with those of the natural phenol it became clear that the latter compound was (-)-7-hydroxy-5-methoxyflavan; this conclusion was supported by synthesis of the isomeric (\pm)-5-hydroxy-7-methoxyflavan (XII) which was readily distinguishable from (V). Consequently it seemed reasonably certain that dracoic acid was the (-)-isomeride of either the 6- or the 8-carboxy-derivative of the flavan (V). The (\pm)-acid (IV; R = H) was therefore synthesised and, except in its optical inactivity, was found to be indistinguishable from dracoic acid. The synthetic (\pm)-methyl ester

* In arriving at this conclusion we were guided by an earlier hypothesis (unpublished) that, in dracorubin and probably in the related colouring matters of the "insoluble red" woods (at present under investigation in these laboratories), the molecular structure is derived from the union of two C_{15} residues having the flavan carbon skeleton in which one or both moieties might contain a pyrylium ring. Owing to the failure of dihydro-*O*-methyl-draconol to form salts and in view of the formulation adopted for dracoic acid by Brockmann *et al.* (*loc. cit.*), now shown to be erroneous, this hypothesis was not developed in Part I (*loc. cit.*) and the partial formula of the type (I), (III), and (IV) of that memoir were employed as they appeared to fit best the experimental findings then available.

Clearly the structure developed for dracorubin in this memoir is only one of several types envisaged in this hypothesis. A. R.

(IV; R = Me) had properties very similar to those of methyl dracoate and its melting point, which was slightly lower than that of the latter compound, was not depressed on admixture with the natural derivative. The structure (IV; R = H) for dracoic acid was ultimately confirmed by resolution of the synthetic (\pm)-isomeride (IV; R = H) by means of its brucine salt, with the isolation of the (-)-7-hydroxy-5-methoxyflavan-8-carboxylic acid and subsequent conversion into the (-)-methyl ester. The identification of the natural and the synthetic acid was confirmed by a comparison of their brucine salts.

From an earlier observation that *O*-methyldraconol formed a hydrochloride unstable in moist air (unpublished work of Dr. Kalya Isarasena, lately of this laboratory) it seemed probable that this compound and the parent draconol contained a γ -pyrone system. Further, the general properties, including colour, solubilities, ferric reaction, and resistance to fusion with alkali, except under drastic conditions, of *O*-methyldraconol were reminiscent of those exhibited by a 1-hydroxyxanthone. In agreement with this draconol and *O*-methyldraconol have been found to form perchlorates and to behave with boroacetic anhydride in a similar manner to 1-hydroxyxanthones (Robertson and Waters, *J.*, 1929, 2239). By its oxidation to dracoic acid (IV; R = H) draconol clearly contains the flavan system. Draconol and its *O*-methyl ether behave as saturated compounds and, therefore, when the empirical formulæ of draconol and dracoic acid



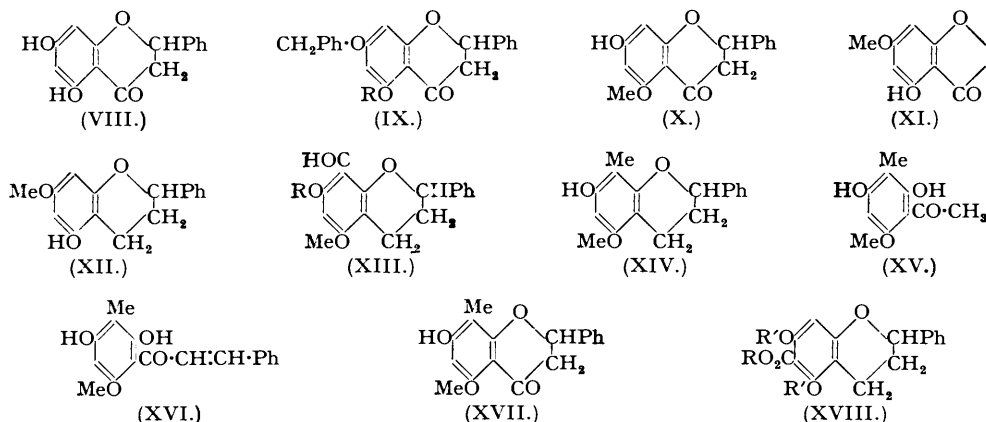
are taken into account, it is clear that the seven carbon atoms removed in this oxidation are present in a *C*-methyl benzenoid system, *e.g.*, of the *C*-methylphloroglucinol type, joined at two of its carbon atoms to the flavan residue. Further, this benzenoid residue contains the two phenolic hydroxyl groups of draconol present in the *m*- and not the *o*- or the *p*-position to each other, and it is, therefore, united to the dracoic acid residue by the oxygen and carbon atoms appearing respectively as the 7-hydroxyl and 8-carboxyl groups in this acid. Consequently, in agreement with their basic properties draconol and *O*-methyldraconol contain a 1-hydroxyxanthone residue and are respectively represented by the structures (III; R = H) and (III; R = Me), in which the presence of the *C*-methylphloroglucinol residue rests on analogy with dracorhodin. This structure, in which the *C*-methyl group may be in the 2- or the 4-position of the xanthone residue, affords a satisfactory basis for a rational interpretation of the properties of draconol and its methyl ether and for the degradation of draconol to dracoic acid which takes place along the broken line in formula (III).

Since draconol (III; R = H) and its methyl ether (III; R = Me) are obtained from dracorubin and *O*-methyldracorubanol respectively by the loss of the elements of acetophenone (Part I, *loc. cit.*) with the simultaneous formation of the carbonyl and the 1-hydroxy-group of the xanthone residue it is clear that dracorubin has either the structure (I) or the alternative structure in which the *C*-methyl group is in the position marked * in the anhydro-2-phenylbenzopyranol residue. Further, the salts formed by dracorubin and the benzpyranol base *O*-methyldracorubanol have formulæ of type (II; R = H) and (II; R = Me) respectively.

Benylation of the 5 : 7-dihydroxyflavanone (VIII) gave the benzyl ether (IX; R = H), the orientation of which follows from its intense ferric reaction and by analogy with the formation of 7-benzyloxy-5-hydroxy-2 : 2-dimethylchromanone (George and Robertson, *J.*, 1937, 1535). Methylation of (IX; R = H) yielded the ether (IX; R = Me) which on catalytic hydrogenolysis gave rise to 7-hydroxy-5-methoxyflavanone (X), identical with a specimen prepared by the less satisfactory method of Zemplén *et al.* (*Ber.*, 1944, 77, 99). Considerable difficulty was encountered in effecting the reduction of the flavanones of the type (X), employed in this

investigation, to the corresponding flavans. With hydrogen and a platinum catalyst (X) gave a minute amount of (V) accompanied by much resinous by-product and, when a palladium-charcoal catalyst was employed at 80—100°, (X) was almost quantitatively converted into 2 : 4-dihydroxy-6-methoxy- β -phenylpropiophenone; with the latter catalyst reduction did not occur at room temperature. By Clemmensen reduction under the usual conditions (X) gave a resin but it was ultimately discovered that when the reaction was carried out at room temperature in a mixture of acetic and hydrochloric acid this flavanone gave an excellent yield of (\pm)-7-hydroxy-5-methoxyflavan (V) which closely resembled the natural phenol obtained by decarboxylation of dracoic acid. Similarly reduction of 5-hydroxy-7-methoxyflavanone (XI), prepared by the partial methylation of (VIII), gave rise to (\pm)-5-hydroxy-7-methoxyflavan (XII) which was readily distinguishable from (V) and the natural ($-$)-isomeride.

Application of the Gattermann aldehyde synthesis to synthetic 7-hydroxy-5-methoxyflavan gave only one aldehyde which must have structure (XIII; R = H) since on reduction by Clemmensen's method it furnished 7-hydroxy-5-methoxy-8-methylflavan (XIV), identical



with a specimen prepared from 2 : 4-dihydroxy-6-methoxy-3-methylacetophenone (XV) by way of the stages (XVI) and (XVII). On oxidation with potassium permanganate in acetone followed by deacetylation of the product the acetate (XIII; R = Ac) of 8-formyl-7-hydroxy-5-methoxyflavan gave rise to the acid (IV; R = H), characterised by the formation of the methyl ester (IV; R = Me) which by the methyl iodide-potassium carbonate method was converted into methyl 5 : 7-dimethoxyflavan-8-carboxylate.

For comparison with the methyl ether of methyl dracoate, methyl 5 : 7-dimethoxyflavan-6-carboxylate was synthesised by the following method. 5 : 7-Dihydroxyflavan was prepared by the reduction of the flavanone (VIII) and on carboxylation by the potassium hydrogen carbonate-glycerol method gave the acid (XVIII; R = R' = H). Etherification of the methyl ester (XVIII; R = Me; R' = H) of this acid furnished methyl 5 : 7-dimethoxyflavan-6-carboxylate (XVIII; R = R' = Me), the orientation of which, and hence that of the parent acid (XVIII; R = R' = H), follows from the fact that it was isomeric and not identical with methyl 5 : 7-dimethoxyflavan-8-carboxylate obtained by the methylation of (IV; R = Me). In agreement with this formulation it was found impossible to effect a stepwise methylation of methyl 5 : 7-dihydroxyflavan-6-carboxylate and it is noteworthy that, as in the case of orcinol (*J.*, 1927, 2196) and 3-(4 : 6-dihydroxy-*o*-tolyl)butan-2-ol (*J.*, 1949, 1563), the carboxylation of 5 : 7-dihydroxyflavan gives the γ -resorcylic acid type.

Note on Alpinetin.—From the ethereal extracts of the seeds of *Alpinia chinensis* Roscoe Kimura (*J. Pharm. Soc., Japan*, 1940, **60**, 151) isolated a flavanone $C_{15}H_{11}O_3 \cdot OMe$, m. p. 223°, which gave 5 : 7-dimethoxyflavanone on methylation. By the partial demethylation of the latter compound Rao and Seshadri (*Proc. Indian Acad. Sci.*, 1946, **23**, A, 213) obtained a mono-methyl ether, m. p. 101—102°, of 5 : 7-dihydroxyflavanone which they believed to be 5-hydroxy-7-methoxyflavanone, a conclusion now supported by the present synthesis of this compound. It is reasonably certain, therefore, that alpinetin, for which Kimura gave m. p. 223°, is 7-hydroxy-5-methoxyflavanone (X), m. p. 227°.

EXPERIMENTAL.

Dracoic Acid (IV; R = H).—Draconol and dracoic acid were prepared by the following modification of the method employed in Part I (*loc. cit.*) (cf. Brockmann *et al.*, *loc. cit.*). A mixture of powdered dracorubin (0.5 g.), 3*N*-aqueous potassium hydroxide (5 ml.), and methanol (30 ml.) at 0° was treated with hydrogen peroxide (1 ml. of 100 vol.), kept at 0° for 3 days with occasional agitation, filtered, and acidified with 2*N*-sulphuric acid. On being cooled a filtered solution of the solid (from 40 experiments) in methanol slowly deposited draconol (2.5–3 g.) which on recrystallisation had m. p. 256° (decomp.) after softening at 180° followed by solidification.

The methanolic mother-liquor from the crude draconol was concentrated in a vacuum, diluted with water (125 ml.), and extracted with ether (120 ml. × 2). The combined ethereal extracts were washed with 2*N*-sodium hydrogen carbonate (50 ml. × 5), the combined washings were acidified with 2*N*-sulphuric acid, and the resulting precipitate was extracted with ether (100 ml. × 3). Evaporation of the dried extracts and crystallisation of the residue from methanol gave dracoic acid (0.8–1.3 g.) in almost colourless needles, m. p. 167°, $[\alpha]_D^{25} - 56.1^\circ$ (*c*, 1.0 in chloroform), readily soluble in benzene, moderately soluble in alcohol, and giving a violet-brown ferric reaction in alcohol (Found : C, 68.1; H, 5.6; OMe, 8.7. Calc. for $C_{16}H_{13}O_4 \cdot OMe$: C, 68.0; H, 5.3; OMe, 10.3%) (cf. Brockmann *et al.*, *loc. cit.*, who give m. p. 163–165°, $[\alpha]_D^{25} - 54.1^\circ$). The acid separated from a little benzene in almost colourless, stout, rhombic prisms, m. p. 167° (Found : C, 68.3; H, 5.5; OMe, 7.1%). Prepared by ethereal diazomethane, *methyl dracoate* formed slender colourless prisms, m. p. 140°, and after repeated crystallisation from methanol, with or without being sublimed in a high vacuum, had m. p. 145°, $[\alpha]_D^{25} - 80.5^\circ$ (*c*, 1.0 in chloroform), and gave a steel-blue ferric reaction in alcohol [Found : C, 69.0; H, 6.1; OMe, 17.2. $C_{16}H_{12}O_3(OMe)_2$ requires C, 68.8; H, 5.7; OMe, 19.7%] (cf. Brockmann *et al.*, who give m. p. 124°, $[\alpha]_D^{20} - 78.5^\circ$). This ester was apparently not readily racemised by heat and after having been kept at 145–150° for 20 hours it sublimed unchanged in a high vacuum, having m. p. 145°, $[\alpha]_D^{25} - 80.0^\circ$ (*c*, 1.0 in chloroform).

Benzoic acid (8.5 g. from 40 g. of dracorubin) and methyl benzoate (0.5 g.) were isolated from the aqueous-methanolic oxidation liquors after the isolation of crude dracoic acid.

A solution of dracoic acid (0.7 g.) in quinoline (10 ml.), containing copper bronze (2 g.), was heated under reflux in an atmosphere of nitrogen for 15 minutes, cooled, diluted with ether, repeatedly extracted with 2*N*-hydrochloric acid, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Distillation of the residue in a high vacuum and crystallisation of the resulting glass-like distillate (0.5 g.) from benzene–light petroleum (b. p. 60–80°) or light petroleum containing a trace of methanol gave *7-hydroxy-5-methoxyflavan* in clusters of long slender, colourless needles, m. p. 95°, $[\alpha]_D^{25} - 11.5^\circ$ (*c*, 1.0 in methanol), very readily soluble in ether, alcohol, or acetone and moderately soluble in benzene (Found : C, 74.9; H, 6.4; OMe, 11.4. $C_{15}H_{13}O_2 \cdot OMe$ requires C, 75.0; H, 6.3; OMe, 12.1%). Small yields of the same phenol were also obtained by sublimation of the acid at temperatures exceeding 180° with or without copper bronze or by heating the acid with boiling 20% aqueous potassium hydroxide for 1 hour. Attempts to carboxylate this phenol under a variety of conditions were unsuccessful.

Derivatives of Draconol.—(a) On the addition of 60% perchloric acid (1 ml.) to a solution of draconol (0.2 g.) in acetic acid (2 ml.) the *perchlorate* quickly separated in bright yellow prisms, m. p. 206–208° (violent decomp.), which could not be satisfactorily recrystallised (Found : Cl, 7.1. $C_{24}H_{21}O_{10}Cl$ requires Cl, 7.1%). Decomposition of this salt with aqueous sodium hydrogen carbonate regenerated draconol.

(b) Prepared by method (a) the *perchlorate* of *O*-methyldraconol (Part I, *loc. cit.*) was obtained in bright greenish-yellow prisms, m. p. 139–140° (vigorous decomp.) (Found : Cl, 6.9. $C_{25}H_{23}O_{10}Cl$ requires Cl, 6.9%), which regenerated the free ether on treatment with water or aqueous sodium hydrogen carbonate.

(c) The addition of a solution of boroacetic anhydride (0.1 g.) in acetic anhydride (2 ml.) to *O*-methyl-draconol (0.5 g.) dissolved in warm acetic anhydride (5 ml.) gave the boroacetic anhydride complex in short, bright lemon-yellow prisms, m. p. 296° (decomp.), after having been washed with acetic anhydride and then ether and dried over sulphuric acid. Decomposed with water (5 ml.) containing methanol (2 ml.) on the steam-bath during 20 minutes, this compound (0.2 g.) regenerated *O*-methyl-draconol [Found : $C_{25}H_{22}O_6$, 72.1. $C_{25}H_{21}O_6B(O \cdot CO \cdot CH_3)_2$ requires $C_{25}H_{22}O_6$, 76.5%].

Oxidation of Draconol.—(a) A solution of potassium permanganate (1 g.) in acetone (100 ml.) was added gradually to draconol (0.5 g.) dissolved in acetone (100 ml.) during 4 hours, and 24 hours later the mixture was cleared with sulphur dioxide. After the removal of the acetone in a vacuum the product was isolated with ether and resolved by means of aqueous sodium hydrogen carbonate into unchanged draconol (50 mg.) and an acid fraction. The latter was esterified with diazomethane, and the product separated by fractional sublimation into (i) a trace of methyl benzoate, (ii) a trace of a solid, m. p. 124°, and (iii) methyl dracoate (20 mg.), identified by comparison with an authentic specimen.

(b) Chromic oxide (0.5 g.) was added to a solution of *O*-diacetyldraconol (Brockmann *et al.*, *loc. cit.*) (0.5 g.) in boiling acetic acid (15 ml.). After having been kept at room temperature for 24 hours the green mixture was diluted with water (30 ml.), and the buff-coloured solid collected and crystallised from acetic acid, giving a *compound* in almost colourless needles (0.1 g.), m. p. 250°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 67.6; H, 4.5. $C_{28}H_{22}O_9$ requires C, 66.9; H, 4.4%). The synthetic flavanones described in this memoir do not give diagnostic carbonyl derivatives and in accordance with the possibility that it is a complex γ -pyronoflavanone derived from draconol by the oxidation of a methylene group this compound did not form an oxime or 2 : 4-dinitrophenylhydrazine.

7-Hydroxy-5-methoxyflavanone (X).—A mixture of phloroglucinol (15 g.), cinnamoyl chloride (16.8 g.), aluminium chloride (17 g.), and nitrobenzene (50 ml.) was kept at room temperature for 24 hours and then poured on ice (250 g.) and concentrated hydrochloric acid (100 ml.). The product and nitrobenzene were

isolated with ether, the nitrobenzene removed with steam, and the residual solid extracted with warm water to remove cinnamic acid. A solution of the product in benzene (3000 ml.) was poured on a column of aluminium oxide, the column was washed with benzene (500 ml.), and the yellow benzene percolate was concentrated to a small volume. On being kept this solution deposited 5 : 7-dihydroxyflavanone (5.6 g.), m. p. 197—198°, which on sublimation in a high vacuum at 190°/0.001 mm. had m. p. 199° (Found : C, 70.2; H, 4.8. Calc. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7%) (cf. Shinoda and Sato, *J. Pharm. Soc. Japan*, 1928, 48, 791, who give m. p. 203—204°).

A mixture of 5 : 7-dihydroxyflavanone (10 g.), benzyl bromide (4.8 ml.), acetone (200 ml.), and potassium carbonate (10 g.) was heated under reflux for 2 hours. On isolation the 7-benzyloxy-5-hydroxyflavanone (IX; R = H) (14 g.) was purified from light petroleum, forming clusters of almost colourless, irregular prisms, m. p. 67°, which gave an intense red ferric reaction in alcohol (Found : C, 76.1; H, 5.3. $C_{22}H_{18}O_4$ requires C, 76.3; H, 5.2%). Methylation of this compound (14.2 g.) with methyl iodide (20 g.) in boiling acetone (600 ml.) containing potassium carbonate (20 g.) was complete in 15 hours. The resulting 7-benzyloxy-5-methoxyflavanone (IX; R = Me) formed clusters of colourless needles, m. p. 134—135°, from light petroleum (b. p. 60—80°), having a negative ferric reaction (Found : C, 76.8; H, 5.7. $C_{23}H_{20}O_4$ requires C, 76.7; H, 5.6%). Debenzylation of this compound (1 g.), dissolved in acetic acid (50 ml.), with hydrogen and palladium-charcoal (from 0.5 g. of charcoal and 0.1 g. of palladium chloride) gave 7-hydroxy-5-methoxyflavanone (X) which formed colourless needles, m. p. 225°, from methanol (Found : C, 71.0; H, 5.2. Calc. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2%), undepressed on admixture with a specimen, m. p. 227°, obtained from 2 : 4-dihydroxy-6-methoxyacetophenone in poor yield by the method of Zemplén *et al.* (*loc. cit.*), who give m. p. 217°.

(±)-7-Hydroxy-5-methoxyflavan (V).—(a) Amalgamated zinc (from 10 g. of zinc dust), which had been washed with water and acetic acid (twice), was added to a solution of 7-hydroxy-5-methoxyflavanone (1 g.) in acetic acid (40 ml.), followed by concentrated hydrochloric acid (5 ml.), with cooling of the mixture for 10 minutes in tap-water. 24 Hours later the solution was decanted, and, after being diluted with water until slightly turbid and seeded with a few crystals of the (–)-flavan, deposited the (±)-flavan (0.8 g.) in colourless needles, m. p. 92°, which on recrystallisation from benzene-light petroleum was obtained in long, slender, glistening needles, m. p. 96°, having a negative ferric reaction (Found : C, 74.9; H, 6.4. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%). The solubilities of this compound were identical with those of the (–)-isomeride, m. p. 95°, and a mixture of the two compounds had m. p. 90—92°.

(b) Reduction of 7-hydroxy-5-methoxyflavanone (0.5 g.), dissolved in acetic acid (125 ml.), with hydrogen and a platinum oxide catalyst (100 mg.) yielded a product which did not crystallise. Sublimation of this in a high vacuum at 140°/0.001 mm. gave a small amount of a colourless glass and a resinous residue. Crystallised from benzene-light petroleum, the sublimate gave 7-hydroxy-5-methoxyflavan in colourless needles (20 mg.), m. p. 94°, undepressed on admixture with specimen prepared by method (a).

When the platinum oxide was replaced by palladium-charcoal hydrogenation occurred at 80—100° giving an almost theoretical yield of 2 : 4-dihydroxy-6-methoxy-β-phenylpropionophenone. This compound formed colourless slender needles, m. p. 192°, from methanol, having an intense violet-brown ferric reaction in alcohol (Found : C, 71.2; H, 5.3. Calc. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2%) (cf. Zemplén *et al.*, *loc. cit.*, who give m. p. 189°).

5-Hydroxy-7-methoxyflavan (XII).—Methylation of 5 : 7-dihydroxyflavanone (1 g.) with potassium carbonate (1 g.) and methyl iodide (0.4 ml.) in boiling acetone (100 ml.) for 2 hours gave 5-hydroxy-7-methoxyflavanone (XI), which formed almost colourless plates (1 g.), m. p. 100°, from methanol, having an intense red ferric reaction in alcohol (Found : C, 70.8; H, 5.1. Calc. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2%). This compound appears to be identical with Rao and Seshadri's product, m. p. 101—102° (*Proc. India Acad. Science*, 1946, 23, A, 213).

Reduction of 5-hydroxy-7-methoxyflavanone (0.25 g.) with amalgamated zinc dust (5 g.) in a mixture of acetic acid (25 ml.) and hydrochloric acid (5 ml.) at room temperature gave 5-hydroxy-7-methoxyflavan (0.2 g.) which separated from light petroleum containing a little methanol in colourless plates, m. p. 148°, having a negative ferric reaction (Found : C, 75.1; H, 6.1. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%).

5 : 7-Dihydroxyflavan.—Prepared by the method employed for its 7-methyl ether, this flavan formed tiny colourless needles, m. p. 196°, from benzene, and had a negative ferric reaction in alcohol (Found : C, 74.7; H, 6.0. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%).

5 : 7-Dihydroxyflavan-6-carboxylic Acid (XVIII; R = R' = H).—An intimate mixture of 5 : 7-dihydroxyflavan (1 g.), potassium hydrogen carbonate (10 g.), and glycerol (125 ml.) was kept at 140° for 6 hours in an atmosphere of carbon dioxide. A solution of the cooled reaction mixture in water (200 ml.) was extracted with ether (75 ml. × 3) to remove phenolic material, and acidified with concentrated hydrochloric acid. Crystallisation of the resulting precipitate (0.7 g.) from aqueous methanol and then from benzene-ethyl acetate gave 5 : 7-dihydroxyflavan-6-carboxylic acid in short colourless needles, m. p. 178—179° (decomp.), having an intense blue-violet ferric reaction in alcohol (Found : C, 67.1; H, 5.0. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.8%). Prepared with ethereal diazomethane, the methyl ester (XVIII; R = Me; R' = H) separated from methanol in rosettes of colourless silky needles, m. p. 109° (Found : C, 67.9; H, 5.3. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

Carboxylation at 160° gave only a trace of acid, and unchanged phenol could not be isolated.

On methylation by the methyl iodide-potassium carbonate method during 6 hours methyl 5 : 7-dihydroxyflavan-6-carboxylate gave a quantitative yield of methyl 5 : 7-dimethoxyflavan-6-carboxylate which separated from aqueous methanol in long, slender prisms, m. p. 95° (Found : C, 69.5; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%).

2 : 4-Dihydroxy-6-methoxy-3-methylacetophenone (XV).—In comparison with the earlier method of Curd and Robertson (*J.*, 1933, 1173) this ketone is more accessible by the following route. The interaction

of 2 : 4-dihydroxy-6-methoxyacetophenone (2 g.), hydrogen cyanide (5 ml.), and zinc cyanide (1 g.) in ether (250 ml.) saturated with hydrogen chloride gave a crystalline product which was isolated 24 hours later. A solution of this in water (250 ml.) was rapidly heated to boiling and allowed to cool, giving 3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone which formed almost colourless, tiny prisms (1.5 g.), m. p. 134°, from methanol or alcohol (Found : C, 56.2; H, 5.0. $C_{10}H_{10}O_5$ requires C, 57.1; H, 4.8%). This aldehyde, which had a red-brown ferric reaction, gave a 2 : 4-dinitrophenylhydrazone, forming orange needles, m. p. 291—293° (decomp.), from much acetic acid (Found : N, 14.1. $C_{16}H_{14}O_8N_4$ requires N, 14.4%).

A solution of the foregoing aldehyde (1.5 g.) in methanol, containing amalgamated zinc (8 g.), was mixed with concentrated hydrochloric acid (10 ml.) and water (5 ml.) and warmed slightly. 3—4 Minutes later the reaction mixture gave a negative reaction with 2 : 4-dinitrophenylhydrazine sulphate, and the liquor was immediately decanted and diluted with water, giving 2 : 4-dihydroxy-6-methoxy-3-methylacetophenone (0.9 g.), m. p. 222°. This compound separated from methanol in almost colourless, slender needles, m. p. 225° (Found : C, 61.4; H, 6.3. Calc. for $C_{16}H_{12}O_4$: C, 61.2; H, 6.1%), and on methylation by the methyl iodide—potassium carbonate method gave 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone, m. p. 141—142° (Curd and Robertson, *J.*, 1933, 437).

7-Hydroxy-5-methoxy-8-methylflavanone (XVII).—A mixture of 2 : 4-dihydroxy-6-methoxy-3-methylacetophenone (1 g.), benzaldehyde (0.9 g.), alcohol (10 ml.), and 60% aqueous potassium hydroxide (16 ml.) was kept at room temperature for 24 hours, diluted with water, and acidified with 2*N*-hydrochloric acid. Crystallised from methanol, the precipitate gave *7-hydroxy-5-methoxy-8-methylflavanone* in colourless prisms (0.5 g.), m. p. 213°, having a negative ferric reaction in alcohol (Found : C, 72.4; H, 5.8. $C_{17}H_{16}O_4$ requires C, 71.9; H, 5.6%). Concentration of the methanolic mother-liquors furnished a small amount of the corresponding *chalkone* which formed pale yellow prisms, m. p. 213°, having a violet-brown ferric reaction in alcohol (Found : C, 71.9; H, 5.7%). Admixed with the flavanone, this compound melted at about 200°.

7-Hydroxy-5-methoxy-8-methylflavan (XIV).—(a) A mixture of *7-hydroxy-5-methoxy-8-methylflavanone* (0.35 g.), amalgamated zinc (7 g.), acetic acid (25 ml.), and concentrated hydrochloric acid (5 ml.) was kept for 15 hours, and the decanted solution was diluted with water. Crystallised from light petroleum (b. p. 60—80°) containing a little methanol, the resulting precipitate (0.3 g.) gave *7-hydroxy-5-methoxy-8-methylflavan* in colourless stout prisms, m. p. 120°, having a negative ferric reaction in alcohol (Found : C, 75.5; H, 6.8. $C_{17}H_{18}O_3$ requires C, 75.6; H, 6.7%).

(b) Interaction of *7-hydroxy-5-methoxyflavan* (1 g.) and hydrogen cyanide (5 ml.) in ether (150 ml.), saturated with hydrogen chloride, for 24 hours gave a small amount of a crystalline aldimine. The residue left on evaporation of the ethereal reaction mixture was dissolved in ice-water (75 ml.) and the solution heated on the water-bath for 5 minutes, giving *8-formyl-7-hydroxy-5-methoxyflavan* (XIII; R = H) (0.7 g.) which formed massive colourless prisms, m. p. 128° (from methanol), having a violet brown ferric reaction in alcohol (Found : C, 71.9; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.9; H, 5.6%). A small amount of the same compound was obtained by the hydrolysis of the crystalline aldimine. Crystallised from much acetic acid, the 2 : 4-dinitrophenylhydrazone formed slender crimson needles, m. p. 284° (decomp.) (Found : N, 11.9. $C_{23}H_{20}O_7N_4$ requires N, 12.1%).

The reduction of 8-formyl-7-hydroxy-5-methoxyflavan (0.2 g.) with amalgamated zinc (5 g.) in a mixture of acetic acid (25 ml.) and concentrated hydrochloric acid (5 ml.) was complete in $\frac{1}{2}$ hour. The resulting *7-hydroxy-5-methoxy-8-methylflavan* separated from light petroleum containing a little methanol in stout prisms, m. p. 120°, identical with a specimen prepared by route (a). Prepared by either route, the flavan rapidly becomes pink on exposure to atmospheric oxygen.

7-Hydroxy-5-methoxyflavan-8-carboxylic Acid (IV; R = H).—Acetylation of 8-formyl-7-hydroxy-5-methoxyflavan (1 g.) by the pyridine method at room temperature during 24 hours gave the *acetate* (XIII; R = Ac) which separated from light petroleum—benzene in stout colourless prisms or from methanol in rosettes of prisms (1 g.), m. p. 129° (Found : C, 70.0; H, 5.6. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.6%), having a negative ferric reaction and readily reacting with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. Potassium permanganate (1.5 g.), dissolved in water (40 ml.), was added during 1 hour to a solution of this acetate (1 g.) in acetone at 40° and 12 hours later the mixture was decolourised with sulphur dioxide, the acetone was evaporated in a vacuum, and after the addition of a little 2*N*-sulphuric acid the residual liquor was extracted with ether (75 ml. \times 4). The acidic oxidation product was separated from the combined ethereal extracts with aqueous sodium hydrogen carbonate (25 ml. \times 3). Acidification of these washings and isolation of the product with ether (75 ml. \times 3) gave crude *7-acetoxy-5-methoxyflavan-8-carboxylic acid* as a pale yellow glass (0.6 g.) which had a weak ferric reaction in alcohol. Deacetylation of this compound with 10% aqueous potassium hydroxide (10 ml.) during 24 hours gave rise to *7-hydroxy-5-methoxyflavan-8-carboxylic acid* (0.3 g.), forming almost colourless rhombic prisms, m. p. 167°, from methanol (Found : C, 67.9; H, 5.4. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). The properties, including the ferric reaction, of this acid are identical with those of dracoic acid. A mixture of the two compounds melted at 167°. Prepared with ethereal diazomethane, the *methyl ester* separated from methanol in colourless prisms, m. p. 130°, which sublimed unchanged in a high vacuum (Found : C, 68.9; H, 5.6. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%). This ester had the steel-blue ferric reaction exhibited by methyl dracoate and on admixture with this compound, m. p. 145°, melted at 136—138°.

On methylation by the methyl iodide—potassium carbonate method methyl *7-hydroxy-5-methoxyflavan-8-carboxylate* during 6 hours gave an almost theoretical yield of *methyl 5 : 7-dimethoxyflavan-8-carboxylate*, forming colourless needles, m. p. 88°, from aqueous methanol and having a negative ferric reaction (Found : C, 69.5; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%). Mixed with methyl 5 : 7-dimethoxyflavan-6-carboxylate this ester melted at about 70°.

(-)-7-Hydroxy-5-methoxyflavan-8-carboxylic Acid (IV; R = H).—A solution of (±)-7-hydroxy-5-methoxyflavan-8-carboxylic acid (250 mg.) and brucine tetrahydrate (400 mg.) in a mixture of acetone (2 ml.) and methanol (15 ml.) was inoculated with a small crystal of the brucine salt of dracoic acid. 4 Hours later the product, which had separated in rosettes of colourless prisms (100 mg.), m. p. 134° (decomp.), $[\alpha]_D^{20} -46.3^\circ$ (*c*, 0.95 in acetone), was collected and washed with methanol. Decomposition of this salt in acetone (5 ml.) with 2*N*-hydrochloric acid followed by the addition of water (5 ml.) gave (-)-7-hydroxy-5-methoxyflavan-8-carboxylic acid, m. p. 165°, which was esterified by diazomethane. Purified from methanol, this ester formed long, slender, colourless needles, m. p. 140°, alone or mixed with a specimen of methyl dracoate, $[\alpha]_D^{25} -74.0^\circ$ (*c*, 0.19 in chloroform).

The brucine salt of natural dracoic acid was prepared by evaporating a solution of the acid (150 mg.) and brucine tetrahydrate (250 mg.) in acetone (10 ml.). Recrystallised from methanol containing a little acetone, the compound was obtained as a *dihydrate* in rosettes of colourless prisms, m. p. 134° (decomp.), $[\alpha]_D^{25} -53.6^\circ$ (*c*, 0.55 in acetone) (Found: C, 65.9; H, 6.3; N, 4.6. $C_{23}H_{26}O_4N_2, C_{17}H_{16}O_5, 2H_2O$ requires C, 65.7; H, 6.1; N, 3.9%). This salt was identical with the specimen from the synthetical acid and a mixture of the two compounds had m. p. 134° (decomp.).

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