XII.—*Anthoxanthins. Part VIII. A Synthesis of Morin and of* 5 : 7 : 2' : 4'-*Tetrahydroxyflavone.*
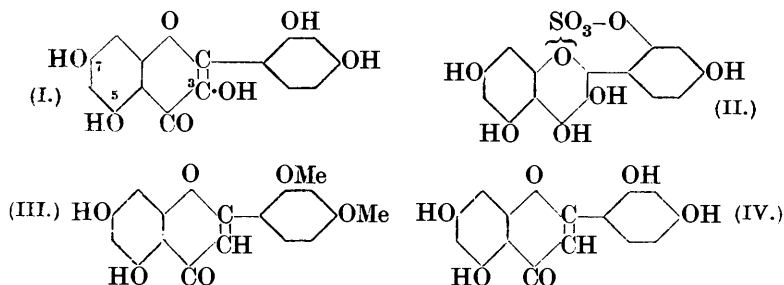
By Robert Robinson and Krishnasami Venkataraman.

The formula $C_{15}H_{10}O_7$ was first assigned to morin, one of the colouring matters of old fustic (the wood of *Chlorophora tinctoria*, Gaudich), by Loewe (*Z. anal. Chem.*, 1875, **14**, 112), and the accepted constitution (I) of the flavonol rests on the researches of Bablich and Perkin (J., 1896, **69**, 792) and on the synthesis by Kostanecki, Lampe, and Tambor (*Ber.*, 1906, **39**, 625). That synthesis did not proceed at all smoothly and therefore it seemed well to include morin in the scope of the application of the more convenient methods of synthesising flavones that have been developed in this series of papers.*

ω-Methoxyphloracetophenone (Slater and Stephen, J., 1920, **117**, 309) was heated with 2 : 4-dimethoxybenzoic anhydride and sodium 2 : 4-dimethoxybenzoate at 180—185°, and the product hydrolysed ;

---

* The earlier parts (J., 1924, **125**, 2192; 1925, **127**, 181, 1968, 1974; 1926, 2334, 2336, 2344) of the investigation were not numbered as such and have dealt *inter alia* with the syntheses of galangin, galangin methyl ether, myricetin, datiscetin, kaempferol, fisetin, quercetin, kæmpferide, *iso*rhamnetin, pratol, chrysin, and acacetin. In view of the contemplated considerable extension of the work which is contemplated, it appears desirable to indicate the connexion between these otherwise isolated papers.

the *morin* 3 : 2′ : 4′-*trimethyl ether* obtained, on demethylation in the usual manner, yielded morin.

O   OH
HO   C   OH
(I.)   5 ^{3}C·OH
HO   CO

SO_3–O
HO   O   OH
OH
HO   OH   (II.)

(III.)   HO   O   OMe
C   OMe
CH
HO   CO

O   OH
HO   C   OH   (IV.)
CH
HO   CO

Perkin and Pate (J., 1895, **67**, 649) showed that morin forms an abnormal sulphuric acid compound, $C_{15}H_{10}O_7,SO_3$, and in view of the fact that other flavonols, *e.g.*, fisetin, quercetin, rhamnetin, and myricetin, give normal sulphates, it is apparent that the hydroxyl group in position 2′ is concerned. Hence the formula (II) probably correctly represents anhydromorin sulphate. The recovery of morin from the derivative shows that no closure of a coumaran ring occurs.

Dunstan and Henry (*Phil. Trans.*, 1901, **194**, 515) suggested that lotoflavin, obtained by the hydrolysis of the cyanogenetic glucoside lotusin, might be 5 : 7 : 2′ : 4′-tetrahydroxyflavone (IV). This flavone has been synthesised by demethylation of its dimethyl ether (III), derived from phloracetophenone by 2 : 4-dimethoxy-benzoylation, but it does not appear to be identical with lotoflavin.

EXPERIMENTAL.

2 : 4-*Dimethoxybenzoic Anhydride.*—In the preparation of β-resor-cylic acid (Kostanecki, *Ber.*, 1885, **18**, 1985) the isolation by ether extraction can be conveniently replaced by separation of the crystals obtained on acidification of the reaction mixture.

A greatly improved yield of 2 : 4-dimethoxybenzoic acid results when the method of Perkin and Schiess (J., 1904, **85**, 189) for the methylation of β-resorcylic acid is modified as follows. Methyl sulphate and concentrated aqueous sodium hydroxide are added alternately to a well-stirred solution of β-resorcylic acid (75 g.) in 10% aqueous sodium hydroxide (700 c.c.) so that a considerable rise of temperature ensues; the addition is stopped when a neutralised test portion gives no violet coloration on the addition of ferric chloride. The mixture is then boiled for an hour, alcohol (200 c.c.) and sufficient sodium hydroxide to maintain a strongly alkaline reaction being added. The acid obtained on acidification of the

cooled liquid is isolated and crystallised from aqueous acetic acid (yield, 82 g. or 92%; m. p. 108°).

The anhydride was not produced when 2 : 4-dimethoxybenzoic acid was boiled for 24 hours with acetic anhydride. It was at first obtained by the action of 2 : 4-dimethoxybenzoyl chloride (best prepared from the acid by means of thionyl chloride) on 2 : 4-dimethoxybenzoic acid in the presence of ether and pyridine, but the method of D.R.-P. 201325 was found to give much better results. It was advantageous to replace the benzene, prescribed as solvent in the patent, by ether. A solution of thionyl chloride (11·9 g.) in ether (50 c.c.) was gradually added with shaking to a suspension of 2 : 4-dimethoxybenzoic acid (36·4 g.) in ether (50 c.c.) and pyridine (15·8 g.), the whole being cooled in melting ice. After 12 hours, crushed ice and dilute hydrochloric acid were added. The anhydride, which separated, was collected, triturated with much very dilute sodium carbonate solution, washed, and dried (yield, 29 g. or 84%; m. p. 76—79°). It crystallised from benzene–ether, ethyl acetate–ether, or light petroleum in large, colourless, rhombic prisms, m. p. 82° (Found : C, 62·3; H, 5·4. Calc. for $C_{18}H_{18}O_7$: C, 62·4; H, 5·2%).

Morin 3 : 2′ : 4′-*Trimethyl Ether.*—As in the preparation of phlor-acetophenone (compare J., 1926, 2347), so in the analogous preparation of ω-methoxyphloracetophenone (Slater and Stephen, *loc. cit.*) it is desirable to add zinc chloride and to keep the reaction mixture for a few days in the ice-chest before separating the ketimine hydrochloride. The ketone is best crystallised from aqueous alcohol and the yield is 75—80%.

A mixture of ω-methoxyphloracetophenone (6 g.), 2 : 4-dimethoxy-benzoic anhydride (50 g.), and sodium 2 : 4-dimethoxybenzoate (12 g.) was heated at 180—185° for 4 hours. The product was dissolved in boiling alcohol (250 c.c.), a solution of potassium hydroxide (30 g.) in water (50 c.c.) added, and the liquid refluxed for 30 minutes and then diluted with water (1000 c.c.). The passage of carbon dioxide caused the slow precipitation of an amorphous brown powder, which was collected and reprecipitated by carbon dioxide from its solution in 2% aqueous potassium hydroxide (yield, 7·3 g.). The *trimethyl ether* was crystallised from 95% alcohol, containing a little acetic acid (charcoal), and then from aqueous alcohol (charcoal) and was obtained in glistening, pale straw-coloured, stout, long, prismatic needles, m. p. 132° (Found : C, 62·4; H, 4·5. $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%). It is moderately readily soluble in most organic solvents on heating, but it is very sparingly soluble in ether and light petroleum. It dissolves in aqueous alkali to yellow solutions and its yellow solution

in concentrated sulphuric acid exhibits a bluish-green fluorescence. The ferric chloride reaction in alcoholic solution is olive-green and addition of lead acetate to an alcoholic solution gives a yellow precipitate.

The pentamethyl ether was obtained by the action of methyl sulphate (4 mols.) and aqueous potassium hydroxide on morin trimethyl ether; the product, twice crystallised from 50% aqueous alcohol, formed colourless feathery needles, m. p. 155—157° (Found : C, 64·3; H, 5·5. Calc. for $C_{20}H_{20}O_7$: C, 64·5; H, 5·4%). The melting point was not depressed on admixture with a specimen of morin pentamethyl ether prepared from morin (Herzig and Hofmann, *Ber.*, 1909, **42**, 155; Perkin and Watson, J., 1915, **107**, 207) and the properties of the two specimens were identical in all respects.

We are greatly indebted to Professor A. G. Perkin, F.R.S., for a specimen of morin from old fustic which has enabled us to make this and other comparisons.

*O-2 : 4-Dimethoxybenzoyl-*O*-acetylmorin* 3 : 2' : 4'-*Trimethyl Ether.* —This substance was produced in an attempt to prepare *O*-diacetyl-*O*-trimethylmorin. The crude product, from which *O*-trimethylmorin can be obtained as described above, was boiled with an excess of acetic anhydride and a drop of pyridine for 2 hours. The derivative was isolated in the usual manner and crystallised from aqueous alcohol in shining colourless needles, m. p. 170° after shrinking at 167° (Found : C, 63·3, 63·1, 63·1; H, 5·0, 5·1, 5·2; MeO, 28·0; $CH_3 \cdot CO$, by the Freudenberg–Weber method, 8·1. $C_{29}H_{26}O_{11}$ requires C, 63·3; H, 4·7; 5MeO, 28·2; $CH_3 \cdot CO$, 7·8%). At the time these micro-analyses were conducted, the values for hydrogen found in many other cases with the same apparatus were about 0·4 unit too high.

It is evident that one of the 2 : 4-dimethoxybenzoyloxy-groups in the original reaction product resists hydrolysis to some extent under the prescribed conditions and that the crude product is a mixture of trimethylmorin and its dimethoxybenzoate.

Morin (I).—A mixture of *O*-trimethylmorin (2·0 g.), hydriodic acid (30 c.c.; *d* 1·7), and acetic anhydride (15 c.c.) was refluxed for 2 hours. The flavonol hydriodide, which separated in minute needles on cooling, was collected, washed with acetic acid, and added to boiling acetic acid (50 c.c.) and after the addition of boiling water (50 c.c.) the whole was quickly filtered; long, pale yellow needles (1·2 g.) separated, m. p. 286—288° after sintering at 281°. The substance was recrystallised from dilute acid without alteration in its properties (Found in material dried at 130° for 6 hours : C, 55·8; H, 3·6. Found after further heating without loss in a high vacuum for 6 hours at 130° : C, 56·0; H, 3·7. $C_{15}H_{10}O_7,H_2O$ requires C,

56·2; H, 3·8%). It thus appears that the substance retains a molecule of water at 130° even in a high vacuum. This behaviour has not been recorded in the case of morin of natural origin. Loewe (*loc. cit.*) states that morin crystallises with $2H_2O$ and loses both molecules of water at 100°.

Our synthetic morin is evidently identical with that of Kosta· necki, Lampe, and Tambor (*loc. cit.*), for the latter had a pale yellow colour and m. p. 290° with decomposition. On the other hand, natural morin is nearly colourless and, according to Bablich and Perkin (*loc. cit.*), melts and decomposes at about 300°. These authors recorded new analyses of morin derivatives but not of morin itself.

A very careful comparison of the solubility relations and of the characteristic reactions of morin disclosed no divergences between the natural and the synthetic specimen. We observed in both cases the qualitative solubilities in organic solvents, the yellow colour and bright bluish-green fluorescence of the solutions in sulphuric acid. the dark olive-green ferric chloride reactions in alcoholic solution. and the change to brown on the addition of water, the formation of lead and barium salts and of salts with mineral acids, the behaviour with magnesium and methyl-alcoholic hydrochloric acid, and the colorations obtained on the addition of sodium amalgam to alcoholic solutions. In this case the solutions are at first yellow and exhibit a yellow fluorescence; the colour slowly changes to bright emerald· green and on dilution the solution exhibits a greenish-yellow fluorescence.

A dye-trial comparison showed that the natural and the synthetic specimen gave identical results on cotton printed with aluminium and iron mordants.

We draw the conclusion from our experiments that the substance synthesised is substantially morin, the properties of which are to some extent modified by the presence of small traces of impurities. This difficulty, which has not been encountered previously in the case of a flavonol synthesis, is probably inherent in the demethyl· ation process. A synthesis of morin not involving demethylation as the final stage is projected.

5 : 7-*Dihydroxy-2′* : 4′-*dimethoxyflavone* (III).—A mixture of phloracetophenone (6 g.), 2 : 4-dimethoxybenzoic anhydride (100 g.), and sodium 2 : 4-dimethoxybenzoate (6 g.) was mechanic- ally stirred at 180—185°, and a further quantity of sodium 2 : 4- dimethoxybenzoate (6 g.) introduced during an hour. The heating was continued for 8 hours, alcohol (350 c.c.) added, and the whole boiled under reflux; a solution of potassium hydroxide (40 g.) in water (50 c.c.) was then introduced and the refluxing continued for

D

30 minutes. Alcohol was removed by distillation under diminished pressure and the residue was dissolved in water and saturated for several hours with carbon dioxide. The crude flavone, a light brown powder (11·8 g.), was redissolved and reprecipitated (10·9 g.) and then dissolved in boiling acetic acid (200 c.c.) and treated with concentrated sulphuric acid (2 c.c.) and boiling water (100 c.c.). After boiling for a few minutes the liquid was filtered, leaving a residue (A). The filtrate was treated with charcoal and again filtered; on cooling, it slowly deposited pale brown, hexagonal plates and rectangular prisms (2·4 g.) that sintered at about 200° and melted at 245—248°. The *flavone* (III) was best recrystallised from aqueous acetic acid containing a little concentrated hydrochloric acid (charcoal) and was ultimately obtained in pale yellow, woolly needles, m. p. 258—259°. The residue (A) crystallised readily from acetic acid (charcoal), in which it was moderately readily soluble at the boiling point and very sparingly soluble in the cold, in pale yellow, woolly needles, m. p. 258—259° (0·8 g.), identical with the specimen previously obtained (Found : C, 63·5; H, 4·6; MeO, 19·3. Found in a recrystallised specimen dried at 140° : C, 63·4; H, 4·6. $C_{17}H_{14}O_6,0·5H_2O$ requires C, 63·2; H, 4·6; MeO, 19·2%). The direct estimation of combined water, the presence of which was proved qualitatively, was vitiated by the sublimation that occurred in a high vacuum at the requisite temperature.

The substance is practically insoluble in boiling water, sparingly soluble in ether, and is moderately readily soluble in boiling alcohol. Alcoholic ferric chloride develops a weak greenish-brown coloration and the solutions in aqueous alkalis are bright yellow. Especially striking is the pure blue fluorescence exhibited by the pale yellow solution in concentrated sulphuric acid.

5 : 7 : 2' : 4'-*Tetrahydroxyflavone* (IV).—A mixture of 5 : 7-dihydroxy - 2' : 4'-dimethoxyflavone (3·1 g.), acetic anhydride (10 c.c.), and hydriodic acid (20 c.c.; *d* 1·7) was boiled for 3 hours and the deep scarlet hydriodide that crystallised was collected, after cooling, on a sintered glass filter and washed with acetic acid. The residue was dissolved in boiling acetic acid, an equal volume of water added, and the crystalline material thus obtained was acetylated by boiling with an excess of acetic anhydride for 4 hours. The derivative crystallised from alcohol in colourless prisms, m. p. 153—156°; after recrystallisation from ethyl acetate it melted at 159°, but some crystals remained unmelted and complete clearing only occurred at 170°. Evidently this apparently homogeneous substance was a mixture, probably containing some triacetate; the ferric chloride reaction was almost negligible. Tests in the Pregl–Zeisel and the Pregl–Herzig–Meyer apparatus proved the

complete absence of methoxyl. The acetate was hydrolysed by means of boiling dilute aqueous alcoholic sodium hydroxide. The almost colourless *flavone* produced crystallised from glacial acetic acid or from alcohol in slender fibrous needles which darkened progressively from 300° and melted at 332—335° with further decomposition (Found in material dried at 160° : C, 62·7; H, 3·6. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%). This isomeride of luteolin differs from it in possessing a much paler yellow colour, just as morin is much more feebly coloured than quercetin ; its dyeing properties are similar to those of apigenin. The pale yellow solution in sulphuric acid exhibits a violet-blue fluorescence.

In these and other properties the substance showed little resemblance to lotoflavin, for a specimen of which we are greatly indebted to Dr. T. A. Henry.

Dye trials on aluminium and iron mordants disclosed great divergences, since lotoflavin proved to be a good dyestuff giving shades generally similar to those from flavonols—it was closest to quercetin—whereas the tetrahydroxyflavone had feeble tinctorial properties.

A solution of lotoflavin in sulphuric acid had a vivid bluish-green fluorescence similar to that produced by morin and it may be that this particular specimen was contaminated by morin, the presence of which masked the exhibition of the properties of $5 : 7 : 2' : 4'$-tetrahydroxyflavone.

Quite recently Cullinane, Algar, and Ryan (*Proc. Roy. Dublin Soc.*, separate issue, Nov., 1928) have described a different synthesis of $5 : 7 : 2' : 4'$-tetrahydroxyflavone (bright yellow plates, decomposing above 270° and giving a greenish-blue fluorescence in sulphuric acid), which, they consider, closely resembles lotoflavin. Definite evidence of identity was not obtained.