CLXXVIII.—*The Methylation of Quercetin.*

By Arthur George Perkin.

Whereas in 1884 Herzig (*Monatsh.*, **5**, 72) observed that quercetin could not be completely methylated by means of methyl iodide and alkali, v. Kostanecki and Dreher, as the result of their experiments with the monohydroxyxanthones (*Ber.*, 1893, **26**, 76), showed that although the methyl ethers of the 2-, 3-, and 4-compounds could be readily prepared by this method, the 1-hydroxyxanthone in which the hydroxyl is adjacent to the carbonyl group was thus not affected. In relation also to the dihydroxyxanthone, chrysin, Kostanecki states (*Ber.*, 1893, **26**, 2901), "Dass im Chrysin beim methyliren ein Hydroxyl unangeriffen bleibt . . . das Hydroxyl welches im Orthostellung steht, sich nicht methyliren lässt." Alizarin (Schunck and Marchlewski, T., 1894, **65**, 185) behaves similarly, and, indeed, this property has been so generally observed in the case of aromatic hydroxy-ketones and acids that the resist-

ance of an hydroxyl group to methylation by this process has in many cases been considered to serve for the detection of a carbonyl group. Although ethyl iodide resembles methyl iodide in this respect, and it appears to have been generally considered that the complete ethylation of such hydroxy-compounds could not be effected by means of this reagent, certain exceptions in this case are to be found in the literature, notably as regards resacetophenone (Gregor, *Monatsh.*, 1894, **15**, 437, and Wechsler, *ibid.*, p. 239) and euxanthone (Graebe and Ebrard, *Ber.*, 1882, **15**, 1678), from which fully ethylated products have been obtained.

More recently it was shown (T., 1902, **81**, 206) that myricetin, an hydroxyquercetin, which without doubt contains an hydroxyl group adjacent to the carbonyl group, readily yields the hexaethyl derivative, and it was accordingly suspected that under suitable conditions a complete ethylation of other flavone colouring matters could also be effected. This proved to be the case, good yields of the fully ethylated derivatives of quercetin, luteolin, apigenin (P., 1912, **28**, 329), gossypetin (this vol., p. 654), and quercetagetin (*ibid.*, p. 209) being obtained by the employment of an excess of ethyl iodide and alkali.

On the other hand, with quercetagetin and gossypetin (*loc. cit.*) it was possible, employing a considerable excess of methyl iodide and alkali, to prepare their fully methylated derivatives, and this was regarded as remarkable because one at least of these compounds must contain an hydroxyl group adjacent to the carbonyl group. It accordingly suggested itself that as in the ethylation process, there was possibly no difficulty in fully methylating compounds of this type, the failures in the past being due to a non-employment of an excess of the reagents, although it was to be borne in mind that whereas in quercetagetin or gossypetin the hydroxyl group adjacent to the carbonyl group is present in a dihydroxyquinol nucleus, in quercetin and the better-known flavones the corresponding group in almost every case is phloroglucinol; thus luteolin (T., 1900, **77**, 1316), with excess of iodide and alkali, gives not only luteolin trimethyl ether, but methylluteolin trimethyl ether, a methyl group having entered the phloroglucinol nucleus, and this behaviour cannot be considered abnormal in view of the well-known properties of phloroglucinol itself under similar conditions. It was accordingly probable that other flavones containing this group would behave similarly rather than yield a compound of the usual type, although remarkably enough only luteolin and the closely allied genistein (*ibid.*, p. 1310) have hitherto been found to give an abnormal result in this respect.

In order to decide this point a study of the methylation of

quercetin, the most readily accessible of all natural yellow colouring matters, has been carried out.

For the preparation of quercetin, commercial flavin, the yellow variety, an extract of quercitron bark, which consists of impure quercitrin, was chiefly employed.* Two hundred grams of the material were exhausted with 1500 c.c. of boiling alcohol, leaving 14 grams of an insoluble, brown powder, the clear liquid being concentrated to 700 c.c. and diluted with 500 c.c. of boiling water. The crystals which were deposited on keeping for several hours were cautiously washed with small amounts of alcohol of increasing dilution, and when dry weighed 145 grams. This product consisted of almost chemically pure quercitrin, and when hydrolysed with boiling 2 per cent. sulphuric acid (20 grams in 1500 c.c.) gave practically a theoretical yield of quercetin.

Twenty grams of quercetin in 220 c.c. of methyl alcohol and 120 c.c. of methyl iodide were boiled with a solution of 40 grams of potassium hydroxide in 150 c.c. of methyl alcohol, 5 c.c. at a time during two days. The yellow, creamy mass of potassium quercetin at first formed gradually disappeared; after about six hours a clear liquid usually resulted, and at the close of the operation the addition of fresh alkali gave little or no colour change. After removal of unattacked methyl iodide and the greater portion of the alcohol by distillation, the residue was diluted with water, the mixture extracted with ether, and the ethereal solution washed with dilute alkali, the aqueous liquid and alkaline washings (*A*) being reserved for examination. On concentrating the ether, crystals gradually separated; these were collected, crystallised twice from acetone, and repeatedly from pyridine until a constant melting point was obtained. The yield of pure substance was approximately 1 gram.

Found: C = 65·10; H = 5·98; CH_3 = 19·30.

$C_{21}H_{22}O_7$ requires C = 65·28; H = 5·70; CH_3 = 19·43 per cent.

This compound melts at 213—215°, is insoluble in alkali, gives no colour change with alcoholic potassium hydroxide, and is evidently completely methylated. It is distinguished by its sparing solubility in ordinary solvents.

The ethereal mother liquor on evaporation gave a yellow, crystalline residue, which was a mixture of substances. By a fractional crystallisation from alcohol, discarding the more insoluble portion, the main product was isolated as yellow prisms (1·5 grams), which sintered at 170° and melted at 176—178°. Suspecting that it was still impure, it was acetylated with boiling acetic anhydride, an

* Quercetin from rutin has also been employed for one experiment with results similar to those given by the quercitron bark preparation.

operation which could not be safely accomplished under three hours. Addition of alcohol caused the separation of colourless needles, which by crystallisation first from acetone and finally from acetic acid melted at 178—180°.

Found: $CH_3 = 14{\cdot}38$.

$C_{20}H_{19}O_7(C_2H_3O)$ requires $CH_3 = 14{\cdot}49$ per cent.

The acetyl derivative was now hydrolysed with boiling dilute alcoholic potassium hydroxide, and the product was isolated, by dilution with water and acidification, as pale yellow needles melting at 184—185°.

Found: $C = 64{\cdot}40$; $H = 5{\cdot}42$; $CH_3 = 16{\cdot}31$.

$C_{15}H_5O_3(CH_3)(O{\cdot}CH_3)_4$ requires $C = 64{\cdot}51$; $H = 5{\cdot}38$; $CH_3 = 16{\cdot}13$ per cent.

This substance resembles quercetin tetramethyl ether (m. p. 156—157°), but differs from it in melting point and by its more sparing solubility in solvents. With 80 per cent. alcoholic potassium hydroxide it yields a bright yellow potassium salt crystallising in needles, and this is decomposed by water with separation of the original compound.

In order to study the hydrolysis of this compound, 0·87 gram was digested with a boiling solution of 1·8 grams of potassium hydroxide in 9 c.c. of 80 per cent. alcohol for several hours, but as little action had thus occurred, the mixture was heated in a sealed tube to 185° for two and a-half hours. The product was evaporated to dryness, the residue dissolved in water, and the solution treated with carbon dioxide, which then gave to ether a small amount of a colourless, viscid, phenolic substance, readily soluble in the usual solvents. In order to identify this compound it was dissolved in dilute sodium carbonate, the solution treated with benzenediazonium sulphate, and the red precipitate of the azobenzene compound, collected, and crystallised from alcohol. It separated as a spongy mass of orange-red needles, melting at 199—201°, and was recognised as identical with the compound obtained in a similar way from the phenolic product of the hydrolysis of methyl-luteolin trimethyl ether (*loc. cit.*), which, with little doubt, is bisbenzeneazomethylphloroglucinol monomethyl ether. The acid product of the hydrolysis isolated in the usual manner melted at 180—182°, and consisted of veratric acid.

Evidently, therefore, this product of the methylation of quercetin which melts at 184—185° is *methylquercetin tetramethyl ether*, and it is accordingly evident that quercetin and luteolin exhibit a similar behaviour when methylated with an excess of methyl iodide and alkali, in that a methyl enters the phloro-

glucinol nucleus of both compounds. The composition and properties of the more sparingly soluble substance, $C_{21}H_{22}O_7$, melting at 213—215°, are in agreement with the suggestion that it is the further methylation product of the compound melting at 184—185°, and is in reality *methylquercetin pentamethyl ether*.

In order to determine if this compound when hydrolysed gives products analogous to those obtained from quercetin pentamethyl ether, which on this assumption should be the case, 0·4 gram was digested with a boiling solution of 2 grams of potassium hydroxide in 80 per cent. alcohol for six hours. After removal of the alcohol the residue was dissolved in a little water, and treated with carbon dioxide, which caused the separation of a colourless, crystalline precipitate; this crystallised from alcohol in fine needles, melting at 148—149°; and in appearance and general properties resembled the methoxyfisetol dimethyl ether, melting at 102—104°, which Herzig (*Ber.*, 1909, **42**, 155) obtained in a similar way from quercetin pentamethyl ether. It is, however, somewhat more sparingly soluble than the latter in solvents, and is to be regarded as *methoxymethylfisetol dimethyl ether*. The acid product of the hydrolysis melted at 180—182°, and consisted of veratric acid. Little doubt can be therefore entertained that the constitution above suggested for the compound $C_{21}H_{22}O_7$ is correct.

By demethylation with hydriodic acid both the tetra- and penta-methyl ethers should give methylquercetin, and this is probably the case. The products obtained in this manner crystallised from dilute alcohol in pale yellow needles, and as was to be anticipated closely resembled quercetin itself, but the amount of substance available was not considered to be sufficient for an accurate comparison of the two substances.

The final mother liquors obtained during the purification of the methylquercetin tetramethyl ether yielded a small amount of quercetin tetramethyl ether, which was identified by its melting point and general properties.

The products, soluble in ether, of the methylation above described, averaged merely 15 per cent. by weight of the quercetin originally employed, and it accordingly became evident that a considerable amount of substance must have been retained in solution by the aqueous liquid (*A*).

Although after remaining for several days it was observed in one experiment that the solution had deposited a small amount of crystalline matter; in other cases this remained almost perfectly clear for long periods. By saturation with salt, however, a voluminous, curdy precipitate separated, which on keeping somewhat increased in quantity, and this was collected, washed with salt

solution, and thoroughly drained on a porous tile. By crystallisation from acetone it was obtained in colourless needles, melting at 150—151°. The yield averaged 10 grams.

Found: C = 64·43; H = 5·72; CH_3 = 20·07.

$C_{15}H_5O_2(O{\cdot}CH_3)_5$ requires C = 64·51; H = 5·38; CH_3 = 20·16 per cent.

It evidently consisted of quercetin pentamethyl ether, and full proof as to its identity was obtained by an examination of the products of its hydrolysis with alcoholic potassium hydroxide, which, as anticipated, proved to consist of veratric acid and the methoxyfisetol dimethyl ether melting at 102—103°.

There is accordingly no difficulty in obtaining from quercetin by means of methyl iodide and alkali considerable amounts of its fully methylated derivative, and it is evident that the presence of the phloroglucinol nucleus does not affect this reaction beyond exerting a tendency to cause the formation of a trifling quantity of the corresponding methyl compound. It is indeed probable that quercetin pentamethyl ether is in reality formed when much smaller amounts of the reagents are employed, but that the peculiar property it possesses of remaining dissolved, probably as a colloid when the methylation product is treated with much water, has escaped the attention of previous workers. Again, Herzig (*loc. cit.*), who prepared this substance with methyl sulphate by the ordinary method, obtained a yield of only 25 per cent., owing, no doubt, to this cause. Possibly a failure to isolate the corresponding derivative of such other flavones, as chrysin, apigenin, and luteolin, is similarly to be accounted for, because there can now be no reason to infer that fully methylated compounds cannot be prepared by this method owing to the presence of an hydroxyl group adjacent to the carbonyl group. Indeed, during the preparation of apigenin dimethyl ether (T., 1900, **77**, 416) the presence of a second compound insoluble in alkali, probably apigenin trimethyl ether, was detected. Further experiments on the methylation of these and other hydroxyketonic compounds will be carried out as soon as opportunity occurs.

An account of a study of the ethylation products of quercetin, apigenin and luteolin has been already described (P., 1912, **28**, 329), although details of the procedure employed have not previously been given. This, it may here be pointed out, was practically identical with that found serviceable for the methylation of quercetin, 5 grams of the substance in 60 c.c. of alcohol and 30 c.c. of ethyl iodide being treated at the boiling temperature with a solution of 10 grams of potassium hydroxide in alcohol during two days, a gradual addition of the alkali being adopted to avoid

hydrolysis of the ethylated product which occurs to some extent when this reagent is added all at once. The ethylated compounds are soluble in ether, and can thus be readily isolated.

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