31. *Synthesis of the Monomethyl Ethers of Kaempferol, and the Constitution of Rhamnocitrin.*

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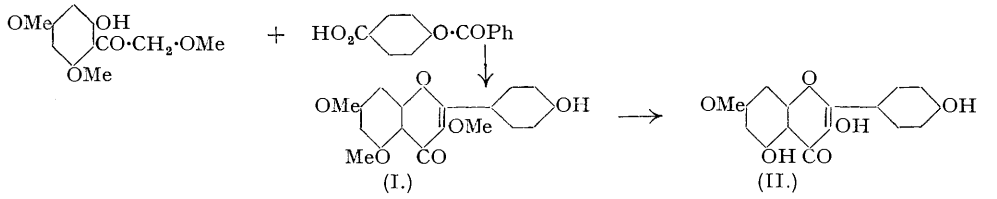
The 3- and 7-monomethyl ethers of kaempferol (3 : 5 : 7 : 4′-tetrahydroxyflavone) have been newly synthesised and the 4′-methyl ether (kaempferide) prepared by a procedure different from that of Heap and Robinson. The 7-methyl ether is identical with rhamnocitrin. The 3-methyl ether is named "*iso*kaempferide".

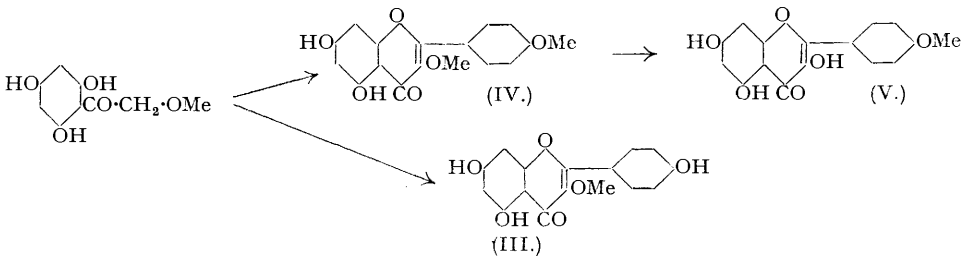
The constitution of kaempferide, a component of galanga root, was confirmed as kaempferol 4′-methyl ether by synthesis (Heap and Robinson, *J.*, 1926, 2336). Tschirch and Polacco (*Arch. Pharm.*, 1900, **238**, 459) gave the name rhamnocitrin to one of the compounds isolated from the berries of *Rhamnus catharticus*; later, Oesch and Perkin (*J.*, 1914, **105**, 2350) determined its composition and showed that it was another monomethyl ether of kaempferol, although it bore considerable resemblance to kaempferide: it crystallised in yellow leaflets, m. p. 221—222°, and its acetyl derivative had m. p. 200—201°, whereas kaempferide crystallised as yellow needles, m. p. 227—229°, and its acetate melted at 193—194°. Oesch and Perkin, however, suggested that further work on this subject was desirable, and we now give synthetic evidence on the matter. We have prepared the 3- and the 7-methyl ether of kaempferol, and for comparison, we have made the 4′-methyl ether by partial demethylation of the 3 : 4′-dimethyl ether.

For the synthesis of the 7-methyl ether (II), 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone was condensed with the potassium salt and anhydride of *p*-benzoyloxybenzoic acid according to the method of Allan and Robinson, and the resulting 4′-*hydroxy*-3 : 5 : 7-*trimethoxyflavone* (I) afforded (II) on partial demethylation with aluminium chloride in nitrobenzene solution.



When ω-methoxyphloroacetophenone is used for the condensation with the same anhydride and potassium salt, the 3-*methyl ether* of kaempferol (III) is directly obtained. By using anisic acid instead, the 3 : 4′-dimethyl ether (IV) (Robinson and Shinoda, *J.*, 1925, **127**, 1973) is produced and this is converted into the 4′-monomethyl ether (V) by partial demethylation. This compound was originally synthesised by Heap and Robinson (*loc. cit.*) from ω-benzoyloxyphloroacetophenone and anisic acid.

Of the three monomethyl ethers, (II) agrees entirely with rhamnocitrin in all its properties. This formulation for rhamnocitrin is also in accordance with expectation, since it occurs in the



berries of *Rhamnus catharticus* along with rhamnetin, the 7-methyl ether of quercetin, the free flavonols kaempferol and quercetin being the other components (Oesch and Perkin, *loc. cit.*). The 5-monomethyl ether would not be expected to occur in Nature since this position is difficult to methylate, and hence it has not been taken into consideration here. Though the 3-methyl ether (III) has not so far been identified among natural products, it may occur just like the 3-methyl ether of galangin present in the galanga root. It is therefore assigned the name of "*iso*kaempferide".

Experimental.

p-*Benzoyloxybenzoic Acid.*—By Schotten–Baumann benzoylation of *p*-hydroxybenzoic acid (10 g.) with benzoyl chloride (10 c.c.), 15 g. of the benzoyl acid were obtained. It crystallised from alcohol as colourless needles, m. p. 221—223° (Found: C, 69·5; H, 4·3. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%).

Anhydride. The acid (10 g.) was suspended in dry carbon tetrachloride (25 c.c.) and treated with portions of phosphorus pentachloride while being heated on a water-bath till a clear solution resulted. The solvent and phosphorus oxychloride were distilled off under reduced pressure and the crude acid chloride (8·5 g.) was taken up in anhydrous ether (400 c.c.). Dry pyridine (50 c.c.) was added to the ethereal solution, which was kept at 0° for 3 hours; small pieces of ice and ice-cold dilute hydrochloric acid were then added, with stirring. The solid *product* was filtered off, macerated successively with cold dilute hydrochloric acid, aqueous sodium carbonate, and cold water, and dried in the vacuum desiccator; it (7 g.) crystallised from dry benzene in rectangular prisms, m. p. 155—157° (Found: C, 72·5; H, 4·2. $C_{28}H_{18}O_7$ requires C, 72·1; H, 3·9%).

Potassium salt. This was prepared by adding alcoholic potash dropwise to a solution of the dry acid in absolute alcohol–ether, using phenolphthalein as indicator. The precipitated potassium salt was filtered off, washed with ether, and dried in a vacuum desiccator.

4′-Hydroxy-3 : 5 : 7-trimethoxyflavone (I).—An intimate mixture of 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone (1 g.), *p*-benzoyloxybenzoic anhydride (5 g.) and potassium *p*-benzoyloxybenzoate (2 g.) was heated in a vacuum at 180—185° for 3 hours. The resulting solid cake was powdered and refluxed with 10% alcoholic potash (50 c.c.) for 20 minutes, giving a clear solution. The solvent was then distilled off under reduced pressure, and the product dissolved in water (150 c.c.). The clear brown solution was saturated with carbon dioxide and a yellow solid separated in good yield. It was filtered off and washed with water; yield, 1 g. This *flavone* was very sparingly soluble in benzene, ethyl acetate, or alcohol and moderately soluble in glacial acetic acid, from which it crystallised in pale yellow, rhombic plates and prisms, m. p. 278—280° (Found: C, 65·9; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). It was readily soluble in aqueous sodium hydroxide to give a yellow solution and did not give any characteristic coloration with ferric chloride. In concentrated sulphuric acid it exhibited a greenish-blue fluorescence.

On acetylation by means of acetic anhydride and a few drops of pyridine it yielded the *acetate*, which crystallised from methyl alcohol as colourless needles, m. p. 147—149° (Found: C, 64·7; H, 4·5. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). On methylation by methyl sulphate and anhydrous potassium carbonate in dry acetone, (I) yielded the methyl ether, which was insoluble in aqueous sodium hydroxide. This crystallised from benzene–light petroleum in colourless, rectangular plates, m. p. 165—166°, not depressed in admixture with an authentic sample of kaempferol tetramethyl ether. The compound gave a bright greenish-blue fluorescence in concentrated sulphuric acid.

3 : 5 : 4′-Trihydroxy-7-methoxyflavone (*Rhamnocitrin*) (II).—The trimethyl ether (I) (0·5 g.), dissolved in dry nitrobenzene (15 c.c.), and aluminium chloride (1 g.) in the same solvent were heated at 100° for 1 hour, and the mixture cooled and treated with excess of light petroleum (100 c.c.). The precipitated yellowish-brown solid was filtered off under suction and washed free from nitrobenzene with light petroleum. The residual aluminium chloride complex was then decomposed by heating with dilute hydrochloric acid (100 c.c.) on a water-bath for ½ hour. The bright yellow solid was collected, washed with water, and crystallised successively from ethyl acetate–light petroleum and methyl alcohol, separating from the latter as yellow leaflets, m. p. 220—222° (Found: C, 63·8; H, 4·2; OMe, 10·2. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0; OMe, 9·7%). This product was easily soluble in alcohol and ethyl acetate and sparingly in toluene. In aqueous sodium hydroxide it formed a yellow solution. With alcoholic ferric chloride an olive-green colour was produced, and with lead acetate an orange-yellow precipitate was formed. In concentrated sulphuric acid it exhibited a brilliant peacock-blue fluorescence.

The acetate (acetic anhydride and pyridine) crystallised from absolute alcohol–light petroleum in colourless, rectangular plates, m. p. 200—201°.

5 : 7 : 4′-*Trihydroxy*-3-*methoxyflavone* (iso***Kaempferide***) (III).—An intimate mixture of ω-methoxyphloroacetophenone (1 g.) and the anhydride (10 g.) and potassium salt (3 g.) of *p*-benzoyloxybenzoic acid was heated at 180—185° for 3 hours. The solid product was finely powdered, and hydrolysed by refluxing with 10% alcoholic potash (150 c.c.) for 20 minutes, whereby a clear solution resulted. After removal of solvent under reduced pressure, the residue was dissolved in water (200 c.c.), and the clear brown solution saturated with carbon dioxide. A dark brown solid separated and this as well as the solution was repeatedly extracted with ether. On distillation of solvent from the extract a light cream-coloured solid was obtained. iso*Kaempferide* was purified by crystallising twice from ethyl alcohol, forming tiny, rectangular plates, m. p. 270—272° (Found : C, 64·3; H, 4·4. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). It was easily soluble in aqueous sodium hydroxide to give a bright yellow solution, and gave a brown colour with ferric chloride; no precipitate was formed with lead acetate. In concentrated sulphuric acid it produced a feeble blue fluorescence.

The *acetate*, prepared in the usual manner, crystallised from ethyl acetate–light petroleum in colourless needles, m. p. 161—163° (Found : C, 61·8; H, 4·2. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·2%).

3 : 5 : 7-*Trihydroxy*-4′-*methoxyflavone* (***Kaempferide***) (V).—5 : 7-Dihydroxy-3 : 4′-dimethoxyflavone (IV) (Robinson and Shinoda, *loc. cit.*) (0·5 g.) was partly demethylated exactly as in the preparation of rhamnocitrin (above), and the yellow solid finally obtained crystallised from methyl alcohol as golden-yellow needles, m. p. 227—229° (Found : C, 63·9; H, 4·0. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). It was soluble in aqueous sodium hydroxide to a yellow solution. It gave a greenish-brown colour with ferric chloride and a yellow precipitate with lead acetate in alcoholic solution. In concentrated sulphuric acid it gave a bright bluish-green fluorescence. The acetate, crystallised from methyl alcohol, formed colourless, narrow, rectangular plates, m. p. 191—193°.

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