VI.—*Natural Glucosides. Part I. The Constitution of Phloridzin.*

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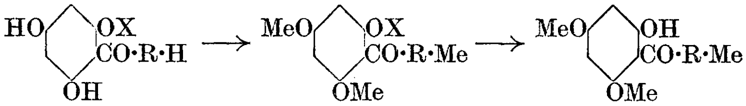
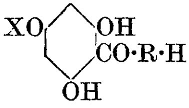
THE glucoside phloridzin, which occurs in the bark of apple, pear, plum, and cherry trees, was first isolated in 1835 by De Koninck (*Annalen*, **15**, 75, 258) from the root bark of the apple tree, and was correctly analysed by Stas (*Ann. Chim. Phys.*, 1836, **61**, 367), who found that it was decomposed by mineral acids into phloretin and a sugar which he believed to be glucose. The glucoside was subsequently examined by a number of workers and the empirical formula $C_{21}H_{24}O_{10},2H_2O$ was established by Rennie (J., 1887, **51**, 634), who effected the hydrolysis by dilute sulphuric acid with the production of phloretin, $C_{15}H_{14}O_5$, and glucose. The latter result was confirmed independently by Fischer (*Ber.*, 1888, **21**, 988) and by Schunck and Marchlewski (*Ber.*, 1893, **26**, 942; *Annalen*, 1894, **278**, 349). A synthesis of phloretin by Fischer and Nouri (*Ber.*, 1917, **50**, 611) definitely established its constitution (compare Zemplén and co-workers, *Ber.*, 1928, **61**, 2486; Rosenmund and Rosenmund, *ibid.*, p. 2608). That the glucose residue of phloridzin is attached to the phloroglucinol nucleus was shown by Cremer and Seuffert (*Ber.*, 1912, **45**, 2565), who, by the action of warm baryta water, obtained phloretic acid and phlorin, phloroglucinol β-glucoside. This glucoside had previously been synthesised by Fischer and Strauss (*Ber.*, 1912, **45**, 2467).

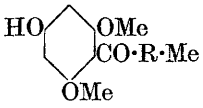
As the result of previous work, phloridzin may be represented by formula (I) or (II), and therefore should, on methylation of the phenolic hydroxyl groups and hydrolysis of the product, give a *trimethylphloretin* (IV or V). The glucoside was methylated in acetone solution by means of methyl iodide and anhydrous potassium carbonate, a method which has been shown by Robinson (J., 1928, 1457) to effect the methylation of *O*-benzoylphloroglucinaldehyde. In order to ensure complete alkylation of the phenolic groups, prolonged treatment with an excess of the methylating agents was essential. The product, which gave no evidence of the presence of an unprotected phenolic hydroxyl group, appeared to be partly methylated in the sugar residue and could not be purified. Hydrolysis of the crude material, however, with aqueous methyl-alcoholic sulphuric acid gave 6-*hydroxy*-2 : 4 : 4′-*trimethoxy*-β-*phenylpropiophenone* (IV); the filtrates containing the sugar residue were not examined. In a subsequent experiment the alkylation was stopped when a sample of the product no longer gave a ferric chloride reaction: a crystalline *hydrate* of *trimethylphloridzin* (III) was isolated which gave the ketone (IV) on hydrolysis. Methylation of phloridzin in a methyl-alcoholic–ethereal solution with diazomethane and hydrolysis of the product also gave (IV).



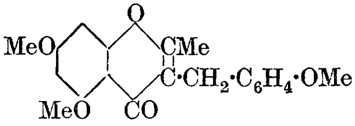
(I.) (III.) (IV.)



(II.)



(V.)



(VI.)

[$X = C_6H_{11}O_5$; $R = \cdot CH_2\cdot CH_2\cdot C_6H_4\cdot O\cdot$]

The orientation of the ketone (IV) is established by ring closure with sodium acetate and acetic anhydride to the 1 : 4-*benzopyrone* (VI). The conclusion that this product is a benzopyrone and not a coumarin is based mainly on the behaviour of analogous ketones under the same conditions (Kostanecki and Różycki, *Ber.*, 1901, **34**, 107; Crabtree and Robinson, J., 1918, **113**, 859; Robinson and co-workers, J., 1929, 61, 152, which see for further references). Ciamician and Silber (*Ber.*, 1894, **27**, 1627; 1895, **28**, 1393), however, by acetylating phloretin, obtained a substance which they believed to be a coumarin. In any case ring closure can take place only if there is a hydroxyl group in the *o*-position to carbonyl in the hydroxytrimethoxy-β-phenylpropiophenone obtained by hydrolysis of the methylated glucoside. The constitution of phloridzin is therefore represented by formula (I).

The experimental proof of the constitutions of (VI) and of

Ciamician and Silber's product (*loc. cit.*) will be the subject of a future communication.

The compound (IV) was prepared by an independent method: condensation of phloroglucinol dimethyl ether and β-4-*methoxyphenylpropionitrile* by the method of Hoesch produced a mixture of ketimine hydrochlorides which, on hydrolysis and separation, gave (IV) and the *isomeride* (V) in almost equal quantities.

Convenient methods for the preparation of *p*-methoxycinnamic acid (compare Perkin, J., 1877, **31**, 408; Einhorn, *Annalen*, 1883, **243**, 363; Knoevenagel, *Ber.*, 1898, **31**, 2606) and of β-4-methoxyphenylpropionyl chloride (compare Barger and Walpole, J., 1909, **95**, 1723) are described. Dehydration of β-4-methoxyphenylpropionamide (Barger and Walpole, *loc. cit.*) with thionyl chloride gave the *nitrile*.

EXPERIMENTAL.

Methylation of Phloridzin. Trimethylphloridzin.—(A) Methyl iodide (14 c.c.) was added to a solution of phloridzin (15 g.) in dry acetone (80 c.c.) containing powdered potassium carbonate (25 g.) in suspension, and the mixture refluxed for 40 hours; a further quantity of iodide (28 c.c.) was added in two portions at intervals of 10 hours. After separation from potassium salts the mixture was acidified with acetic acid and the acetone and the excess of methyl iodide were removed by distillation. The pale straw-coloured viscous residue, which could not be crystallised, was insoluble in cold 10% alkali solution and did not give a ferric chloride reaction. A solution of the product in a mixture of 50% methyl alcohol (120 c.c.) and 15% sulphuric acid (50 c.c.) was refluxed for 20 minutes; on cooling, 6-*hydroxy*-2 : 4 : 4′-*trimethoxy*-β-*phenylpropiophenone* (IV) separated, which crystallised from alcohol in colourless squat prisms (7·2 g.), melting at 110° [Found: C, 68·5; H, 6·3; OMe, 29·4. $C_{15}H_{11}O_2(OMe)_3$ requires C, 68·3; H, 6·4; OMe, 29·4%]. This substance is slightly soluble in methyl alcohol and insoluble in warm water and in cold 2% aqueous sodium hydroxide solution. Ferric chloride added to an alcoholic solution gives a wine-red coloration. Acetylation with acetic anhydride and sodium acetate on the steam-bath during 3 hours gave the *acetyl* derivative, which separated from warm methyl alcohol in rhombic prisms, m. p. 62—63° (Found: C, 67·3; H, 6·2. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·9%). It is readily soluble in warm alcohol and in ether, and does not give a ferric chloride reaction. Hydrolysis in alcohol with a little concentrated potassium hydroxide solution gave the parent ketone (III).

Phloridzin (10 g.) in acetone (50 c.c.) was methylated during 20 hours with methyl iodide and potassium carbonate. The product, isolated as before, solidified, but separated from warm benzene as an oil which gradually crystallised [Found in material dried at 110° : OMe, 20·7. $C_{21}H_{21}O_7(OMe)_3$ requires OMe, 19·5%]. Repeated crystallisation from warm water (charcoal) gave a *monohydrate* of *trimethylphloridzin* (III) in colourless elongated prisms, m. p. 63—65° after softening at 60° [Found in material dried at 110° : C, 60·2; H, 5·9; OMe, 19·8. $C_{21}H_{21}O_7(OMe)_3$ requires C, 60·2; H, 6·3; OMe, 19·5%. Found : loss on drying at 110°, 7·5. A monohydrate requires loss, 7·0%]. The hydrate is readily soluble in alcohol and does not give a ferric chloride reaction. Hydrolysis gave (IV), m. p. and mixed m. p. 110°.

(B) Diazomethane (3·5 g.) in dry ether (400 c.c.) was added to a solution of anhydrous phloridzin (5 g.) in absolute methyl alcohol (70 c.c.). A brisk evolution of nitrogen ensued and after 12 hours the ether and alcohol were removed under diminished pressure. The residual syrup, which was readily soluble in alcohol and in warm water and did not give a ferric chloride reaction, could not be crystallised. The crude product on hydrolysis with aqueous methyl-alcoholic sulphuric acid gave (IV), m. p. and mixed m. p. 110° after crystallisation from alcohol.

5 : 7 : 4′-*Trimethoxy*-3-*benzyl*-2-*methyl*-1 : 4-*benzopyrone* (VI).—A mixture of the ketone (IV) (6·5 g.), acetic anhydride (100 c.c.), and fused sodium acetate (40 g.) was heated at 180° for 16 hours. Water (400 c.c.) was then added to the cooled mixture and after 3 days the semi-solid product which had separated was extracted with ether. The *benzopyrone* (VI) remained as an insoluble residue, which crystallised from alcohol (charcoal) in clusters of colourless needles, m. p. 165—166° (Found : C, 70·7; H, 6·0. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). It is soluble in cold concentrated sulphuric acid to a colourless solution exhibiting a blue fluorescence in the light of a carbon arc, and in warm concentrated hydrochloric acid to a pale straw-coloured solution. An alcoholic solution is non-fluorescent.

The ether-soluble fraction of the reaction mixture consisted mainly of impure acetyltrimethylphloretin, which, on being refluxed with acetic anhydride and sodium acetate at 180° for 18 hours, gave a further quantity of the benzopyrone, m. p. 165—166°.

β-4-*Methoxyphenylpropionamide*.—A mixture of anisaldehyde (50 g.), malonic acid (45 g.), pyridine (150 c.c.), and piperidine (0·5 c.c.) was heated on the steam-bath for 9 hours and then under reflux for 2 hours. After dilution with water (400 c.c.) and acidification with concentrated hydrochloric acid (300 c.c.), it deposited *p*-methoxycinnamic acid (47 g.), which crystallised from alcohol in colourless needles, m. p. 186—187° after sintering to an opaque mass at 169—171°. Reduction with sodium amalgam gave an almost theoretical yield of β-4-methoxyphenylpropionic acid, m. p. 101—103° (Perkin, *loc. cit.*).

β-4-Methoxyphenylpropionyl chloride was prepared by warming a mixture of the acid (60 g.) and thionyl chloride (84 c.c.) on the steam-bath until the evolution of hydrogen chloride ceased. The excess of thionyl chloride was removed by distillation, the residual acid chloride dissolved in benzene (120 c.c.), and the solution saturated with ammonia; the amide (32 g.) then separated, m. p. 123—124° after crystallisation from water (compare Barger and Walpole, J., 1909, **95**, 1723).

β-4-*Methoxyphenylpropionitrile.*—A mixture of β-4-methoxyphenylpropionamide (31 g.) and thionyl chloride (45 c.c.) was heated under reflux for 1 hour. The excess of thionyl chloride was removed by distillation and an ethereal solution of the residue was washed with dilute sodium carbonate solution and then with water. The dried solution was freed from solvent and the resulting oil, on distillation under diminished pressure, gave the *nitrile* (16 g.) as a colourless oil, b. p. 172—173°/17 mm. (Found: C, 74·1; H, 7·0; N, 8·6. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·9; N, 8·7%).

Condensation of β-4-*Methoxyphenylpropionitrile with Phloroglucinol Dimethyl Ether.*—A solution of phloroglucinol dimethyl ether (13·8 g.) and β-4-methoxyphenylpropionitrile (14·5 g.) in dry ether (160 c.c.) was saturated with dry hydrogen chloride at 0° in the presence of anhydrous zinc chloride (7 g.). The mixed ketimine hydrochlorides separated as a semi-solid and after 4 days a further quantity was precipitated on the addition of dry ether (500 c.c.). A suspension of the mixture in water (250 c.c.) was heated on the steam-bath for 15 minutes; on cooling, the product solidified. Ethyl acetate extracted the ketone (IV) (6·5 g.), which crystallised from alcohol in squat prisms, m. p. and mixed m. p. 110° (Found: C, 68·2; H, 6·4%). Acetylation with acetic anhydride and sodium acetate at 100° gave the acetyl derivative, m. p. and mixed m. p. 62—63°. The latter, on being heated with acetic anhydride and sodium acetate at 180° for 18 hours, was converted into the benzopyrone (VI), which separated from warm alcohol in clusters of colourless needles, m. p. and mixed m. p. 165—166°.

The residue insoluble in ethyl acetate consisted of unchanged ketimine hydrochloride and was readily soluble in warm alcohol, from which it separated in colourless prisms on the addition of an excess of ethyl acetate. It was hydrolysed by boiling for 2 hours with water (300 c.c.). A solution of the solid product in cold 2%

aqueous sodium hydroxide (filtered to remove traces of insoluble impurities), on acidification with concentrated hydrochloric acid, gave 4-*hydroxy*-2 : 6 : 4′-*trimethoxy*-β-*phenylpropiophenone* (V) (8 g.), which, on recrystallisation from 70% methyl alcohol and then from benzene, was obtained in colourless rectangular plates, m. p. 142° (Found : C, 68·2 ; H, 6·4. $C_{18}H_{20}O_5$ requires C, 68·4 ; H, 6·3%). It is more readily soluble in alcohol and in benzene than the isomeric ketone (IV) and does not give a ferric chloride reaction. The acetyl derivative could not be crystallised.

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