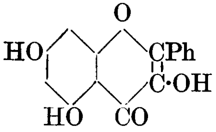
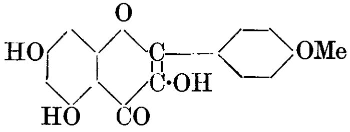
CCCX.—*A Synthesis of Kaempferide and of* iso-*Rhamnetin.*

By Tom Heap and Robert Robinson.

The new direct method of preparation of flavonol derivatives has up to the present been restricted to the synthesis of members of the series which have a methoxyl group situated in position 3 in the pyrone nucleus. We have now devised a modification applicable to the synthesis of 3-hydroxyflavones without demethylation and have employed the process in the synthesis of galangin (I), kaempferide (II), and *iso*rhamnetin (III).

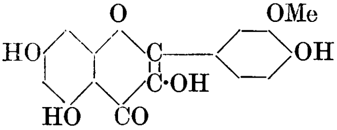
(I.)





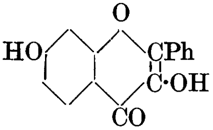
(II.)

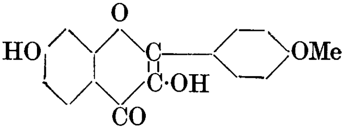
(III.)



The first experiments were made with resorcinol derivatives and it was found that the protection of hydroxyl groups could be most satisfactorily effected by benzoylation. Ethylcarbonato-derivatives were not found to be sufficiently stable and the use of acetates was prohibited by the experience of Kalff and Robinson (J., 1925, **127**, 1972) who noted that *o*-acetoxybenzoic anhydride as a component in an attempted flavonol synthesis led to the formation of a 2-methylchromone derivative. *ω-Benzoyloxyresacetophenone* (IV) is obtained by a Hoesch reaction from benzoyloxyacetonitrile, $CH_2(OBz)\cdot CN$ (Aloy and Rabaut, *Bull. Soc. chim.*, 1913, **13**, 457), and resorcinol. On benzoylation and anisoylation followed by hydrolysis, resogalangin (V) and resokaempferide (VI) were respectively obtained.

(V.)

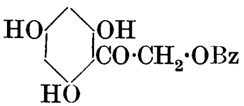


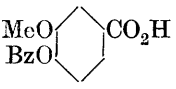


(VI.)

The analogous preparation of *ω-benzoyloxyphloracetophenone* (VII) involved experimental difficulties, but these having been overcome, benzoylation and anisoylation followed by hydrolysis, afforded galangin (I) and kaempferide (II) respectively.

(VII.)





(VIII.)

The synthetical kaempferide had m. p. 225° and its triacetyl derivative had m. p. 193—194°. Jahns (*Ber.*, 1881, **14**, 2385) was the first to obtain the pure substance from galangal root and assigned the m. p. 221—222°. Ciamician and Silber (*Ber.*, 1899, **32**, 861) gave the m. p. 227—229° for the flavonol, and 193—195° for its triacetate. Testoni (*Gazzetta*, 1900, **30**, ii, 327) stated that the triacetyl derivative melted at 193—194°. We were unable to obtain a specimen of the natural product but the properties of kaempferide and its derivatives recorded by these authors and by Perkin and Wilson (J., 1903, **83**, 136) are characteristic and were exhibited by the synthetical material. The question of the identity or non-identity of the kaempferol methyl ether, isolated by Oesch and Perkin (J., 1914, **105**, 2350) from *Rhamnus catharticus*, with kaempferide remains an open one. This product had m. p. 221—222° and its acetyl derivative had m. p. 200—201°. The extension of the general process to the synthesis of *iso*rhamnetin was accomplished by the use of benzoylvanillic acid (VIII), the anhydride and sodium salt of which were heated with ω-benzoyloxyphloracetophenone at 180—185°. The product, probably a tetrabenzoyltrivanilloyl *iso*rhamnetin, yields *iso*rhamnetin (III) on hydrolysis. This flavonol was first isolated by Perkin and Hummel (J., 1896, **69**, 1566) from yellow wallflowers and subsequently it was found to be obtainable from asbarg (*Delphinium zalil*) (Perkin and Pilgrim, J., 1898, **73**, 268) and from red clover flowers (Power and Salway, J., 1910, **97**, 245). The m. p. of the tetra-acetyl derivative is given as 195—196° and 198—200°, but the synthetical material has m. p. 205—207°, and there is also a discrepancy in the m. p.'s of the natural and synthetic flavonols. We have, however, succeeded in isolating from yellow wallflower petals a flavonol the acetyl derivative of which has m. p. 205—207° not depressed by admixture with the synthetical specimen.

EXPERIMENTAL.

ω-Benzoyloxyresacetophenone (IV).—Hydrogen chloride was passed into an ice-cooled solution of benzoyloxyacetonitrile (7·4 g.) and resorcinol (5·1 g.) in anhydrous ether (30 c.c.) for 5 hours. On the following day the ether was decanted and the hard deposit washed with fresh ether. A further quantity of the solid separated when the ethereal washings were added to the mother-liquor. The ketimine hydrochloride was hydrolysed by heating with water for an hour on the steam-bath when the material did not dissolve but changed completely in appearance. The product (10 g.) was collected, dried at 100°, and crystallised from absolute alcohol (yield 9 g.) in colourless, well-formed plates, m. p. 202—203° (Found: C, 66·4; H, 4·6. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%). The alcoholic solution develops a deep brownish-violet coloration (red in thick layers) on the addition of ferric chloride. The substance is readily soluble in acetone, ethyl acetate and hot alcohol, sparingly soluble in chloroform and benzene, and very sparingly in water, ether, and light petroleum. The *diacetyl* derivative, obtained by the action during 1 hour of boiling acetic anhydride in presence of a drop of pyridine, crystallised from alcohol in long, lustrous, colourless needles, m. p. 112—113° (Found: C, 63·9; H, 4·7. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%).

3 : 7-*Dihydroxyflavone* (V).—ω-Benzoyloxyresacetophenone (7 g.), benzoic anhydride (15 g.) and sodium benzoate (6 g.) were heated together for 3 hours at 180—185° with mechanical stirring. The cooled product was crushed and added to alcohol (100 c.c.), and a solution of potassium hydroxide (10·3 g.) in water (15 c.c.) was gradually introduced to the heated mixture, which was finally boiled for 30 minutes and then concentrated by distillation of the alcohol. The residue was dissolved in water and the flavonol precipitated by the passage of carbon dioxide as a brown powder (dried, 6·1 g.). The substance was purified by precipitation from an alcoholic solution by water and by repeated crystallisation (charcoal) from methyl alcohol, finally in a mass (2·5 g.) of pale yellow, hair-fine, silky, needles, m. p. 258°, which, air-dried, lost 11·5% at 110° (Found in dried material: C, 70·6; H, 4·2. Calc. for $C_{15}H_{10}O_4$, CH_4O : CH_4O, 11·2%; and for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%). The substance has been previously obtained by Kostanecki and Stoppani (*Ber.*, 1904, **37**, 1180) and by Robinson and Shinoda (J., 1925, **127**, 1973). The specimen now described melted at 258° when mixed with that of the same m. p. prepared by the last-named authors. The diacetyl derivative crystallised from alcohol in colourless needles, m. p. 157·5—158·5° (Found: C, 67·3; H, 4·3. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·1%). Kostanecki and Stoppani (*loc. cit.*) give m. p. 157°.

3 : 7-*Dihydroxy*-4′-*methoxyflavone* (VI).—The preparation of this resokaempferide resembled that of resogalangin just described. The starting materials were ω-benzoyloxyresacetophenone (7 g.), anisic anhydride (29 g.) and sodium anisate (7 g.), and hydrolysis was effected by means of alcohol (50 c.c.) and 20% alcoholic potassium hydroxide (152 c.c.). The yield of crude product was 6·2 g.; this was acetylated by boiling for 1 hour with acetic anhydride (20 g.) and a drop of pyridine, and the *diacetyl* derivative crystallised from alcohol (charcoal) as a mass of fine, white, silky needles, m. p. 197° (yield 2·2 g.) (Found: C, 65·1; H, 4·4. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·3%). The substance was hydrolysed by means of 10% aqueous potassium hydroxide on the steam-bath and the pale yellow 3 : 7-*dihydroxy*-4′-*methoxyflavone* obtained on acidification with hydrochloric acid crystallised from methyl alcohol in glistening, pale yellow leaflets, m. p. 283—284° (Found: C, 67·3; H, 4·4. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%). The substance also crystallises well from acetic acid in clusters of needles and its pale yellow

solutions exhibit a green fluorescence. The lemon-yellow solution in concentrated sulphuric acid exhibits an intense bluish-green fluorescence which is a little greener than that characteristic of kaempferide. On standing, the fluorescence becomes much bluer. An alcoholic solution of the flavonol becomes deep brown on the addition of ferric chloride. The *lead* salt is a lemon-yellow precipitate. On mixing saturated boiling methyl-alcoholic solutions of the flavonol and potassium acetate, a pale yellow *potassium* salt is deposited and this is decomposed on boiling with water (compare A. G. Perkin and Wilson, J., 1903, **83**, 136).

ω-Benzoyloxyphloracetophenone (VII).—An ice-cooled solution of benzoyloxyacetonitrile (10 g.) and anhydrous phloroglucinol (8·6 g.) in ether (70 c.c.) was saturated with hydrogen chloride during 5 hours and the mixture allowed to remain in the ice-bath for 12 hours. The ketimine hydrochloride was deposited as a pale yellow crust and was collected and washed with ether. Many unsuccessful experiments were made before it was found that the hydrolysis of the salt could be conveniently effected by boiling with 50% aqueous alcohol (200 c.c.) for 21 hours under reflux. Most of the alcohol was removed by distillation and the material which crystallised on cooling was collected, washed with boiling water and dried (11 g.). A further quantity (2·5 g.) was recovered from the mother-liquor and one crystallisation of the whole crude product from aqueous alcohol gave 12 g. of pale yellow leaflets, m. p. 231—233°. This material is sufficiently pure for most purposes, but repeated crystallisation from aqueous methyl alcohol furnished fine, colourless needles, m. p. 234—235° (Found: C, 62·3; H, 4·4. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%). The alcoholic solution gives an intense reddish-violet coloration on the addition of ferric chloride. On acetylation with boiling acetic anhydride in presence of a little pyridine, the *triacetyl* derivative is obtained and may be crystallised from alcohol in colourless, lustrous needles, m. p. 115—116° (Found: C, 61·0; H, 4·4. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·3%). It should be noted that inefficient hydrolysis of the ketimine results in nitrogenous products which, although crystalline and consisting largely of benzoyloxyphloracetophenone, cannot be employed in the following syntheses.

Galangin (I).—A stirred mixture of ω-benzoyloxyphloracetophenone (7·4 g.), benzoic anhydride (30 g.) and sodium benzoate (6 g.) was heated (oil-bath at 165—170°) for 3 hours and worked up as in similar cases. Alcohol (80 c.c.) and 10% alcoholic potassium hydroxide (188 c.c.) were employed in the hydrolysis and the light buff crude product (6·4 g.) was boiled for 1 hour with acetic anhydride (20 c.c.) and a drop of pyridine. After decomposition with water, the triacetyl derivative was collected, and after one crystallisation from alcohol weighed 4·3 g. Repeated crystallisation gave 1·5 g. of colourless, lustrous needles, m. p. 142·5—143·5° (Found : C, 63·5; H, 4·2. Calc. for $C_{21}H_{16}O_8$: C, 63·6; H, 4·0%). Jahns (*Ber.*, 1881, **14**, 2807) and Kostanecki, Lampe and Tambor (*Ber.*, 1904, **37**, 2803) both state that the triacetyl derivative of natural and synthetic galangin has m. p. 142°. The triacetylgalangin (0·6 g.) was hydrolysed by heating with 10% aqueous potassium hydroxide for 1 hour on the steam-bath and the yellow precipitate obtained on acidification of the orange-yellow solution was isolated (0·4 g.). The substance crystallised from aqueous methyl alcohol in yellow needles, m. p. 214—215° (Found, in air-dried material: loss at 100° in a vacuum, 6·2. $C_{15}H_{10}O_5$, H_2O requires H_2O, 6·3%). The fact that galangin forms a hydrate has been previously observed by Jahns (*loc. cit.*). The m. p. of the substance was not depressed by admixture with an authentic specimen of the flavonol.

Kaempferide (II).—A mechanically stirred mixture of ω-benzoyloxyphloracetophenone (7·4 g.), anisic anhydride (40 g.) and sodium anisate (7·5 g.) was heated at 165—170° for 3 hours and then crushed and boiled with alcohol (100 c.c.) for 20 minutes. On the gradual addition of 10% alcoholic potassium hydroxide (200 c.c.) a granular, yellow precipitate was formed and the mixture was boiled for 30 minutes. The alcohol was removed by distillation and carbon dioxide precipitated 4·2 g. from the aqueous solution of the orange-brown residue. Acetylation and crystallisation of the product from alcohol (charcoal) furnished light fawn needles (2·7 g.), m. p. 190—192°, and by recrystallisation, slender, colourless needles, m. p. 193—194° (Found : C, 62·0; H, 4·5. Calc. for $C_{22}H_{18}O_9$: C, 62·0; H, 4·2%). Hydrolysis of the *triacetyl* derivative (1·0 g.) gave a yellow crude product (0·8 g.) which was repeatedly crystallised from methyl alcohol, finally giving long, golden-yellow needles, m. p. 225°. (Loss on heating at 110° for 40 hours, 9·4. Found, in heated material: C, 63·9 ; H, 4·2. $C_{16}H_{12}O_6,CH_4O$ requires CH_4O, 9·6%. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). The substance sublimes in extremely fine, silky needles. An alcoholic solution becomes olive-green on the addition of ferric chloride, the tone being browner than that produced by galangin. The *lead* salt is an orange-yellow precipitate, and the *potassium* salt, obtained by means of methyl alcoholic potassium acetate, is a yellow precipitate which is decomposed by boiling water. The lemon-yellow solution of the flavonol in sulphuric acid exhibits a brilliant bluish-green fluorescence which soon becomes greenish-blue.

Benzoylvanillic Acid. (VIII).—This substance, m. p. 178°, was obtained by Tiemann and Kraaz (*Ber.*, 1882, **15**, 2068) by the oxidation of benzoyleugenol; we have employed the following method: Benzoyl chloride (62·5 g.) was vigorously shaken with a solution of vanillic acid (50 g.) in aqueous sodium hydroxide (48 g. in 800 c.c.) until the odour of the chloride had disappeared. The mixture of acids precipitated by hydrochloric acid was extracted with two successive volumes of boiling water (900 c.c.), the undissolved product being also well washed on the filter and then dried (yield 47·4 g.; 58·4%). This material has m. p. 161—164° and may be employed for most purposes.

Benzoylvanilloyl Chloride, $BzO{\cdot}C_6H_3(OMe){\cdot}COCl$.—An intimate mixture of benzoylvanillic acid (20 g.) and phosphorus pentachloride (19 g.) soon became a semi-fluid mass and the reaction was completed by heating on the steam-bath for 1 hour. The phosphoryl chloride was removed by distillation under diminished pressure and the residue dissolved—a slow process—in boiling light petroleum (350 c.c.; b. p. 60—80°). The filtered solution deposited clusters of slender, white needles (yield 18·7 g.), which, crystallised from light petroleum, had m. p. 96—98° (Found: C, 61·9; H, 4·0; Cl, 12·2. $C_{15}H_{11}O_4Cl$ requires C, 62·0; H, 3·8; Cl, 12·2%). The substance is sparingly soluble in light petroleum, moderately readily soluble in acetone, and very readily in benzene, chloroform, and ether.

Benzoylvanillic Anhydride.—Anhydrous pyridine (100 c.c.) was gradually added with vigorous shaking to a solution and suspension of finely-powdered benzoylvanillic acid (36 g.) and benzoylvanilloyl chloride (40 g.) in dry ether (500 c.c.). On the following day the mixture was shaken for 10 minutes with crushed ice and filtered, the granular solid being then triturated successively with ice-cold water, ice-cold, very dilute hydrochloric acid, and ice-cold aqueous sodium carbonate, and finally washed with water and dried in a vacuum (yield 65 g.), m. p. 169—173°; the material was employed in the synthesis of *iso*rhamnetin without further purification. The substance crystallises from ethyl acetate in slender, cream needles, m. p. 179—180°, after softening at 172° (Found: C, 68·5; H, 4·6. $C_{30}H_{22}O_9$ requires C, 68·4; H, 4·2%). It is sparingly soluble in cold alcohol and acetic acid, moderately readily in benzene and cold ethyl acetate, readily in chloroform, and very sparingly in ether and light petroleum.

iso*Rhamnetin* (III).—Benzoylvanillic anhydride (92·4 g.), sodium benzoylvanillate (11·9 g.) and ω-benzoyloxyphloracetophenone were ground together and the mixture was heated at 180—185° for 6·5 hours; mechanical stirring was used until the hardening of the mass prevented it. After cooling, the flask was broken and the brittle product was powdered, added to alcohol (400 c.c.), and the mixture boiled for 20 minutes. A solution of potassium hydroxide (68·5 g.)

in water (100 c.c.) was then gradually introduced and, after boiling for a further 30 minutes, the alcohol was removed by distillation. The filtered solution of the residue in 600 c.c. of water was diluted to 900 c.c. and saturated with carbon dioxide. After a day, the product was collected (5·43 g.) and 4·4 g. of it were acetylated in the usual manner. The *tetra-acetyl* derivative crystallised from alcohol in long, slender, colourless needles, m. p. 203—205° (yield 2·33 g.), and by further crystallisation the m. p. was raised to 205—207° (Found: C, 59·6; 59·7; H, 4·4, 4·3. Calc. for $C_{24}H_{20}O_{11}$: C, 59·5; H, 4·1%). The derivative is sparingly soluble in methyl or ethyl alcohol, acetic acid, and benzene, moderately readily in acetone or chloroform, and very sparingly in ether. On heating with 10% aqueous potassium hydroxide, hydrolysis and consequent dissolution occur but slowly, and it was found preferable to employ hydrochloric acid for the conversion to *iso*rhamnetin. The tetra-acetate (2·3 g.; m. p. 203—205°) was treated with boiling concentrated hydrochloric acid (200 c.c.) for 1 hour and the bright orange-red precipitate * became pale yellow on the addition of water and was collected (1·52 g.). The substance was crystallised from alcohol and then from acetic acid in greenish-yellow needles, m. p. 305° (decomp.) after darkening at 300°. Power and Salway give the m. p. 295° (decomp.). The crude flavonols obtained by hydrolysis of the glucosides in an aqueous extract of yellow wallflower petals were isolated and purified by solution in aqueous sodium hydroxide and reprecipitation with carbon dioxide. This material was collected and extracted with boiling alcohol, and the extract acetylated in the usual manner. After four crystallisations from alcohol, faintly brown needles, m. p. 185—191°, were obtained. From the vivid fluorescence exhibited in sulphuric acid solution, we judge this product to be contaminated with a kaempferol derivative. It was hydrolysed by means of hot concentrated hydrochloric acid, the flavonol extracted with hot alcohol and the sparingly soluble fraction re-acetylated. After two crystallisations, woolly needles were obtained which, alone or mixed with the synthetic specimen, had m. p. 205—207°. The substance is coloured orange-red by sulphuric acid and dissolves to a yellow solution exhibiting a green fluorescence that becomes bluer and more intense on keeping.

p-*Ethylcarbonato*-m-*methoxybenzoic Acid*,

$$CO(OEt)\cdot O\cdot C_6H_3(OMe)\cdot CO_2H,$$

and its Anhydride.—Vanillic acid was carbethoxylated by a method analogous to that of Fischer (*Ber.*, 1908, **41**, 2877): Ethyl chloroformate (36 g.) was gradually added to an ice-cold, mechanically

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* The colour is due to an impurity, since pure synthetical tetra-acetyl *iso*rhamnetin did not exhibit it.

stirred solution of vanillic acid (50 g.) in *N*-aqueous sodium hydroxide (595 c.c.). When the odour of the ester was no longer perceptible, the solution was acidified and the precipitate collected and dried in a vacuum. The product was dissolved in hot acetone, and hot water was added until a turbidity resulted; on cooling, a mass of white needles was deposited and this was collected, washed with aqueous acetone and dried (yield 54·5 g., m. p. 144—146°, and 6·1 g. from the mother-liquor; total 71·4%). The substance separates from a mixture of acetone (2 vols.) and water (1 vol.) in colourless needles, m. p. 147—148° (Found: C, 54·9; H, 5·0. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). A solution of carbethoxyvanillic acid (60 g.) in thionyl chloride (150 c.c.) was boiled for 45 minutes and the excess of the reagent then removed in a vacuum. The residue was dissolved in dry ether (100 c.c.) and mixed with a suspension of carbethoxyvanillic acid (30 g.) in ether (250 c.c.), and anhydrous pyridine (80 c.c.) was gradually added with shaking. The solid which separated was broken up on the following day, mixed with crushed ice, collected, and well washed with water and with dilute hydrochloric acid (yield 65 g.), m. p. 86—88·5°. p-*Ethylcarbonato*-m-*methoxybenzoic anhydride* crystallises from ethyl acetate in short prisms, m. p. 87—88·5° (Found: C, 57·0; H, 4·6. $C_{22}H_{22}O_{11}$ requires C, 57·1; H, 4·8%).

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