S 6. *Furochromones. Part I. The Synthesis of Khellin.*

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Methyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate (III; R = H) failed to undergo the Hoesch and other reactions for the introduction of an acetyl group. On the other hand, *6-hydroxy-4 : 7-dimethoxycoumaran* (IV) has been readily converted by the Hoesch reaction into *6-hydroxy-4 : 7-dimethoxy-5-acetylcoumaran* (V) which, after dehydrogenation to 6-hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (khellinone) (VI) and subsequent completion of the γ-pyrone ring, has furnished khellin (VII).

It was shown by Fantl and Salem (*Biochem. Z.*, 1930, **226**, 166) and by Samaan (*Quart. J. Pharm. Pharmacol.*, 1930, **3**, 25, and subsequent papers) that extracts of the fruit of *Ammi visnaga*, which were used by the peoples of the Eastern Mediterranean regions as an antispasmodic in renal colic and uteral spasm, contained, amongst others, an active principle called khellin (or visammin). Anrep, Barsoum, Kenaway, and Misrahy (*Lancet*, 1947, i, 557) and Ayed (*ibid.*, 1948, i, 305) have recently demonstrated the value of khellin as a coronary vasodilator in the treatment of bronchial asthma and angina.

The structure of khellin was established analytically by Späth and Gruber (*Ber.*, 1938, **71**, 106) as 5 : 8-dimethoxy-2-methylfuro(4′ : 5′ : 6 : 7)chromone (VII), which on alkaline hydrolysis gave 6-hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (khellinone) (VI). A partial synthesis of khellin from the latter compound was achieved by these authors by long heating with sodium acetate and acetic anhydride and hydrolysis of the resulting product.

The total synthesis of khellin has now been achieved, confirming the structure given by Späth and Gruber. As at first envisaged, the method was based on the preparation of a suitably substituted coumarone derivative such as (III), and introduction therein of an acetyl group, followed by completion of the γ-pyrone ring. For the preparation of (III), 2 : 6-dibenzyloxy-1 : 4-dimethoxybenzene was obtained from pyrogallol essentially by the method of Baker, Nodzu, and Robinson (*J.*, 1929, 74). The preparation of the intermediate pyrogallol tribenzyl ether was very considerably improved by the addition of sodium iodide in the alkylation process.

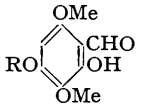
When 2 : 6-dibenzyloxy-1 : 4-dimethoxybenzene was subjected to a modified Gattermann reaction (employing zinc cyanide), *2 : 4-dihydroxy-3 : 6-dimethoxybenzaldehyde* (I; R = H) was obtained in good yield. The same aldehyde was obtained, though less conveniently, from 1 : 3-dihydroxy-2 : 5-dimethoxybenzene, prepared by catalytic hydrogenolysis of the benzyl groups of the dibenzyl ether. Treatment of (I; R = H) with phenyldiazomethane, with benzyl chloride and potassium carbonate, or, more satisfactorily, with benzyl bromide and potassium carbonate, gave *2-hydroxy-4-benzyloxy-3 : 6-dimethoxybenzaldehyde* (I; R = C_7H_7). This compound condensed with methyl bromoacetate in acetone in the presence of potassium carbonate to give *methyl 5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetate* (II; R = C_7H_7, R_1 = Me). Cyclisation of this compound with sodium or potassium methoxide (cf. Birch and Robertson, *J.*, 1938, 306) gave a 30% yield of *methyl 6-benzyloxy-4 : 7-dimethoxycoumarone-2-carboxylate* (III; R = C_7H_7) together with *5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetic acid* (II; R = C_7H_7, R_1 = H). However, magnesium methoxide was found to be a better condensing agent in this type of reaction and gave a 60% yield of the coumarone. Catalytic hydrogenolysis of the cyclised ester (III; R = C_7H_7) gave *methyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate* (III; R = H).

All attempts to make (III; R = H) react under Hoesch or Gattermann conditions failed, and the acetyl group could not be introduced by the Friedel–Crafts reaction or by Fries rearrangement of the *O*-acetate.

Attention was then directed to the coumaran series for the introduction of the acetyl group. Cyclisation and simultaneous decarboxylation of 5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetic acid with acetic anhydride and sodium acetate gave *6-benzyloxy-4 : 7-dimethoxycoumarone*, which on catalytic reduction at 3 atmospheres' pressure absorbed two molecular proportions of hydrogen to give *6-hydroxy-4 : 7-dimethoxycoumaran* (IV). This coumaran reacted satisfactorily with acetonitrile in the presence of zinc chloride under Hoesch conditions, but the intermediate imine hydrochloride required refluxing with 2N-sulphuric acid to give *6-hydroxy-4 : 7-dimethoxy-5-acetylcoumaran* (V). Dehydrogenation of this coumaran to 6-hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (khellinone) (VI) was effected by subliming it

* Patents pending.

under reduced pressure through a heated column containing palladium–norit (30%) prepared as described by Linstead and Thomas (*J.*, 1940, 1127).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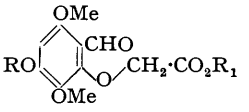
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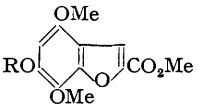
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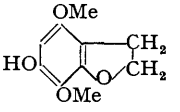
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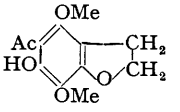
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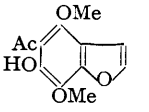
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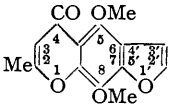
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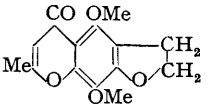
(VIII.)

The γ-pyrone ring was most conveniently completed by the method of Cheema, Gulati, and Venkataraman (*J.*, 1932, 925). Condensation with ethyl acetate in the presence of powdered sodium gave 6-*hydroxy*-4 : 7-*dimethoxy*-5-*acetoacetylcoumarone*, which cyclised readily with ethanolic sulphuric acid or ethanolic hydrogen chloride to give khellin (VII), identical with a specimen obtained from *Ammi visnaga*.

When 6-hydroxy-4 : 7-dimethoxy-5-acetylcoumaran was condensed with ethyl acetate and the resulting *diketone* cyclised, 5 : 8-*dimethoxy*-2-*methyl*-2′ : 3′-*dihydrofuro*(4′ : 5′ : 6 : 7)*chromone* (dihydrokhellin) (VIII) was obtained.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Pyrogallol Tribenzyl Ether.—Anhydrous potassium carbonate (225 g.) was carefully added to a stirred solution of pyrogallol (100 g.) in acetone (1 l.) containing anhydrous sodium iodide (120 g.) and benzyl chloride (305 g.). The mixture was refluxed with stirring for 24 hours, a further addition of potassium carbonate (225 g.) being made after 6 hours. The solid, obtained after distilling the acetone and treating the residue with water (2 l.), was washed with dilute sodium hydroxide and distilled in steam to remove traces of benzyl halide. The residue (295 g., 94%), which was sufficiently pure for oxidation, could be purified by crystallisation from a mixture of methanol and ethanol (4 : 1 by vol.), giving pyrogallol tribenzyl ether (250 g., 80%), m. p. 69—70°.

2 : 6-*Dibenzyloxy*-1 : 4-*dimethoxybenzene.*—This was prepared by the method of Baker, Nodzu, and Robinson (*loc. cit.*). Reduction of the quinone, crystallised from methyl ethyl ketone, and methylation of the product without purification, employing a 10% excess of methyl sulphate, gave 2 : 6-dibenzyloxy-1 : 4-dimethoxybenzene in an overall yield of 85%.

2 : 4-*Dihydroxy*-3 : 6-*dimethoxybenzaldehyde.*—(*a*) An ice-cooled mixture of 2 : 6-dibenzyloxy-1 : 4-dimethoxybenzene (20 g.), zinc cyanide (35 g.), and anhydrous ether (250 c.c.) was rapidly stirred and saturated with dry hydrogen chloride. The mixture was left for 15 hours, and the ethereal layer decanted from the residual oil, which was then decomposed with sufficient sodium hydroxide (about 300 c.c., 2N) to leave the solution just acid to Congo-red paper. The mixture was then heated at 100° for 1 hour, cooled, the solid product filtered off and washed once with ether to remove benzyl chloride. 2 : 4-*Dihydroxy*-3 : 6-*dimethoxybenzaldehyde* (9·0 g.), which formed golden needles, m. p. 198°, after crystallisation from methanol, was obtained (Found : C, 54·7; H, 5·0. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%).

(*b*) 2 : 6-Dibenzyloxy-1 : 4-dimethoxybenzene (3 g.) was dissolved in methanol (100 c.c.) and shaken with hydrogen at the ordinary pressure in the presence of palladium–charcoal (3 g., 10%). Hydrogen uptake was completed in 30 minutes and the filtered solution was evaporated in a vacuum, being finally heated at 60—65°/1 mm. for 30 minutes. The resulting gum was used directly in the Gattermann reaction, giving 2 : 4-dihydroxy-3 : 6-dimethoxybenzaldehyde (0·6 g.), identical with the above product from the dibenzyl ether.

2-*Hydroxy*-4-*benzyloxy*-3 : 6-*dimethoxybenzaldehyde* (I; R = C_7H_7).—A mixture of 2 : 4-dihydroxy-3 : 6-dimethoxybenzaldehyde (6·9 g.), anhydrous potassium carbonate (11 g.), and benzyl bromide (5·7 g.) in acetone (80 c.c.) was stirred and refluxed for 2 hours. The acetone was distilled off, and the residue treated with water (100 c.c.). The solid product was collected, dissolved in sodium hydroxide (2N), and the solution acidified after extraction with ether to remove dibenzyloxy-compound. There was obtained 2-*hydroxy*-4-*benzyloxy*-3 : 6-*dimethoxybenzaldehyde* (6·4 g.) as colourless needles, m. p. 122°, from methanol (Found : C, 66·8; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Unchanged aldehyde (0·5 g.) can be recovered from the aqueous potassium carbonate filtrate.

5-*Benzyloxy*-3 : 6-*dimethoxy*-2-*formylphenoxyacetic Acid* (II; R = C_7H_7, R_1 = H).—A mixture of 2-hydroxy-4-benzyloxy-3 : 6-dimethoxybenzaldehyde (10·4 g.), anhydrous potassium carbonate (18 g.), and methyl bromoacetate (7·0 g.) in acetone (150 c.c.) was refluxed with stirring for 8 hours. Inorganic

material was filtered off and washed with a little acetone, and the solvent removed from the combined filtrate and washings. The residue solidified and crystallised from benzene–light petroleum (b. p. 60—80°) to give *methyl 5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetate* (10·1 g.), m. p. 103° (Found : C, 63·6; H, 5·7. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%). The ethyl ester, prepared similarly from ethyl bromoacetate, formed plates, m. p. 84—86°.

The methyl ester (10 g.) was dissolved in methanol (40 c.c.) and sodium hydroxide (40 c.c., 2N) was added. The solution was heated on the water-bath for 20 minutes, cooled, and acidified with dilute hydrochloric acid, giving *5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetic acid* (9·7 g.), which formed long, colourless needles, m. p. 150—151°, from aqueous methanol (Found : C, 62·3; H, 5·2. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2%).

Methyl 6-Benzyloxy-4 : 7-dimethoxycoumarone-2-carboxylate (III; R = C_7H_7).—Methyl 5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetate (3 g.) in sodium methoxide solution (from sodium, 0·25 g., in anhydrous methanol, 15 c.c.) was heated under reflux for 15 minutes. The solution was diluted with ether, and washed with hydrochloric acid (10 c.c., 2N) and then with water. The ethereal layer was extracted with sodium carbonate, and 5-benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetic acid (1·6 g.) recovered by acidification. Distillation of the solvent from the dried ethereal solution and crystallisation of the residue from methanol gave *methyl 6-benzyloxy-4 : 7-dimethoxycoumarone-2-carboxylate* as prisms, m. p. 105° (Found : C, 66·3; H, 5·5. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

Methyl 6-Hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate (III; R = H).—The above benzyl ether (1 g.) in methanol (50 c.c.) was shaken with hydrogen at atmospheric temperature and pressure in the presence of palladium–charcoal (1 g., 10%). Absorption (75 c.c., 1 mol.) was complete in 20 minutes, and after separation of the catalyst and removal of the solvent the resulting *methyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate* crystallised from aqueous methanol in needles (0·7 g.), m. p. 135—136° (Found : C, 57·0; H, 5·1. $C_{12}H_{12}O_6$ requires C, 57·2; H, 4·8%). The hydroxy-ester was soluble in dilute sodium carbonate and was reprecipitated on acidification.

6-Benzyloxy-4 : 7-dimethoxycoumarone.—5-Benzyloxy-3 : 6-dimethoxy-2-formylphenoxyacetic acid (9·7 g.) and anhydrous sodium acetate (15 g.) were dissolved in acetic anhydride (100 c.c.), and the solution heated under reflux for 1 hour, cooled, poured into water (500 c.c.), and allowed to stand for 15 hours. The product was isolated with ether, the ethereal layer washed free from acid with sodium carbonate solution and dried, and the solvent removed. Distillation of the residue gave *6-benzyloxy-4 : 7-dimethoxycoumarone* (6·7 g.), b. p. 170—175°/1 mm., which solidified to a crystalline solid and formed plates, m. p. 47°, from light petroleum (b. p. 40—60°) in which it was easily soluble (Found : C, 71·8; H, 5·5. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%).

6-Hydroxy-4 : 7-dimethoxycoumaran (IV).—6-Benzyloxy-4 : 7-dimethoxycoumarone (6·7 g.) in methanol (100 c.c.) containing palladium–charcoal catalyst (4 g., 10%) was shaken with hydrogen at room temperature and an initial pressure of 5 atm., the theoretical amount of hydrogen (2 mols.) being absorbed. The catalyst was filtered off, the solvent removed under reduced pressure, and the residue distilled to give a colourless distillate (4·4 g.), rapidly solidifying in prisms. *6-Hydroxy-4 : 7-dimethoxycoumaran* had m. p. 114° after crystallisation from aqueous methanol and could be readily sublimed at 100°/10^{-3} mm. (Found : C, 60·7; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumaran (V).—A well-stirred mixture of 6-hydroxy-4 : 7-dimethoxycoumaran (7·5 g.), anhydrous zinc chloride (15 g.), and acetonitrile (7 g.) in anhydrous ether (150 c.c.) was saturated with dry hydrogen chloride with ice-cooling and set aside for 3 days. The solid product was filtered off, washed well with ether, and dissolved in water (10 c.c.); the imine hydrochloride rapidly crystallised. This was filtered off and heated under reflux in dilute sulphuric acid (50 c.c., 2N) for 2 hours. After cooling, the product was extracted with ethyl acetate and the extract washed, dried, and the solvent removed. The residue was distilled under reduced pressure before crystallisation of the product from methanol. *6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumaran* (5·0 g.) was obtained as pale yellow prisms, m. p. 105° (Found : C, 60·3; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). A further small quantity of less pure ketone could be obtained by refluxing the aqueous mother-liquor from which the imine hydrochloride had crystallised.

6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (*Khellinone*) (VI).—6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumaran (1 g.) was sublimed by heating at 150°/10^{-4} mm. through a 30-cm. column of palladium–norit (0·7 g., 30%) on glass wool (1·5 g.) maintained at 150°. The product (0·9 g.) collecting on a cold finger during 8—10 hours had m. p. 84—87° and was not completely dehydrogenated; as this could not be purified by crystallisation, the sublimation was repeated through fresh catalyst. The resulting product (0·8 g.), m. p. 87—90°, was crystallised from methanol, giving khellinone, m. p. 95—97°, raised by further crystallisation to 99—100° (Found : C, 61·1; H, 5·3. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). The m. p. was depressed to *ca.* 75° on admixture with the starting coumaran. The success of the dehydrogenation depended on the nature of the catalyst, and the best results were obtained with norit of pre-war quality.

6-Hydroxy-4 : 7-dimethoxy-5-acetoacetylcoumarone.—6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (1·7 g.) was condensed with ethyl acetate (5 c.c.) and powdered sodium (0·7 g.) in the manner described below for the dihydro-compound. *6-Hydroxy-4 : 7-dimethoxy-5-acetoacetylcoumarone* was obtained as colourless, elongated plates (1·6 g.), m. p. 79—80°, after crystallisation from aqueous methanol (Found : C, 60·9; H, 5·3. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1%).

5 : 8-Dimethoxy-2-methylfuro(4′ : 5′ : 6 : 7)chromone (*Khellin*) (VII).—(*a*) The diketone (0·5 g.) was refluxed with ethanolic sulphuric acid (5 c.c., 20% by weight) on the water-bath for 1 hour. After removal of part of the alcohol in a vacuum and addition of water, the product (0·4 g., m. p. 150—151°) crystallised from aqueous methanol to give khellin as colourless needles, m. p. 153°, not depressed on admixture with an authentic specimen from *Ammi visnaga*.

(*b*) When ethanolic hydrogen chloride was employed, the product, m. p. 140—145°, was difficult to purify by further crystallisation. After passage of a benzene solution through a column of alumina, khellin (0·18 g.), m. p. 153°, was obtained (Found : C, 64·8; H, 4·9. Calc. for $C_{12}H_{12}O_5$: C, 64·6; H, 4·65%).

6-*Hydroxy*-4:7-*dimethoxy*-5-*acetoacetylcoumaran*.—6-Hydroxy-4:7-dimethoxy-5-acetylcoumaran (2g.) in ethyl acetate (5 c.c.) was added to sodium (0·8 g., powdered under xylene and the hydrocarbon decanted). After the initial reaction had subsided, the mixture was heated on the water-bath for 2 hours. The excess ethyl acetate was distilled off in a vacuum, and the residue decomposed with dilute acetic acid (15 c.c.). After cooling to 0°, the product (1·85 g.) was collected and washed free from oil with a little ether. After crystallisation from very dilute ethanol, 6-*hydroxy*-4:7-*dimethoxy*-5-*aceto-acetylcoumaran* was obtained as colourless prisms, m. p. 116—117° (Found: C, 60·4; H, 5·7. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%).

5:8-*Dimethoxy*-2-*methyl*-2′:3′-*dihydrofuro*(4′:5′:6:7)*chromone* (*Dihydrokhellin*) (VIII).—The above diketone (1·8 g.) in ethanolic hydrogen chloride (15 c.c., saturated at room temp.) was heated under reflux for 10 minutes, and the solvent removed in a vacuum. Water was added, and the resulting product (1·4 g.) collected. 5:8-*Dimethoxy*-2-*methyl*-2′:3′-*dihydrofuro*(4′:5′:6:7)*chromone* formed needles, m. p. 150—151°, from aqueous methanol (Found: C, 64·0; H, 5·4. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·4%).

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