624. *Furanochromones. Part II. The Synthesis of Visnagin and Related Compounds.**

By J. S. H. Davies and W. L. Norris.

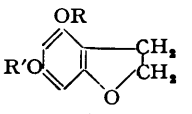
5- and 7-Acetyl-4 : 6-dihydroxycoumaran have been obtained from 4 : 6-dihydroxycoumaran by the Hoesch reaction. The 5-acetyl compound gave two isomeric monomethyl ethers; one of them 5-acetyl-6-hydroxy-4-methoxycoumaran (dihydrovisnaginone : II; R = Me, R′ = H) has been dehydrogenated to 5-acetyl-6-hydroxy-4-methoxycoumarone (visnaginone : V; R = H), thereby completing the total synthesis of 5-methoxy-2-methylfurano(3′ : 2′-6 : 7)chromone (visnagin : VI).† 4′ : 5′-Dihydro-5-methoxy-2-methylfurano(3′ : 2′-6 : 7)chromone (dihydrovisnagin : VII; R = Me, R′ = H), 4′ : 5′-dihydro-5-methoxy-2-methylfurano(2′ : 3′-7 : 8)-chromone (VIII), and 4′ : 5′-dihydro-7-methoxy-2-methylfurano(2′ : 3′-5 : 6)chromone (IX) have also been synthesised.

Recently, Clarke, Glaser, and Robertson (*J.*, 1948, 2260) and Gruber and Hoyos (*Monatsh.*, 1948, **78**, 417; *Chem. Abstr.*, 1948, **42**, 7290) have reported a partial synthesis of 5-methoxy-2-methylfurano(3′ : 2′-6 : 7)chromone (visnagin : VI), a constituent of the seeds of *Ammi visnaga* (Späth and Gruber, *Ber.*, 1941, **74**, 1492), from its hydrolysis product, 5-acetyl-6-hydroxy-4-methoxycoumarone (visnaginone) (V; R = H).† In synthetical approaches to (V; R = H), Clarke, Glaser, and Robertson (*loc. cit.*) showed that ethyl 6-hydroxy-4-methoxycoumarone-2-carboxylate with acetonitrile under Hoesch conditions, and with acetyl chloride under Friedel–Crafts conditions, gave, not the desired 5-acetyl derivative, but only the 7-acetyl derivative, and a parallel result was obtained with 6-hydroxy-4-methoxycoumaran. These intermediates served for the preparation of 7-methoxy-2-methylfurano(2′ : 3′-5 : 6)chromone (*iso*visnagin) and its 4′ : 5′-dihydro-derivative (IX), respectively. *iso*Visnagin has also been obtained by Gruber and Horváth (*Monatsh.*, 1949, **80**, 563; *Chem. Abstr.*, 1950, **44**, 3969) from 7-acetyl-4 : 6-diacetoxycoumarone.

* Patents pending.

† Since this paper was submitted, Dr. Gruber has informed us that he has synthesised visnagin from ethyl phloroacetophenonecarboxylate (for summary see Gruber and Horváth, *Monatsh.*, 1949, **80**, 874).

The synthesis of 5-acetyl-6-hydroxy-4-methoxycoumarone (visnaginone) from 4 : 6-dihydroxycoumaran (I; R = R′ = H) is now described, and, in the course of the work, inter-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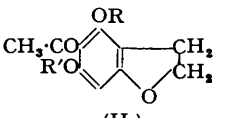
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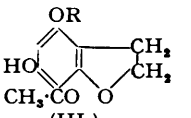
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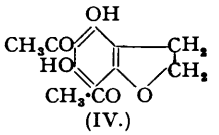
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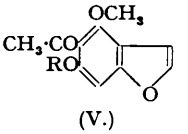
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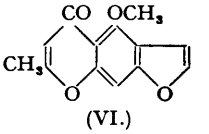
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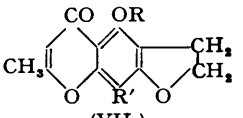
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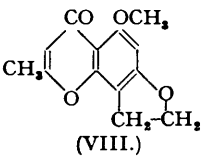
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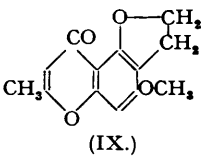

(IX.)

mediates suitable for the preparation of 4′ : 5′-dihydro-5-methoxy-2-methylfurano(3′ : 2′-6 : 7)-chromone (dihydrovisnagin) (VII; R = Me, R′ = H) and two of its possible isomers (VIII) and (IX; dihydro*iso*visnagin) have become available. The starting material, 4 : 6-dihydroxycoumaran, was obtained by hydrogenating 3 : 4 : 6-triacetoxycoumarone as suggested by Späth, Wessely, and Kubiczek (*Ber.*, 1937, **70**, 243). The triacetoxycoumarone was obtained directly from 4 : 6-dihydroxycoumaran-3-one, prepared from phloroglucinol and acetonitrile (Sonn, *Ber.*, 1917, **50**, 1262), by treatment with acetic anhydride and pyridine, instead of first preparing 4 : 6-diacetoxycoumaran-3-one with acetic anhydride and acetylating the latter with acetic anhydride containing a few drops of acetyl chloride as described by Späth, Wessely, and Kubiczek (*loc. cit.*). Hydrogenation of the triacetoxycoumarone in glacial acetic acid over palladium–charcoal readily gave 4 : 6-diacetoxycoumaran, m. p. 69°, from which 4 : 6-dihydroxycoumaran, m. p. 118·5—119·5°, was obtained by alkaline hydrolysis. Dean and Nierenstein (*J. Amer. Chem. Soc.*, 1924, **46**, 2798) claim to have prepared 4 : 6-dihydroxycoumaran from 4 : 6-dimethoxycoumaran, obtained by the action of sodium ethoxide on 4 : 6-dimethoxycoumaran-3-one hydrazone. The dihydroxycoumaran described by these authors had m. p. 176—178° and gave a diacetyl derivative, m. p. 177°. It is, therefore, not identical with 4 : 6-dihydroxycoumaran described above, and moreover, their dimethoxycoumaran is not identical with the 4 : 6-dimethoxycoumaran prepared by Foster and Robertson (*J.*, 1939, 921), who comment on the discrepancy.

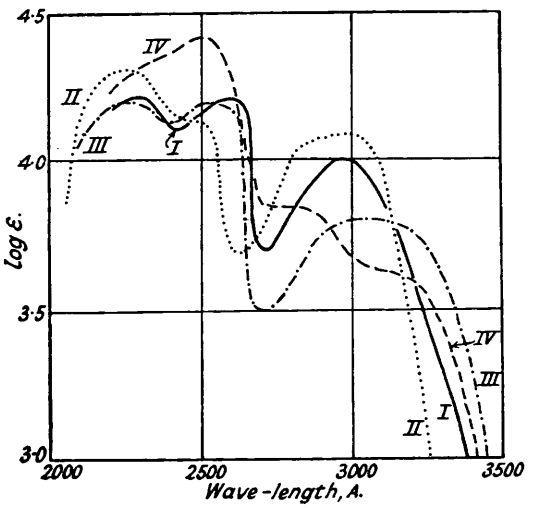
4 : 6-Dihydroxycoumaran with acetonitrile under Hoesch conditions gave, after hydrolysis of the mixture of intermediate imine hydrochlorides, two *C*-monoacetyldihydroxycoumarans, m. p. 239—240° and 197—199°, respectively. The compound, m. p. 239—240, proved to be 7-acetyl-4 : 6-dihydroxycoumaran (III; R = H), since the single product obtained by monomethylation was identical with an authentic specimen of 7-acetyl-6-hydroxy-4-methoxycoumaran, m. p. 129—129·5° (dihydro*iso*visnaginone : II; R = Me), kindly supplied by Professor A. Robertson. The product, m. p. 197—199°, proved to be 5-acetyl-4 : 6-dihydroxycoumaran, since its dimethyl ether was identical with the methyl ether of dihydrovisnaginone, prepared by the successive hydrogenation and methylation of visnaginone (V; R = H; cf. Clarke, Glaser, and Robertson, *loc. cit.*), which was obtained by the hydrolysis of chellol glucoside, another constituent of the seeds of *Ammi visnaga* (Späth and Gruber, *Ber.*, 1941, **74**, 1549).

Whereas 7-acetyl-4 : 6-dihydroxycoumaran gave a single monomethyl ether, *viz.*, 7-acetyl-6-hydroxy-4-methoxycoumaran, 5-acetyl-4 : 6-dihydroxycoumaran gave a mixture of two monomethyl ethers, m. p. 100—101° and 108—109°, respectively. The former was identical with dihydrovisnaginone, 5-acetyl-6-hydroxy-4-methoxycoumaran (II; R = Me, R′ = H); the latter was, therefore, 5-acetyl-4-hydroxy-6-methoxycoumaran (II; R = H, R′ = Me). The results obtained in these methylation experiments show that any co-ordination of the acetyl group in 5-acetyl-4 : 6-dihydroxycoumaran is not confined to a particular hydroxyl group, in contrast to the 7-acetyl isomer where the 6-hydroxyl group only can be involved.

The separation of the mixture of monomethyl ethers calls for comment : it was effected by allowing a benzene solution of the mixture (after preliminary removal of unchanged 5-acetyl-4 : 6-

dihydroxycoumaran by extraction with aqueous sodium carbonate) to flow through a column of untreated (alkaline) alumina. Under the conditions employed, the filtrate was found to contain almost pure 5-acetyl-4-hydroxy-6-methoxycoumaran, m. p. 108—109° (II; R = H, R′ = Me); when no further material was obtained by benzene, elution of the column with a dilute solution of glacial acetic acid in ether then gave a crude product, from which 5-acetyl-6-hydroxy-4-methoxycoumaran, m. p. 100—101° (II; R = Me, R′ = H), was obtained by crystallisation. That adsorption on the column was partly due to the residual alkalinity of the alumina was indicated by the method of removal of the second fraction; moreover, when double the usual quantity of untreated adsorbent was used, the whole of the material remained on the column and resisted elution with large volumes of benzene. It appeared, therefore, that differential adsorption of the components was due to a difference in the acidity of the two ethers, and, in support of this, it was found that when alumina, previously neutralised by treatment with ethyl acetate, was used, no appreciable separation of isomers occurred, even though both the alkaline and the neutral alumina had the same activity in the Brockmann and Schodder test (*Ber.*, 1941,

Absorption spectra of dihydrofuranochromones.



I. (————) 4′ : 5′-*Dihydro*-5 : 8-*dimethoxy*-2-*methylfurano*(3′ : 2′-6 : 7)*chromone* (*Dihydrokellin*: VII; R = Me, R′ = OMe).
II. (· · · · · · ·) 4′ : 5′-*Dihydro*-5-*methoxy*-2 *methylfurano*(3′ : 2′-6 : 7)*chromone* (*Dihydrovisnagin*: VII; R = Me, R′ = H).
III. (— · — · —) 4′ : 5′-*Dihydro*-5-*methoxy*-2-*methylfurano*(2′ : 3′-7 : 8)*chromone* (VIII).
IV. (— — —) 4′ : 5′-*Dihydro*-7-*methoxy*-2-*methylfurano*(2′ : 3′-5 : 6)*chromone* (IX).

74, 73). 5-Acetyl-6-hydroxy-4-methoxycoumaran, being the more strongly adsorbed, appeared to be the more acidic isomer, and in this connection it is of interest that, in the dimethylation of 5-acetyl-4 : 6-dihydroxycoumaran in alkaline solution, the more weakly acidic 5-acetyl-4-hydroxy-6-methoxycoumaran was isolated as a by-product.

Dehydrogenation of 5-acetyl-6-hydroxy-4-methoxycoumaran by the method outlined in Part I (Baxter, Ramage, and Timson, *J.*, 1949, S30) gave visnaginone (V; R = H), identical with that obtained by Späth and Gruber (*loc. cit.*, p. 1549). It was converted into visnagin by the method of Clarke, Glaser, and Robertson (*loc. cit.*).

5-Acetyl-6-hydroxy-4-methoxycoumaran (II; R = Me, R′ = H) with ethyl acetate and powdered sodium gave 6-hydroxy-5-β-ketobutyryl-4-methoxycoumaran, but, when the latter was boiled for 15 minutes in glacial acetic acid containing one drop of concentrated hydrochloric acid to effect ring-closure to the chromone, the resulting product was a mixture, which gave a positive ferric chloride reaction. This persisted with material subjected to prolonged boiling in the acid solution, indicating demethylation rather than incomplete ring-closure. This was confirmed by the isolation of two products from the reaction mixture: the expected 4′ : 5′-dihydro-5-methoxy-2-methyl(3′ : 2′-6 : 7)chromone (VII; R = Me, R′ = H) and the corresponding 5-hydroxy-compound (VII; R = R′ = H), the structure of the latter being confirmed by analysis, a positive ferric colour, and remethylation to (VII; R = Me, R′ = H). In order to

avoid demethylation during ring-closure, the diketone was cyclised at 50° giving only (VII; R = Me, R′ = H) in a high state of purity.

5-Acetyl-4-hydroxy-6-methoxycoumaran (II; R = H, R′ = Me) gave the 5-β-ketobutyryl compound in the usual way with ethyl acetate and powdered sodium, and no difficulty was experienced in ring-closure when using boiling glacial acetic acid containing one drop of concentrated hydrochloric acid, the product being homogeneous and giving a negative ferric reaction. The resulting 4′ : 5′-dihydro-5-methoxy-2-methylfurano(2′ : 3′-7 : 8)chromone (VIII) was hygroscopic and in the atmosphere took up 1 mole of water of crystallisation.

In an examination of other possible methods of introducing an acetyl group into the 5-position of 4 : 6-dihydroxycoumaran, the Fries rearrangement of 4 : 6-diacetoxycoumaran (I; R = R′ = Ac) was studied. When a solution of the diacetate in nitrobenzene was treated with aluminium trichloride, the only pure product isolated was isomeric with the starting material. It gave a positive ferric reaction and contained no *O*-acetyl groups (Freudenberg). The formation of a diacetate and a dimethyl ether confirmed the view that a double Fries rearrangement had occurred, giving 5 : 7-diacetyl-4 : 6-dihydroxycoumaran (IV). The possibility of eliminating one of the nuclear acetyl groups appeared feasible from the work of Heller (*Ber.*, 1912, **45**, 418), and, in fact, when a solution of (IV) in aqueous sodium hydroxide was boiled for 1 hour, the 5-acetyl group was lost, and there was obtained 7-acetyl-4 : 6-dihydroxycoumaran (III; R = H) identical with the material described above. The monomethyl ether (III; R = Me) was converted into 4′ : 5′-dihydro-7-methoxy-2-methylfurano(2′ : 3′-5 : 6)chromone (dihydro*iso*-visnagin : IX) by the method of Clarke, Glaser, and Robertson (*loc. cit.*), but there were certain discrepancies in the melting points of 6-hydroxy-7-β-ketobutyryl-4-methoxycoumaran and of (IX) in the two investigations; these are noted in the Experimental Section. Through the courtesy of Professor Robertson, we were able to compare the two sets of products, and found no depression of the melting point on admixture.

The ultra-violet absorption curves of the dihydrofuranochromones, including 4′ : 5′-dihydrokellin (VII; R = Me, R′ = OMe; Part I, *loc. cit.*) are annexed : for comments see Part IV (*J.*, 1950, paper no. 626).

Experimental.

(Carbon and hydrogen analyses and ultra-violet absorption curves are by Drs. Weiler and Strauss, Oxford.)

4 : 6-*Dihydroxycoumaran*-3-*one*.—By Sonn's procedure (*loc. cit.*), 4 : 6-dihydrocoumaran-3-one, m. p. 247—249° (decomp.), was obtained in an average yield of 80% in a series of experiments; but the modification proposed by Shriner and Grosser (*J. Amer. Chem. Soc.*, 1942, **64**, 382) gave variable results.

3 : 4 : 6-*Triacetoxycoumarone*.—A mixture of 4 : 6-dihydroxycoumaran-3-one (54 g.), freshly distilled acetic anhydride (360 c.c.), and dry pyridine (36 c.c.) was stirred at 15° for 1 hour and then kept for 16 hours. The small quantity of insoluble material dissolved on gentle warming. The crude reaction product (88·6 g.) separated on pouring the mixture into ice-water (1500 c.c.) and was filtered off. Repeated crystallisation from ethanol gave 3 : 4 : 6-triacetoxycoumarone as colourless needles (72·25 g., 76%), m. p. 102° (Found : C, 57·5; H, 4·1; Ac, 44·4. Calc. for $C_{14}H_{12}O_7$: C, 57·5; H, 4·1; Ac, 44·2%). Acetyl chloride in ethyl acetate gave a product which was more difficult to purify.

4 : 6-*Diacetoxycoumaran* (I; R = R′ = Ac).—A solution of 3 : 4 : 6-triacetoxycoumarone (29·2 g.) in glacial acetic acid (55 c.c.) at 60—70° was shaken in hydrogen under atmospheric pressure in presence of palladium–charcoal previously saturated with hydrogen (2 g. of 30%; Linstead and Thomas, *J.*, 1940, 1127). The theoretical quantity of hydrogen was rapidly absorbed. After removal of the catalyst, the filtrate was distilled under reduced pressure to remove solvent, the residue dissolved in ether, and the ethereal extract washed with aqueous sodium hydrogen carbonate and dried. The solvent was distilled off, and 4 : 6-*diacetoxycoumaran* was obtained as a colourless oil (22·6 g., 96%), which slowly solidified. It crystallised from a mixture (2 : 1 by vol.) of ether and light petroleum (b. p. 40—60°) in colourless prisms, m. p. 69° (Found : C, 60·95; H, 5·3; Ac, 37·05. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1; Ac, 36·45%). It was readily soluble in methanol, acetone, chloroform, or benzene.

5 : 7-*Diacetyl*-4 : 6-*dihydroxycoumaran* (IV).—Powdered aluminium chloride (7 g.) was added in portions to a solution of 4 : 6-diacetoxycoumaran (10 g.) in nitrobenzene (100 c.c.), and the whole kept at 60—70° for 2 hours. After cooling, the reaction mixture was poured into a mixture of ice (200 g.) and dilute hydrochloric acid (200 c.c., 2N.). The organic layer was separated after 16—24 hours, and the aqueous portion was extracted with chloroform (600 c.c. in portions). The combined extracts were washed successively with dilute hydrochloric acid and water. They were then shaken with aqueous sodium hydroxide (80 c.c.; N.), and the alkaline extract acidified with dilute hydrochloric acid. The precipitate (8·2 g.) crystallised from ethanol (90 c.c.) to give 5 : 7-*diacetyl*-4 : 6-*dihydroxycoumaran* as cream-coloured needles (4·6 g., 46%), m. p. 145—146° (Found : C, 61·0; H, 5·05; *O*-Ac, 0%; equiv. wt., 113. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·05%; equiv. wt., 118). It gave a wine-red ferric colour in ethanol, and was readily soluble in chloroform, moderately soluble in ethyl acetate, and sparingly soluble in acetone, benzene, or acetic acid. With acetic anhydride and pyridine, it gave the *diacetate*, which crystallised from a mixture (3 : 1 by vol.) of light petroleum (b. p. 40—60°) and ethyl acetate in colourless prisms, m. p. 87° (Found : C, 59·85; H, 5·25; *O*-Ac, 27·25. $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0; *O*-Ac,

26·9%). With methyl sulphate in acetone containing potassium carbonate, it gave a *monomethyl ether*, which crystallised from methanol as pale yellow needles, m. p. 113·5—114°, and gave a dark, reddish-violet ferric colour in ethanol (Found : C, 62·5; H, 5·6; OMe, 12·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·65; OMe, 12·4%). The monomethyl ether with methyl sulphate in acetone containing potassium hydroxide (cf. Baker and Lothian, *J.*, 1935, 628) gave the *dimethyl ether*, which crystallised from a large volume of light petroleum (b. p. 40—60°) as colourless prisms, m. p. 69—70° (Found : C, 63·5; H, 5·8. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). It gave no colour with ferric chloride in ethanol. The *dioxime* of the dimethyl ether crystallised from benzene in colourless prisms, m. p. 191—193° (softening at 189°) (Found : N, 8·9. $C_{14}H_{18}O_5N_2$ requires N, 9·5%).

With benzyl bromide and potassium carbonate in acetone, 5 : 7-diacetyl-4 : 6-dihydroxycoumaran gave a mixture of a *monobenzyl ether*, yellow needles (from methanol), m. p. 104° (Found : C, 69·8; H, 5·4. $C_{19}H_{18}O_5$ requires C, 69·95; H, 5·55%), and the *dibenzyl ether*, colourless needles (from methanol), m. p. 138° (Found : C, 74·7; H, 5·7. $C_{26}H_{24}O_5$ requires C, 75·0; H, 5·8%). The latter gave no ferric colour reaction.

4 : 6-*Dihydroxycoumaran* (I; R = R′ = H).—A solution of 4 : 6-diacetoxycoumaran (22·1 g.) in aqueous sodium hydroxide (300 c.c.; 2N.) was boiled for 1 hour, cooled, and acidified with hydrochloric acid. The solution was extracted with ether, and the acetic acid neutralised with sodium hydrogen carbonate. After removal of the solvent, there remained a brown syrup (14 g., 98%), which slowly solidified. This was re-dissolved in ether, and the solution decolorised by passage through a short column of alumina; after the solvent had been distilled off, the residue crystallised from benzene, in which it was only moderately soluble. 4 : 6-*Dihydroxycoumaran* formed colourless prisms, m. p. 118·5—119·5°, readily soluble in methanol, acetone, acetic acid, or warm chloroform (Found : C, 63·15; H, 5·4. $C_8H_8O_3$ requires C, 63·2; H, 5·3%).

5-*Acetyl*-4 : 6-*dihydroxycoumaran* (II; R = R′ = H) *and* 7-*Acetyl*-4 : 6-*dihydroxycoumaran* (III; R = H).—Dry hydrogen chloride was passed for 6 hours into a stirred, ice-cooled mixture of 4 : 6-dihydroxycoumaran (21·5 g.), acetonitrile (9·63 g.), and freshly fused and powdered zinc chloride (33·1 g.) in anhydrous ether (285 c.c.). The gummy precipitate first formed became powdery during the reaction. After 48 hours, the ether was decanted, and the residue washed with a little more ether. Ice-water (275 c.c.) was then added; the solid imine hydrochloride was collected and hydrolysed by boiling it for 1 hour with sulphuric acid (175 c.c.; 2N.), a pink powder (17·6 g.) separating. The second crop (3·4 g.), obtained by further boiling of the acid mother-liquor, was kept separate. The main crop was purified by crystallisation first from benzene (1760 c.c.) and then from a mixture (300 c.c.; 2 : 1 by vol.) of water and methanol to give 5-*acetyl*-4 : 6-*dihydroxycoumaran* (9·64 g., 34·4%) as yellow needles, m. p. 197—199° (Found : C, 62·1; H, 5·25. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·15%). Its solution in ethanol gave a wine-red colour with ferric chloride; it was readily soluble in ethyl acetate or acetone, sparingly soluble in chloroform, and insoluble in light petroleum. It dissolved freely in aqueous sodium carbonate, and when its solution in aqueous sodium hydroxide (2N.) was boiled deacetylation occurred to give 4 : 6-dihydroxycoumaran. The *diacetate*, colourless, prismatic needles, m. p. 100—101°, obtained by means of acetic anhydride–pyridine at 20° overnight, crystallised from a mixture (1 : 2 by vol.) of ethyl acetate and light petroleum (b. p. 40—60°) (Found : C, 60·65; H, 5·0; *O*-Ac, 30·55. $C_{14}H_{14}O_6$ requires C, 60·45; H, 5·05; *O*-Ac, 30·95%).

When 5-acetyl-4 : 6-dihydroxycoumaran was boiled for 1 hour under a reflux with benzyl chloride (1·1 mols.) in ethanol containing sodium ethoxide (0·9 mol.), a mixture of, probably, a *monobenzyl ether*, cream-coloured needles (from ethanol), m. p. 141—142° (Found : C, 72·1; H, 5·75. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·65%), and a *dibenzyl* derivative, pale yellow blades (from ethanol), m. p. 143° (Found : C, 76·8; H, 5·9. $C_{24}H_{22}O_4$ requires C, 76·95; H, 5·9%), was obtained. Both products in ethanol gave colours with ferric chloride; the dibenzyl derivative must, therefore, have been benzylated in the nucleus.

The second crop (3·4 g.), obtained above from the acid mother-liquors, after crystallisation from benzene and then repeatedly from ethanol, gave 7-*acetyl*-4 : 6-*dihydroxycoumaran* as pale yellow needles, m. p. 239—240°, which depressed the m. p. of the 5-acetyl isomer (Found : C, 61·7; H, 5·15%). The 7-acetyl compound was also obtained by boiling for 45 minutes a solution of 5 : 7-diacetyl-4 : 6-dihydroxycoumaran (5·26 g.) in aqueous sodium hydroxide (70 c.c.; 2N.). Acidification of the cooled solution gave a precipitate (4·24 g., 98%), m. p. 234—237°. This crystallised from ethanol as pale yellow needles, m. p. 239—240°, which did not depress the m. p. of the 7-acetyl compound described above. The 7-acetyl compound in ethanol gave a dark green colour with ferric chloride, and was moderately soluble in acetone, but sparingly soluble in chloroform, benzene, or acetic acid. It dissolved readily in dilute aqueous sodium carbonate. The *diacetate* crystallised from a mixture (2 : 1 by vol.) of light petroleum (b. p. 40—60°) and ethyl acetate as colourless prisms, m. p. 108—109° (Found : C, 60·55; H, 5·2; *O*-Ac, 31·05%).

The *dimethyl ether*, prepared by the method of Baker and Lothian (*loc. cit.*) using methyl sulphate and potassium hydroxide in acetone, crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 93—94° (Found : C, 64·95; H, 6·25. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). It gave a *semicarbazone*, colourless prismatic needles (from ethanol), m. p. 230° (Found : N, 15·5. $C_{13}H_{17}O_4N_3$ requires N, 15·05%), a *phenylhydrazone*, very pale yellow prismatic needles (from ethanol), m. p. 168° (Found : N, 9·25. $C_{18}H_{20}O_3N_2$ requires N, 8·97%), and an *oxime*, colourless flakes (from ethanol), m. p. 182—184° (Found : N, 5·6. $C_{12}H_{15}O_4N$ requires N, 5·9%).

7-*Acetyl*-6-*hydroxy*-4-*methoxycoumaran* (*Dihydro*isovisnaginone) (III; R = Me).—A solution of 7-acetyl-4 : 6-dihydroxycoumaran (4·24 g.) in anhydrous acetone (50 c.c.) containing methyl sulphate (3·03 g., 1·1 mols.) and potassium carbonate (10·4 g.) was boiled for 3 hours under a reflux. The hot reaction mixture was filtered from inorganic material, and the latter washed with fresh acetone. The

combined filtrates were distilled to remove solvent, water was added to the residue, and the crude 7-acetyl-6-hydroxy-4-methoxycoumaran (3·57 g., 78%), m. p. 124—126°, collected. It crystallised from methanol in pale yellow needles, m. p. and mixed m. p. 129—129·5° with an authentic specimen from Professor Robertson (Found : C, 63·55; H, 5·95. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%).

4′ : 5′-*Dihydro-7-methoxy-2-methylfurano*(2′ : 3′-5 : 6)*chromone* (*Dihydroisovisnagin*) (IX).—7-Acetyl-6-hydroxy-4-methoxycoumaran (2·89 g.) was treated with ethyl acetate (77 c.c.) and sodium (5·14 g.) as described by Clark, Glaser, and Robertson (*loc. cit.*). The reaction mixture was then concentrated in a vacuum, and the residue treated with ether and dilute acetic acid. The aqueous portion was extracted several times with ether, and the combined extracts were washed in turn with aqueous sodium hydrogen carbonate and water. The dried, ethereal solution was distilled to remove solvent, and a large volume of light petroleum (b. p. 40—60°) was added to the residue. The crude product (2·84 g.) crystallised from ethanol to give 6-hydroxy-7-β-ketobutyryl-4-methoxycoumaran (1·91 g., 55%) as minute, yellow, prismatic needles, m. p. 142—142·5°. This material did not depress the m. p. of the diketone, m. p. 135—136° (Clarke, Glaser, and Robertson, *loc. cit.*; m. p. by our thermometer, 139—140°), supplied by Professor Robertson. When the diketone was boiled for 15 minutes in glacial acetic acid (10 c.c.) containing 1 drop of concentrated hydrochloric acid, dihydro*iso*visnagin was obtained, which crystallised from light petroleum (b. p. 100—120°) in colourless needles (1·52 g., 86%), m. p. 183—184° (Found : C, 67·15; H, 5·2. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%). Clarke, Glaser, and Robertson (*loc. cit.*) gave the m. p. as 193—194° (decomp.) after sintering at 187°. A mixture of the two samples had an intermediate, indefinite melting point.

5-*Acetyl*-4 : 6-*dimethoxycoumaran* (II; R = R′ = Me).—The hydrogenation of visnaginone was effected as described by Clarke, Glaser, and Robertson (*loc. cit.*) except that palladium–barium sulphate catalyst (5%) was used. 5-Acetyl-6-hydroxy-4-methoxycoumaran (dihydrovisnaginone) crystallised from methanol as colourless blades, m. p. 100—101° (Found : C, 63·3; H, 5·9. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). A mixture of the product (0·7 g.), methyl sulphate (1 c.c.), and potassium carbonate (3 g.) in acetone (10 c.c.) was boiled for 7 hours under a reflux. The same quantities of methyl sulphate and acetone, together with a little potassium carbonate, were added after 16 hours at room temperature, and heating resumed for a further 7 hours. The acetone was then distilled from the filtered solution, the semi-solid residue dissolved in ether, and the ethereal solution washed in turn with aqueous sodium hydroxide and water. After removal of the solvent, crystallisation of the residue from a mixture (4 : 1 by vol.) of light petroleum (b. p. 40—60°) and ethyl acetate gave 5-*acetyl*-4 : 6-*dimethoxycoumaran* as colourless prisms, m. p. 94·5—95·5° (Found : C, 65·05; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). It was readily soluble in acetone or benzene, moderately soluble in ether, and sparingly soluble in ethanol.

Methylation of 5-*Acetyl*-4 : 6-*dihydroxycoumaran.*—(a) *Monomethylation.* 5-Acetyl-4 : 6-dihydroxycoumaran (7·02 g.) was dissolved in ethanolic sodium ethoxide, prepared from sodium (0·83 g.) and ethanol (90 c.c.); methyl sulphate (4·56 g.) was added, and the mixture was boiled under a reflux for 1½ hours. Water (1 l.) was then added, and, after acidification, organic material was extracted with ether. The ethereal solution was extracted first with aqueous sodium carbonate (N.), which removed unchanged material (1·17 g.; m. p. 191—199°). It was then extracted with aqueous sodium hydroxide (N.), which on acidification gave a mixture of monomethyl ethers (5·81 g.). A small quantity of material (0·24 g.), probably containing the dimethyl ether, remained in the ether. The monomethyl ethers were separated as follows : the mixture (5·81 g.) was dissolved in thiophen-free benzene (200 c.c.), and the solution allowed to pass down a column of alumina (Grade II, Brockmann and Schodder, *loc. cit.*; 150 g.); the column was then eluted with benzene (*ca.* 1200 c.c.). Evaporation of the eluate gave a white solid (1·6 g.), m. p. 106—108°, and crystallisation of the latter from methanol gave 5-*acetyl*-4-*hydroxy*-6-*methoxycoumaran* (1·34 g.) as fine, pale yellow needles, m. p. 108—109° (Found : C, 63·5; H, 5·8; OMe, 14·3. $C_{11}H_{10}O_4$ requires C, 63·45; H, 5·8; OMe, 14·9%), identical with the by-product of dimethylation (see below). It gave a wine-red ferric colour in ethanol, and was readily soluble in chloroform, benzene, or ethyl acetate. The 2 : 4-*dinitrophenylhydrazone* formed glistening, scarlet needles, m. p. 236° (decomp.), from ethyl acetate (Found : N, 14·1. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

Further elution of the column with benzene (600 c.c.) gave only 0·19 g. of a product, m. p. 99—103°. The column was then eluted with a 1% solution of acetic acid in ether (*ca.* 1 l.). The eluate was neutralised with sodium hydrogen carbonate and dried and the solvent distilled off. The residual yellow solid (3·84 g.), m. p. 76—85°, crystallised from methanol giving a mixture (1·42 g.), which consisted mainly of long, colourless, prismatic needles, together with a little of the above 6-methoxy-compound. A further crystallisation from methanol gave 5-acetyl-6-hydroxy-4-methoxycoumaran (dihydrovisnaginone; 1·03 g.), m. p. 100—101°, identical with the hydrogenation product of visnaginone described above. The residues, obtained by evaporation of the mother-liquors from a series of experiments, were collected and treated in the same way to obtain additional quantities of the two monomethyl ethers. A suspension of the alumina used (10 g.) in water (100 c.c.) had pH 8·4.

(b) *Dimethylation.* 5-Acetyl-4 : 6-dihydroxycoumaran (3 g.) in acetone (30 c.c.) containing anhydrous potassium carbonate (15 g.) was boiled under a reflux for 6 hours with methyl sulphate (7 g.) and then kept for 48 hours. After filtration of the mixture and evaporation of the filtrate, the residue was dissolved in ethyl acetate. This solution was extracted with dilute aqueous sodium hydroxide, and, on acidification of the alkaline extract, 5-acetyl-4-hydroxy-6-methoxycoumaran (0·3 g.), m. p. 102—106°, was obtained. Crystallisation from methanol raised the m. p. to 108—109°, and the product was identical with the monomethyl ether, m. p. 108—109°, described above.

The main ethyl acetate solution was washed and dried, then distilled to remove solvent; the residue (2·95 g.) crystallised from ethyl acetate–light petroleum (b. p. 40—60°) to give 5-acetyl-4 : 6-dimethoxycoumaran as colourless prisms, m. p. 94·5—95·5°, identical in all respects with the product obtained by methylating the hydrogenation product of visnaginone (above).

5-Acetyl-6-hydroxy-4-methoxycoumarone (*Visnaginone*) (V; R = H).—(a) *From chellol glucoside.* A solution of the glucoside (2 g.; obtained from the seeds of *Ammi visnaga*) in aqueous potassium hydroxide (100 c.c.; 1%) was boiled for 1 hour in an atmosphere of nitrogen. Visnaginone, obtained by acidification of the cooled solution, crystallised from methanol as bright yellow needles (0·7 g., 75%), m. p. 109—110°, which gave an emerald-green ferric colour in ethanol (cf. Späth and Gruber, *loc. cit.*, p. 1549).

(b) *From 5-acetyl-6-hydroxy-4-methoxycoumaran.* Dehydrogenation of the above product (0·5 g.) was effected by slow sublimation at low pressure through a 30-cm. column of palladium–charcoal (0·35 g.; 30%) supported on glass-wool (1·5 g.) maintained at 150°(see Baxter, Ramage, and Timson, *loc. cit.*). The crude visnaginone (0·41 g.), m. p. 103·5—106°, crystallised from methanol as fine, bright yellow needles, m. p. 109—110°, identical with the product obtained by method (a) above (Found : C, 64·05; H, 5·05. Calc. for $C_{11}H_{10}O_4$: C, 64·05; H, 4·9%).

5-Methoxy-2-methylfurano(3′ : 2′-6 : 7)*chromone* (*Visnagin*) (VI).—6-Hydroxy-5-β-ketobutyryl-4-methoxycoumarone was prepared by a slight modification of the method of Clarke, Glaser, and Robertson (*loc. cit.*) : visnaginone (0·5 g.), ethyl acetate (6 c.c.), and powdered sodium (0·2 g.) were boiled under a reflux for 2¼ hours. The solvent was distilled off and ice-water (20 c.c.) added to the residue. Acidification with glacial acetic acid yielded the crude diketone, which crystallised from aqueous ethanol in minute plates (0·3 g.), m. p. 94—96°, after drying in a vacuum over phosphoric oxide. Ring-closure was effected as described by the above authors and gave visnagin (0·2 g.), m. p. 140°, identical with the natural product.

4′ : 5′-Dihydro-5-methoxy-2-methylfurano(3′ : 2′-6 : 7)*chromone* (*Dihydrovisnagin*) (VII; R = Me, R′ = H) *and 4′ : 5′-Dihydro-5-hydroxy-2-methylfurano*(3′ : 2′-6 : 7)*chromone.*—A solution of 5-acetyl-6-hydroxy-4-methoxycoumaran (dihydrovisnaginone) (0·5 g.) in ethyl acetate (6 c.c.) was added to powdered sodium (0·2 g.), and the mixture boiled under a reflux for 2¼ hours with a further addition of ethyl acetate (2—3 c.c.) after 1½ hours. The solvent was distilled in a vacuum, and the residue treated with ice-water (20 c.c.) and acidified with glacial acetic acid. The solid product was filtered off, washed with water, then with a little ether, and dried. Crystallisation from 50% aqueous ethanol yielded *6-hydroxy-5-β-ketobutyryl-4-methoxycoumaran* (0·37 g.) as pale brown, short needles, m. p. 99—101°, depressed on admixture with the starting material (Found : C, 61·95, H, 5·4. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). It gave a wine-red ferric colour in ethanol, and was moderately soluble in acetone or chloroform, sparingly soluble in ethyl acetate. A solution of the diketone (0·2 g.) in glacial acetic acid (2·5 c.c.) containing 1 drop of concentrated hydrochloric acid was kept at 50° for 2¼ hours. After the addition of hot water (13 c.c.), *4′ : 5′-dihydro-5-methoxy-2-methylfurano*(3′ : 2′-6 : 7)*chromone* crystallised as colourless, silky, matted needles (0·16 g.), m. p. 113·5—114°, unchanged by a further crystallisation from aqueous methanol (Found : C, 67·05; H, 5·1. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). The pale yellow solution of the chromone in concentrated sulphuric acid became dark, greenish-brown when warmed.

When the ring-closure was carried out by boiling for 15 minutes a solution of the diketone (0·24 g.) in glacial acetic acid (2·5 c.c.) containing 1 drop of concentrated hydrochloric acid, repeated crystallisation of the product from light petroleum (b. p. 60—80°), then from methanol, gave *4′ : 5′-dihydro-5-hydroxy-2-methylfurano*(3′ : 2′-6 : 7)*chromone* as minute, colourless needles (50 mg.), m. p. 165—167° with sintering at 162° (Found : C, 65·6; H, 4·35. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%). It gave a dark red ferric colour in ethanol. Remethylation by boiling it for 16 hours with methyl sulphate in acetone containing potassium carbonate gave dihydrovisnagin, m. p.113°, identical with the product described above.

When a glacial acetic–hydrochloric acid solution of the diketone was boiled for 1 hour, it was possible to obtain both dihydrovisnagin and the demethylated product by chromatography of the benzene solution on alumina.

4′ : 5′-Dihydro-5-methoxy-2-methylfurano(2′ : 3′-7 : 8)*chromone* (VIII).—Treatment of 5-acetyl-4-hydroxy-6-methoxycoumaran (1 g.) with sodium (1 g.) and ethyl acetate (12 c.c.) as described in the previous experiment gave *4-hydroxy-5-β-ketobutyryl-6-methoxycoumaran* (0·8 g.), which crystallised from ethanol as clusters of tiny, colourless needles, m. p. 147—148°, with slight sintering at 144° (Found : C, 62·2; H, 5·65. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). In ethanol it gave a dark, wine-red ferric colour and was readily soluble in chloroform, and moderately soluble in acetone or benzene. Ring-closure was effected by boiling for 75 minutes a solution of the β-diketone (0·8 g.) in glacial acetic acid (7 c.c.) containing 1 drop of concentrated hydrochloric acid, or by keeping the solution at 50° for 2 hours. *4′ : 5′-Dihydro-5-methoxy-2-methylfurano*(2′ : 3′-7 : 8)*chromone*, which separated on the addition of water (30 c.c.), crystallised from aqueous ethanol (60%) as colourless, matted needles (0·45 g.), m. p. 193—194° (Found, after drying at 80° in a vacuum over phosphoric oxide immediately before analysis : C, 66·85; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2. Found, after keeping : C, 62·0; H, 5·5. $C_{13}H_{12}O_4.H_2O$ requires C, 62·4; H, 5·6%). The yellow solution of the chromone in concentrated sulphuric acid became emerald-green and finally bluish-purple when warmed. It was readily soluble in chloroform, moderately soluble in acetone, and sparingly soluble in benzene.

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