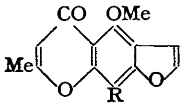
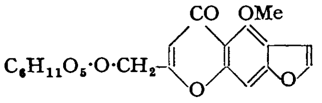
723. *Furanochromones derived from Quinol.*

By G. R. Ramage and C. V. Stead.

5-Methoxycoumaran-3-one (III; R = Me) has been reduced to the coumarone (IV) and to the coumaran (V; R = Me). Simultaneous acetylation and demethylation of this coumaran has led to 6-acetyl-5-hydroxycoumaran (VI; R = H). This compound and its dehydrogenation product have given, by extension of the side-chain and subsequent cyclisation, 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromones (XI; R = Me, H, or CO_2H) and the corresponding furanochromones (XIII).

The seeds of *Ammi visnaga*, a plant growing wild in the Eastern Mediterranean regions, have been shown to contain three compounds containing a furanochromone nucleus (see Huttrer and Dale, *Chem. Reviews*, 1951, **48**, 543). These are kellin (I; R = OMe), visnagin (I; R = H), and kellol glucoside (II). The first syntheses of one of these compounds, namely, kellin, occurred recently (Clarke and Robertson, *J.*, 1949, 302; Baxter, Ramage, and Timson, *ibid.*, p. S 30). Since the review by Huttrer and Dale (*loc. cit.*) visnagin has been synthesised by Gruber and Horváth (*Monatsh.*, 1950, **81**, 819), and kellol by Geissman and Bolger (*J. Amer. Chem. Soc.*, 1951, **73**, 5875).


(I)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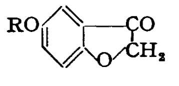
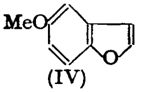

(III)

In all these furanochromes, the oxygen atoms which are involved in heterocyclic ring formation are situated in *meta*-positions. The preparation of compounds in which the heterocyclic oxygen atoms are *para* to one another is being undertaken in order to see whether the *meta*-orientation is of importance in determining the pharmacological activity. The simplest furanochromone of this type would result from the use of quinol as starting material.

Quinol dimethyl ether (Dyson, George, and Hunter, *J.*, 1927, 440) underwent reaction with chloroacetyl chloride in carbon disulphide solution and gave 2-hydroxy-5-methoxyphenacyl chloride, cyclisation of which yielded 5-methoxycoumaran-3-one (III; R = Me) (von Auwers and Pohl, *Annalen*, 1914, **405**, 281). Hydrogenation of this coumaranone at atmospheric pressure in the presence of Raney nickel gave a mixture from which 5-methoxycoumarone (IV) was isolated. This compound has been previously described by Stoermer (*Annalen*, 1900, **312**, 335), who prepared it by refluxing *p*-methoxyphenoxyacetaldehyde diethyl acetal with zinc chloride in acetic acid, and also, in a higher state of purity, by Tanaka (*J. Amer. Chem. Soc.*, 1951, **73**, 872) who obtained it from 2-hydroxy-5-methoxybenzaldehyde by condensation with ethyl bromomalonate, followed by cyclisation and decarboxylation.

On hydrogenation with Raney nickel at 60°/50 atm., (III; R = Me) yielded 5-methoxycoumaran (V; R = Me). This was a liquid which readily formed a highly crystalline dinitro-compound, presumably 5-methoxy-4 : 6-dinitrocoumaran. The coumaran (V; R = Me) was treated with acetyl chloride and aluminium chloride in carbon disulphide solution, and the product was separated into phenolic and non-phenolic fractions. The former gave 6-acetyl-5-hydroxycoumaran (VI; R = H) whereas the latter furnished a liquid ketone. Formation of tar made purification of both components difficult, but when reaction was effected in ether (cf. Oliverio and Lugli, *Gazzetta*, 1948, **78**, 16) the phenolic component was obtained in higher yield and in a purer state. The non-phenolic fraction, which distilled over the same temperature range as that from the reaction in carbon disulphide, then solidified to give 6-acetyl-5-methoxycoumaran (VI; R = Me). The relation of these two compounds as a phenol and its methyl ether was demonstrated by demethylating (VI; R = Me) with aluminium chloride in refluxing ether and yielded (VI; R = H), which on methylation re-formed (VI; R = Me).



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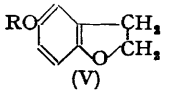

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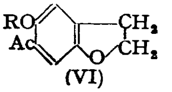

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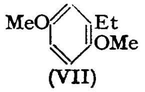
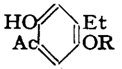


(VII)

The formulation of the product from the Friedel–Crafts reaction on (V; R = Me) as 6-acetyl-5-hydroxycoumaran was based on the fact that the structurally similar ethylquinol dimethyl ether (VII) was acetylated, under the conditions used for (V; R = Me), in the analogous position and gave 4-ethyl-2-hydroxy-5-methoxyacetophenone (VIII; R = Me). The orientation of (VIII; R = Me) followed from its preparation from *m*-ethylphenyl acetate by means of a Fries rearrangement which gave (IX), followed by nuclear oxidation with ammonium persulphate in alkaline solution giving (VIII; R = H), the monomethyl ether of which was identical with (VIII; R = Me).



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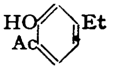

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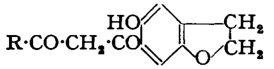
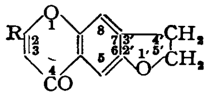
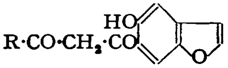


(X)

In the preparation of dihydrofuranochromones from (VI; R = H), the second heterocyclic ring system was readily built up by the method of Cheema, Gulati, and Venkataraman (*J.*, 1932, 925). Treatment of (VI; R = H) with ethyl acetate in the presence of powdered sodium gave, after crystallisation from water, 4′ : 5′-dihydro-2-methylfurano(2′ : 3′-6 : 7)chromone (XI; R = Me) instead of the expected (X; R = Me). The latter compound was probably formed first, but, during the heating inherent in crystallisation from water, cyclised to the chromone. Use of ethyl oxalate instead of ethyl acetate in the Claisen condensation gave the diketo-ester (X; R = CO_2Et). This compound cyclised to 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (XI; R = CO_2H). Decarboxylation of this acid was readily accomplished by heating it *in vacuo*, giving 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromone (XI; R = H).



(XI)



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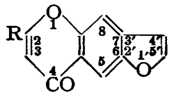

(XIII)

Subliming (VI; R = H) under reduced pressure through an electrically heated column of palladium–Norit (30%), prepared as described by Linstead and Thomas (*J.*, 1940, 1127), dehydrogenated it to 6-acetyl-5-hydroxycoumarone which undergoes Claisen condensations and cyclisations in the same manner as does the coumaran (VI; R = H). Thus, with ethyl acetate it gave 2-methylfurano(2′ : 3′-6 : 7)chromone (XIII; R = Me), and with ethyl oxalate the diketo-ester (XII; R = CO_2Et). The latter compound cyclised in acid to furano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (XIII; R = CO_2H) which was smoothly decarboxylated *in vacuo* to furano(2′ : 3′-6 : 7)chromone (XIII; R = H).

EXPERIMENTAL

5-*Methoxycoumarone* (IV).—5-Methoxycoumaran-3-one (10 g.) (von Auwers and Pohl, *loc. cit.*) was hydrogenated in ethanol (100 c.c.) in presence of Raney nickel catalyst (35 c.c.) at 60° for 4 hr. and then cooled. Filtration followed by distillation of the solvent left an oil which was fractionated. The portion, b. p. 156—160°/60 mm. (5·5 g., 60%), solidified in a refrigerator. It was crystallised from aqueous ethanol and sublimed at 50°/10^{-2} mm., to yield 5-methoxycoumarone as colourless needles, m. p. 31·5° (Found: C, 72·5; H, 5·4. Calc. for $C_9H_8O_2$: C, 73·0; H, 5·4%).

5-Methoxycoumaran (V; R = Me).—5-Methoxycoumaran-3-one (50 g.) and Raney nickel catalyst (20 c.c.) together with ethanol (400 c.c.) were agitated at 80° under hydrogen at 50 atm. for 4 hr. Cooling, filtration, evaporation, and fractionation gave *5-methoxycoumaran* (46 g., 92%) as a colourless oil, b. p. 134°/20 mm. (Found: C, 72·2; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

5-Methoxy-4 : 6-dinitrocoumaran.—By cautiously adding a solution of nitric acid (*d* 1·5; 1 c.c.) in glacial acetic acid (3 c.c.) to one of 5-methoxycoumaran (2 g.) in glacial acetic acid (3 c.c.), *5-methoxy-4 : 6-dinitrocoumaran*, obtained on dilution, formed light yellow needles, m. p. 107°, from methanol (Found: C, 45·4; H, 3·5. $C_9H_8O_6N_2$ requires C, 45·0; H, 3·4%).

6-Acetyl-5-methoxycoumaran (VI; R = Me) *and 6-Acetyl-5-hydroxycoumaran* (VI; R = H).—(*a*) Freshly sublimed aluminium chloride (6 g.) was added to a solution of 5-methoxycoumaran (6 g.) in carbon disulphide (40 c.c.), followed by a solution of acetyl chloride (5 c.c.) in carbon disulphide (10 c.c.). The mixture was refluxed for 20 hr., the solvent distilled off, and the residue powdered and added to ice (100 g.) and concentrated hydrochloric acid (5 c.c.). The resulting emulsion was extracted with ether, and the ethereal layer filtered and shaken with sodium hydroxide solution (25 c.c., 20%). The residual oil from the ethereal layer was distilled under reduced pressure (b. p. 153—158°/20 mm.) to yield an oil (2 g.), believed to be 6-acetyl-5-methoxycoumaran. After the alkaline layer had been freed from ether, it was cooled and acidified with 20% hydrochloric acid (20 c.c.). The fawn precipitate crystallised from ligroin, to yield yellow needles of *6-acetyl-5-hydroxycoumaran* (1·4 g., 20%), m. p. 109—111° (Found: C, 67·5; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%).

(*b*) Freshly sublimed aluminium chloride (30 g.) was dissolved in anhydrous ether (250 c.c.) with cooling. 5-Methoxycoumaran (20 g.) was then added, followed by acetyl chloride (10 c.c.), and the resulting mixture refluxed overnight. After cooling, ice (200 g.) and concentrated hydrochloric acid (20 c.c.) were added and the ethereal layer removed. This was extracted with sodium hydroxide solution (200 c.c., 5%) and the residual oil from the dried ethereal layer was distilled, to yield a colourless oil, b. p. 156°/20 mm., which solidified to a lemon-yellow solid. *6-Acetyl-5-methoxycoumaran* (5·4 g., 21%) crystallised from methanol in pale yellow needles, m. p. 82° (Found: C, 69·1; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). Its *2 : 4-dinitrophenylhydrazone*, prepared in methanol, crystallised from ethyl acetate in dark red needles, m. p. 212° (Found: C, 55·5; H, 4·4. $C_{17}H_{16}O_6N_4$ requires C, 54·8; H, 4·3%).

The alkaline layer was freed from ether and acidified with concentrated hydrochloric acid (25 c.c.). The pale yellow precipitate crystallised from ligroin, to yield 6-acetyl-5-hydroxycoumaran (8·5 g., 33%), m. p. 109—111°. Its *2 : 4-dinitrophenylhydrazone*, prepared in water, crystallised from 2-ethoxyethanol in red needles, m. p. 240° (Found: C, 53·3; H, 3·9. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9%).

Demethylation of 6-Acetyl-5-methoxycoumaran.—6-Acetyl-5-methoxycoumaran (1 g.) was added to a solution of freshly sublimed aluminium chloride (5 g.) in anhydrous ether (50 c.c.). The solution was refluxed for 20 hr., cooled, and added to ice (20 g.). An orange precipitate, presumably the aluminium chloride complex, dissolved on addition of concentrated hydrochloric acid (5 c.c.) and warming under reflux for 30 min. The ethereal layer was extracted with sodium hydroxide solution (20 c.c., 5%). The separated alkaline layer, freed from ether, was added to ice-cold concentrated hydrochloric acid (5 c.c.), and the precipitated phenol filtered off. Crystallisation from ligroin yielded 6-acetyl-5-hydroxycoumaran as yellow needles (0·3 g., 36%), m. p. 109—111°, identical with the product described above.

Ethylquinol Dimethyl Ether (VII).—To ethylquinol (30 g.) in potassium hydroxide solution (150 g., 33%), methyl sulphate (60 c.c.) was added in portions during 15 min. with shaking and ice-cooling. The mixture was shaken for a further 15 min. and then warmed on a steam-bath for 1 hr. The product was removed by steam-distillation and extracted from the distillate with carbon tetrachloride. Evaporation of the dried extract left *ethylquinol dimethyl ether* (26 g., 70%), b. p. 232° (Found: C, 72·8; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

4-Ethyl-2-hydroxy-5-methoxyacetophenone (VIII; R = Me).—Ethylquinol dimethyl ether (2·6 g.) was added to freshly sublimed aluminium chloride (3·4 g.) in anhydrous ether (30 c.c.). Acetyl chloride (1·3 g.) was added and the resulting mixture refluxed overnight. Ice (50 g.) and concentrated hydrochloric acid (5 c.c.) were added to the cooled solution, and the yellow ethereal layer removed and extracted with potassium hydroxide solution (20 c.c., 20%). The alkaline layer was freed from ether and acidified with concentrated hydrochloric acid. The light yellow precipitate crystallised from methanol, yielding *4-ethyl-2-hydroxy-5-methoxyacetophenone* as pale lemon-yellow needles (1·7 g., 27%), m. p. 60° (Found: C, 68·1; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). The *2 : 4-dinitrophenylhydrazone*, prepared in methanol, formed red needles (from ethyl acetate), m. p. 229° (Found : C, 54·3; H, 4·7. $C_{17}H_{18}O_6N_4$ requires C, 54·5; H, 4·8%).

m-*Ethylphenyl Acetate*.—*m*-Ethylphenol (56 g.) and acetyl chloride (75 c.c.) (1 hr. on a water-bath) gave *m*-ethylphenyl acetate (67 g., 89%), b. p. 234°.

2-*Hydroxy*-4-*ethylacetophenone* (IX).—*m*-Ethylphenyl acetate (45 g.) was mixed with powdered aluminium chloride (56 g.) and, after evolution of hydrogen chloride had ceased, the mixture was quickly heated to 120° in an oil-bath and the temperature was then raised to 165° during 15 min. Ice (500 g.) and concentrated hydrochloric acid (50 c.c.) were added and the light brown oil which separated was extracted with ether. Removal of the solvent from the dried ethereal solution left an oil which was fractionated. The fraction, b. p. 140—144°/20 mm., gave 4-*ethyl*-2-*hydroxyacetophenone* as a light yellow oil (37 g., 81%), b. p. 142°/20 mm. (Found : C, 73·0; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%). This was followed by a fraction of b. p. 195—200°/20 mm. which solidified to give 2-ethyl-4-hydroxyacetophenone, crystallising from carbon tetrachloride in colourless leaflets (3 g., 7%), m. p. 102° (Kenner and Statham, *J.*, 1935, 302, give m. p. 102°).

4-*Ethyl*-2 : 5-*dihydroxyacetophenone* (VIII; R = H).—4-Ethyl-2-hydroxyacetophenone (17·6 g.) was dissolved in potassium hydroxide solution (10%, 200 c.c.), and pyridine (50 c.c.) was added to keep the potassium salt in solution. Ammonium persulphate solution (28·2 g., in 300 c.c. of water) was added dropwise during 4 hr. with stirring and ice-cooling. The solution was left overnight, made just acid to Congo-red with concentrated hydrochloric acid, and extracted with chloroform to remove unchanged material (10 g.). The aqueous solution was then made strongly acid with concentrated hydrochloric acid (50 c.c.), and the mixture heated on a steam-bath for 30 min. On cooling, a pale yellow solid crystallised. This was filtered off and recrystallised from light petroleum (b. p. 60—80°), to yield 4-*ethyl*-2 : 5-*dihydroxyacetophenone* as yellow plates (0·45 g.), m. p. 100°, giving a transient green colour followed by a brown precipitate with ferric chloride solution (Found : C, 66·7; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). Extraction with ether failed to give a further quantity of pure material.

4-*Ethyl*-2-*hydroxy*-5-*methoxyacetophenone* (VIII; R = Me).—4-Ethyl-2 : 5-dihydroxyacetophenone (0·4 g.), anhydrous potassium carbonate (2·0 g.), methyl sulphate (0·32 g.), and acetone (10 c.c.) were heated on a water-bath under reflux for 5 hr. The acetone was then distilled off and dilute hydrochloric acid (20 c.c., from 3 c.c. of concentrated acid) added. The fawn solid crystallised from methanol, yielding 4-ethyl-2-hydroxy-5-methoxyacetophenone (0·2 g., 47%) as pale lemon-yellow needles, m. p. 58°, undepressed on admixture with a sample obtained by Friedel–Crafts acetylation of ethylquinol dimethyl ether as above, and gave the same 2 : 4-dinitrophenylhydrazone, m. p. 229°.

4′ : 5′-*Dihydro*-2-*methylfurano*(2′ : 3′-6 : 7)*chromone* (XI; R = Me).—6-Acetyl-5-hydroxycoumaran (1 g.), powdered sodium (0·6 g.), and dry ethyl acetate (10 c.c.) were heated under reflux on a steam-bath for 3 hr. and the excess of ethyl acetate then removed by distillation. The yellow sodium salt which remained was decomposed by ice (10 g.) and glacial acetic acid (0·5 c.c.), and the precipitate filtered off. On crystallisation from water, 4′ : 5′-*dihydro*-2-*methylfurano*(2′ : 3′-6 : 7)*chromone* formed colourless needles (0·5 g., 44%), m. p. 139° (Found : C, 71·7; H, 4·8. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%).

6-(β-*Ethoxycarbonyl*-β-*oxopropionyl*)-5-*hydroxycoumaran* (X; R = CO_2Et).—6-Acetyl-5-hydroxycoumaran (2 g.) was added to powdered sodium (1·2 g.), covered with dry ethyl oxalate (10 c.c.), and the mixture heated on a water-bath until vigorous evolution of hydrogen commenced. At this point, the reaction vessel was removed from the source of heat until the reaction had moderated. Heating was then continued until evolution of gas had ceased and for a further 30 min. (2 hr. in all). The dark red mass was then macerated with benzene (20 c.c.), and the insoluble sodium salt filtered off, washed with benzene, and dried. It was decomposed with ice (20 g.) and acetic acid (1 c.c.), and the precipitate removed. 6-(β-*Ethoxycarbonyl*-β-*oxopropionyl*)-5-*hydroxycoumaran* formed colourless needles, m. p. 133—134° (2·3 g., 74%), from ethanol (Found : C, 60·5; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1%).

4′ : 5′-*Dihydrofurano*(2′ : 3′-6 : 7)*chromone*-2-*carboxylic Acid* (XI; R = CO_2H).—The foregoing ester (1 g.) was heated with concentrated hydrochloric acid (1·25 c.c.) and glacial acetic acid (6 c.c.) for 1½ hr. After cooling, the crystalline precipitate of 4′ : 5′-*dihydrofurano*(2′ : 3′-6 : 7)*chromone*-2-*carboxylic acid* was filtered off and recrystallised from a large volume of glacial acetic acid, forming colourless needles (0·6 g., 72%), m. p. 307° (decomp.) (Found : C, 62·7; H, 3·6. $C_{12}H_8O_5$ requires C, 62·1; H, 3·5%).

4′ : 5′-*Dihydrofurano*(2′ : 3′-6 : 7)*chromone* (XI; R = H).—4′ : 5′-Dihydrofurano(2′ : 3′-6 : 7)-chromone-2-carboxylic acid (0·75 g.) was placed in a bent test-tube, covered with a glass wool plug, and heated. Smooth decarboxylation took place at a pressure of 4 mm. and the resulting dihydrofuranochromone sublimed, and was resublimed at 150°/10^{-4} mm. to yield colourless 4′ : *5′-dihydrofurano*(2′ : 3′-6 : 7)*chromone* (0·55 g., 83%), m. p. 170° (Found: C, 70·4; H, 4·3. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3%).

6-Acetyl-5-hydroxycoumarone.—6-Acetyl-5-hydroxycoumaran (2 g.) was sublimed at 100° into a 25″ column of 30% palladium–Norit (0·8 g.) prepared as described by Linstead and Thomas (*J.*, 1940, 1127) supported on glass wool (3·0 g.) and maintained at 150° by means of an external heating coil. Sublimation was carried out at 10^{-4} mm. When the reactant reached the catalyst, the pressure fell to about 10^{-2} mm., but after approx. 3 hr. the initial pressure was restored. The product was collected on a cold finger at the top of the catalyst tube. *6-Acetyl-5-hydroxycoumarone* condensed as a pale lemon-coloured solid (1·95 g., 98%) crystallising in squat needles, m. p. 89°, from ligroin (Found: C, 67·7; H, 4·5. $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%).

2-Methylfurano(2′ : 3′-6 : 7)*chromone* (XIII; R = Me).—6-Acetyl-5-hydroxycoumarone (2 g.) was added to dry ethyl acetate (20 c.c.) and powdered sodium (1·2 g.), and the whole refluxed on a water-bath for 3 hr. The excess of ethyl acetate was then distilled off and the sodium salt which remained was decomposed with ice (10 g.) and glacial acetic acid (0·5 c.c.). The precipitate crystallised from water, giving *2-methylfurano*(2′ : 3′-6 : 7)*chromone* as colourless needles (1·0 g., 44%), m. p. 167°. Further purification was effected by sublimation (140°/10^{-4} mm.), this raising the m. p. to 169° (Found: C, 71·7; H, 4·0. $C_{12}H_8O_3$ requires C, 72·0; H, 4·0%).

6-(β-*Ethoxycarbonyl*-β-*oxopropionyl*)-*5-hydroxycoumarone* (XII; R = CO_2Et).—6-Acetyl-5-hydroxycoumarone (2 g.) was added to ethyl oxalate (10 c.c.) and powdered sodium (1·2 g.) and the mixture warmed on a steam-bath until reaction commenced. The flask was then removed from the source of heat until the evolution of gas had moderated, then heated again until evolution of hydrogen had ceased and for a further 30 min. (about 2½ hr. in all). The cooled mixture was then macerated with benzene, and the dark red sodium salt filtered off and dried. The salt was decomposed with ice (20 g.) and acetic acid (1·5 c.c.) and the precipitate removed. 6-(β-Ethoxycarbonyl-β-oxopropionyl)-5-hydroxycoumarone was obtained as a light brown solid (2·8 g., 89%), m. p. 145°, and was not further purified.

Furano(2′ : 3′-6 : 7)*chromone-2-carboxylic acid* (XIII; R = CO_2H).—Crude diketo-ester (2 g.) was refluxed in glacial acetic acid (12 c.c.) containing concentrated hydrochloric acid (2·5 c.c.) for 1½ hr. and then cooled. The crystalline precipitate was removed and recrystallised from glacial acetic acid. *Furano*(2′ : 3′-6 : 7)*chromone-2-carboxylic acid* formed colourless rosettes (1·1 g., 66%), m. p. 341° (decomp.) (Found: C, 62·0; H, 3·1. $C_{12}H_6O_5$ requires C, 62·6; H, 2·6%).

Furano(2′ : 3′-6 : 7)*chromone* (XIII; R = H).—Furano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (0·75 g.) was decarboxylated as above. The material which sublimed was removed and resublimed (100°/10^{-4} mm.), giving colourless needles of *furano*(2′ : 3′-6 : 7)*chromone* (0·55 g., 83%), m. p. 149° (Found: C, 70·5; H, 3·7. $C_{11}H_6O_3$ requires C, 71·0; H, 3·2%).

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