229. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XVII. The Rotenonone Nucleus.*

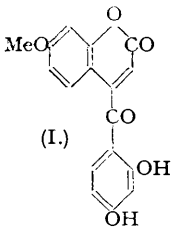
By G. Parker and Alexander Robertson.

Prepared from 7-methoxycoumarin-4-carboxyl chloride (VI; R = H) and resorcinol by the method of Friedel and Crafts, the 4-acylcoumarin (I) did not undergo cyclisation to the chromanonocoumarin (II). The analogous 3-acylcoumarin (III; R = H) was readily cyclised, yielding chromanonodihydrocoumarin (IV; R = H), whilst the condensation of 7-methoxycoumarin-3-carboxyl chloride with resorcinol gave (IV; R = OMe) directly. When 3 : 7-dimethoxycoumarin-4-carboxyl chloride (VI; R = OMe) was employed in place of (VI; R = H) the acylcoumarin (VII) was obtained which on treatment with hot hydrobromic acid in acetic acid furnished the chromonocoumarin (VIII).

As far as we are aware chromono(2′ : 3′-3 : 4)coumarins of the rotenonone type (Part XVI, *J.*, 1949, 2049) have not been synthesised previously and the experiments in the present communication represent the successful outcome of an investigation undertaken with this objective. In the first instance, it appeared that a direct route to compounds containing the rotenonone heterocyclic nucleus of type (VIII) was by cyclisation of acylcoumarins of type (I) to give the chromanono(2′ : 3′-3 : 4)-3 : 4-dihydrocoumarins of type (II), followed by dehydrogenation at the 3- and the 4-position. Although on general grounds the cyclisation of (I) would be expected to be difficult, it appeared desirable to explore this route, more especially in view of the ready accessibility of the intermediate coumarin-4-carboxylic acids required for the preparation of acylcoumarins of type (I).

The acid chloride of 7-methoxycoumarin-4-carboxylic acid was conveniently prepared by means of phosphorus pentachloride in chloroform and, on Friedel–Crafts condensation with resorcinol in nitrobenzene, gave a good yield of 2′ : 4′-*dihydroxy*-7-*methoxy*-4-*benzoylcoumarin* (I) which had the expected ferric reaction in alcohol and formed a *diacetate*. All attempts, however, to cyclise (I) with boiling alcohol containing hydrochloric, sulphuric, or phosphoric acid or with aluminium chloride in nitrobenzene were unsuccessful. In contrast with the behaviour of the compound (I), the analogous 2′ : 4′-*dihydroxy*-3-*benzoylcoumarin* (III; R = H), as expected, readily underwent cyclisation, giving 7′-*hydroxychromanono*(3′ : 2′-3 : 4)-3 : 4-*dihydrocoumarin* (IV; R = H) under the standard conditions employed for the conversion of chalkones into flavanones and even on being boiled with acetic acid or alcohol. The acylcoumarin (III; R = H) prepared by the interaction of coumarin-3-carboxyl chloride with resorcinol in nitrobenzene containing aluminium chloride was accompanied by a small amount of the chromanono(3′ : 2′-3 : 4)-3 : 4-dihydrocoumarin (IV; R = H). Unfortunately, in subsequent

experiments the product consisted almost entirely of the latter compound and we were unable to repeat the preparation of the ketone (III; R = H) in quantity.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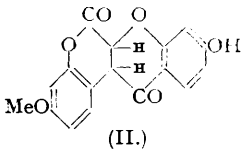
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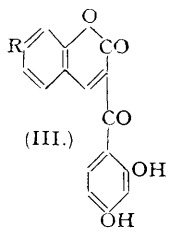
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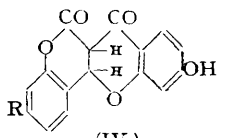
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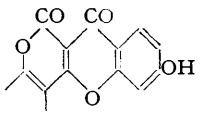
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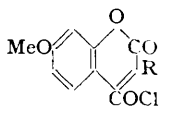
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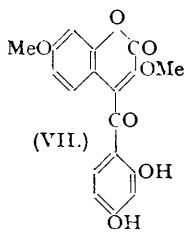
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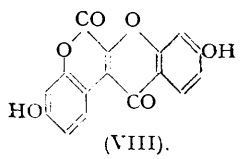
(VIII).

Similarly, when 7-methoxycoumarin-3-carboxyl chloride was employed the product from the Friedel–Crafts reaction with resorcinol consisted entirely of *7′-hydroxy-7-methoxychromanono-(3′ : 2′-3 : 4)-3 : 4-dihydrocoumarin* (IV; R = OMe). Attempts to effect the dehydrogenation of (IV; R = H) or its *methyl ether* by the usual methods employed for the conversion of rotenone derivatives into the corresponding dehydro-compounds, *e.g.*, iodine and sodium acetate, chromic oxide in acetic acid, nitrous acid, or selenium dioxide, were unsuccessful. Ultimately, it was found that on treatment with lead tetra-acetate in warm acetic acid the chromanono-3 : 4-dihydrocoumarin (IV; R = H) was almost quantitatively converted into *7′-hydroxychromono-(3′ : 2′-3 : 4)coumarin* (V), characterised by the formation of the *acetate*.

In view of the failure to prepare the intermediate chromanono-3 : 4-dihydrocoumarins of type (II) which could be dehydrogenated to give the rotenonone nucleus we turned our attention to the possibility of employing a suitable oxidation product of the coumarin acid residue which could be cyclised to give the required chromono(2′ : 3′-3 : 4)coumarins directly. For this purpose the 3-methoxycoumarin-4-carboxylic acids, which are now readily accessible (Part XVI, *loc. cit.*), seemed to be suitable. Accordingly, the acid chloride (VI; R = OMe) of *3 : 7-dimethoxycoumarin-4-carboxylic acid* was condensed with resorcinol in nitrobenzene by means of aluminium chloride, giving a satisfactory yield of *2′ : 4′-dihydroxy-3 : 7-dimethoxy-4-benzoylcoumarin* (VII) which had the expected properties and formed a *diacetate*. Attempts to cyclise the keto-coumarin (VII) by means of hot concentrated hydrochloric acid in acetic acid were unsuccessful, but use of hydrobromic acid led to cyclisation with simultaneous demethylation, thus furnishing *7 : 7′-dihydroxychromono(2′ : 3′-3 : 4)coumarin* (VIII) which, on treatment with ethereal diazomethane, gave the *dimethyl ether*. When 3 : 7-dimethoxycoumarin-4-carboxyl chloride (VI; R = OMe) was replaced by 3-chloro-7-methoxycoumarin-4-carboxyl chloride (VI; R = Cl) the condensation with resorcinol could not be effected with aluminium chloride under the usual conditions. The use of aluminium bromide, however, gave a small yield of 7 : 7′-dihydroxychromono(2′ : 3′-3 : 4)coumarin (VIII). In preliminary experiments on the synthesis of tetrahydrorotenonone by means of the requisite 3-methoxycoumarin derivative we were unable, *e.g.*, to effect the condensation of (VI; R = OMe) with tetrahydrotubanol, but further studies on this and allied problems are being pursued.

Experimental.

2′ : 4′-Dihydroxy-7-methoxy-4-benzoylcoumarin (I).—A mixture of 7-methoxycoumarin-4-carboxylic acid (von Pechmann and Graeger, *Ber.*, 1901, **34**, 384) (5 g.) and phosphorus pentachloride (4·73 g.) in chloroform (60 ml.) was gently warmed on the water-bath until the evolution of hydrogen chloride had ceased (1½ hours), and the solvent and phosphorus oxychloride were distilled off in a vacuum. To remove a little residual phosphorus oxychloride the product was dissolved in chloroform (50 ml.) and the solution evaporated in a vacuum, leaving the acid chloride as a pale yellow solid which was used in the Friedel–Crafts reaction without further purification. Warmed gently with aniline for 5 minutes a specimen of the chloride gave the *anilide* which separated from alcohol in pale greenish-yellow needles, m. p. 181° (Found: C, 69·2; H, 4·86; N, 4·9. $C_{17}H_{13}O_4N$ requires C, 69·2; H, 4·4; N, 4·7%).

A solution of the foregoing acid chloride (from 10 g. of acid) and resorcinol (5 g.) in nitrobenzene (40 ml.) was mixed with aluminium chloride (7 g.), and the resulting dark mixture kept at 60° for 6 hours, cooled, and treated with water (75 ml.), followed by concentrated hydrochloric acid (75 ml.). The nitrobenzene was removed with a current of stream, and on being cooled the residue deposited 2′ : 4′-*dihydroxy-7-methoxy-4-benzoylcoumarin* which was collected, triturated with aqueous sodium hydrogen carbonate, well washed with water, and crystallised from 50% acetic acid (charcoal), forming almost colourless rhombic prisms (6·7 g.), m. p. 237—238° (Found : C, 65·5; H, 4·0; OMe, 9·6. $C_{16}H_9O_5$·OMe requires C, 65·4; H, 3·8; OMe, 9·9%). This compound, which was soluble in methanol, alcohol, or ethyl acetate and gave a wine-red ferric reaction in alcohol, furnished a *diacetate* with pyridine–acetic anhydride at 100° or sodium acetate–acetic anhydride at 145°. This derivative separated from a small volume of acetic acid in rosettes of colourless needles, m. p. 88° (Found : C, 63·4; H, 4·3. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%).

In the course of numerous attempts to convert this ketone into the isomeric chromanono-3 : 4-dihydrocoumarin it was observed that prolonged warming of the compound with alcoholic hydrogen chloride or boiling with alcoholic sulphuric acid gave rise to small quantities of ethyl 7-methoxycoumarin-4-carboxylate (Part XVI, *loc. cit.*) along with unchanged ketone. The ester separated from a little alcohol or aqueous acetic acid in needles, m. p. 63° [Found : C, 63·0; H, 4·8; Alkyl-O, 11·5%; *M*, 257. Calc. for $C_{10}H_4O_3(OMe)(OEt)$: C, 62·9; H, 4·8; Alkyl-O, 12·9%; *M*, 248].

7′-*Hydroxychromanono*(3′ : 2′-3 : 4)-3 : 4-*dihydrocoumarin* (IV; R = H).—Prepared from coumarin-3-carboxylic acid (Khan *et al.*, *Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 440) by the phosphorus pentachloride–chloroform procedure, the acid chloride formed needles (from chloroform or chloroform–light petroleum), which invariably had m. p. 137° (bath pre-heated to 130°) (cf. Lampe and Trenknerowna, *Roczniki Chem.*, 1934. **14**, 1231, and Boehm and Schumann, *Arch. Pharm.*, 1933, **271**, 490, who respectively give m. p. 136—137° and 147—149°). The anilide separated from benzene or much alcohol in yellow prisms, m. p. 249—250° (Found : N, 5·4. Calc. for $C_{15}H_{11}O_3N$: N, 5·2%) (cf. Ahluwalia, Haq, and Ray, *J.*, 1931, 2059, who give m. p. 247°). Interaction of the acid chloride (5 g.), phenol (2·5 g.), and aluminium chloride (4·5 g.) at room temperature for 3 days gave *phenyl coumarin-3-carboxylate* which was isolated by treatment of the reaction mixture with ice (200 g.), followed by the removal of the nitrobenzene with steam. The solid was isolated from the cooled residue, triturated with an excess of aqueous sodium hydrogen carbonate, and crystallised from alcohol, giving the ester (3·2 g.) in colourless flat prisms, m. p. 160°, identical with a specimen prepared by the interaction of the acid chloride with pyridine and phenol on the steam-bath for 15 minutes (Found : C, 72·2; H, 3·8. $C_{16}H_{10}O_4$ requires C, 72·1; H, 4·0%). When phenol was replaced by *p*-cresol in the foregoing Friedel–Crafts reaction carried out at room temperature for 3 days, at 120° for 20 minutes, or at 140° for 45 minutes the p-*tolyl* ester (3·3—4·5 g.) was obtained. This separated from alcohol in elongated prisms or from benzene in feather-like masses of needles, m. p. 159°, having a negative ferric reaction (Found : C, 73·0; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%).

Aluminium chloride (3·6 g.) was added in small portions to an agitated mixture of the acid chloride (from 5 g. of coumarin-3-carboxylic acid) and resorcinol (2·8 g.) in nitrobenzene (30 ml.) kept at room temperature, and 2 days later the nitrobenzene was removed with steam, leaving a brownish-yellow solid in the aqueous liquor. This product was extracted with boiling alcohol (25 ml.) for 5 minutes, and the extract was filtered to remove the insoluble residue and diluted with water to precipitate 2′ : 4′-*dihydroxy-3-benzoylcoumarin* (III; R = H). Crystallised from a small volume of acetone, this keto-coumarin formed yellow pointed prisms (3·1 g.), m. p. 234° (decomp.), soluble in alcohol or ethyl acetate, sparingly soluble in warm benzene, and having a deep red ferric reaction in alcohol (Found : C, 67·8; H, 3·5. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·5%).

The insoluble residue, left after the extraction of the foregoing ketone with alcohol, was crystallised from acetic acid or much dioxan, giving the 7′-*hydroxychromanono*(3′ : 2′-3 : 4)-3 : 4-*dihydrocoumarin* (IV; R = H) in yellow irregular prisms (1·2 g.), which melt above 320° and have a negative ferric reaction in alcohol (Found : C, 68·2; H, 3·7%). This compound, which is sparingly soluble in the usual organic solvents except acetic acid, formed a pale green solution in concentrated sulphuric acid which had an intense green fluorescence. The same chromanono-3 : 4-dihydrocoumarin was obtained in almost theoretical yield when 2′ : 4′-dihydroxy-3-benzoylcoumarin was dissolved in boiling acetic acid and the solution allowed to cool, or on prolonged boiling of alcoholic solutions of the ketone with or without the addition of a few drops of concentrated hydrochloric acid. The *acetate* of the compound (IV; R = H) separated from dilute acetic acid in almost colourless plates, m. p. 230—231° (Found : C, 66·9; H, 3·8. $C_{18}H_{12}O_6$ requires C, 66·7; H, 3·7%). Prepared by means of methyl sulphate and potassium carbonate in boiling acetone, the *methyl ether* formed rosettes of pale yellow needles, m. p. 250° (Found : C, 68·9; H, 4·3; OMe, 10·0. $C_{16}H_9O_4$·OMe requires C, 68·9; H, 4·0; OMe, 10·5%). The chromanono-3 : 4-dihydrocoumarin and its methyl ether dissolve in warm aqueous sodium hydroxide giving a yellow solution.

[With G. W. K. Cavill] 7′-*Hydroxychromono*(3′ : 2′-3 : 4)*coumarin* (V).—The foregoing chromanono-(3′ : 2′-3 : 4)-3 : 4-dihydrocoumarin (0·7 g.) in acetic acid (100 ml.) was treated with lead tetra-acetate (1·1 g.), and the mixture kept at 50—60° for 6 hours and then at 80° for 2 hours. On cooling, the reaction mixture was filtered to remove unchanged material (0·4 g.), and the filtrate evaporated in a vacuum, leaving the *chromono*(3′ : 2′-3 : 4)*coumarin* which separated as a *hydrate* from aqueous dioxan in clusters of tiny, orange-yellow prisms (0·2 g.), m. p. above 360° (Found, in a specimen dried at room temperature : C, 64·3; H, 3·9. $C_{16}H_8O_5,H_2O$ requires C, 64·4; H, 3·4%. Found, in specimen dried in a high vacuum at 110° : C, 68·5; H, 2·9. $C_{16}H_8O_5$ requires C, 68·6; H, 2·9%). This compound, which is sparingly soluble in alcohol or chloroform, forms a pale yellow solution in concentrated sulphuric acid, exhibiting a green fluorescence. The *acetate* formed characteristic irregular plates, m. p. 224° (decomp.), from aqueous dioxan (Found : C, 67·2; H, 3·1. $C_{18}H_{10}O_6$ requires C, 67·1; H, 3·1%). Mixed with a specimen of 7-acetoxychromanono(3′ : 2′-3 : 4)-3 : 4-dihydrocoumarin, m. p. 231°, this compound melted at 194—196° (decomp.).

7′-*Hydroxy-7-methoxychromanono*(3′ : 2′-3 : 4)-3 : 4-*dihydrocoumarin* (IV; R = OMe).—The acid

chloride was prepared from 7-methoxycoumarin-3-carboxylic acid (von Pechmann and Graeger, *Ber.*, 1901, **34**, 381) by the phosphorus pentachloride–chloroform method and gave the *anilide* which formed pale green prisms, m. p. 232°, from acetic acid (Found : N, 4·6; OMe, 10·4. $C_{16}H_{10}O_3N{\cdot}OMe$ requires N, 4·7; OMe, 10·5%).

Interaction of the crude acid chloride (from 5 g. of acid), resorcinol (2·7 g.), and aluminium chloride (4·5 g.) in nitrobenzene (20 ml.) at room temperature for 48 hours gave *7′-hydroxy-7-methoxychromanono-(3′ : 2′-3 : 4)-3 : 4-dihydrocoumarin*. This separated from 80% acetic acid or aqueous dioxan in orange-yellow polyhedra, m. p. 214° (decomp.), which contained solvent of crystallisation and on being dried in a high vacuum at 100° did not melt below 300° (Found, in dried material : C, 65·4; H, 4·5. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·8%). Both the solvated and the anhydrous form dissolve instantaneously in 2N-aqueous sodium hydroxide, giving a scarlet solution which becomes colourless in a few seconds. The *acetate* crystallised from 50% acetic acid or alcohol in colourless prisms, m. p. 167° (Found : C, 64·2; H, 4·1. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%)

3 : 7-Dimethoxycoumarin-4-carboxylic Acid.—Ethyl 3 : 7-dimethoxycoumarin-4-carboxylate (Part XVI, *loc. cit.*) (3 g.) was heated under reflux with sulphuric acid (40 ml. of concentrated acid and 100 ml. of water) for 45 minutes, cooled, diluted with water (150 ml.), and extracted with ether (150 ml. × 5). *3 : 7-Dimethoxycoumarin-4-carboxylic acid* was isolated from the combined ethereal extracts by means of aqueous sodium hydrogen carbonate (100 ml. × 3) and crystallised from ether, forming colourless rectangular plates (1·7 g.), m. p. 212°, readily soluble in the usual organic solvents except benzene, chloroform, or light petroleum (Found : C, 57·2; H, 4·1%; *M*, 240. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%; *M*, 250). Prepared by the phosphorus pentachloride–chloroform method, the acid chloride (VI; R = OMe) was obtained as a light-brown solid which gave the *anilide* as colourless prisms, m. p. 191°, from alcohol or acetic acid (Found : C, 66·4; H. 4·8. $C_{18}H_{15}O_5N$ requires C, 66·5; H, 4·6%).

2′ : 4′-Dihydroxy-3 : 7-dimethoxy-4-benzoylcoumarin (VII).—A mixture of the foregoing acid chloride (from 3 g. of acid), resorcinol (1·4 g.), aluminium chloride (2 g.), and nitrobenzene (20 ml.) was kept at 70° until the evolution of hydrogen chloride had ceased (about 7 hours). The cooled reaction mixture was treated with water (40 ml.) and concentrated hydrochloric acid (40 ml.), kept for an hour, and extracted with ether (70 ml. × 4). The dried ethereal extracts were evaporated and on treatment with light petroleum (b. p. 40—60°) (250 ml.) the dark residual liquor deposited a dark brown viscous product which, on trituration with fresh light petroleum, became semi-solid and was then washed with aqueous sodium hydrogen carbonate, triturated with a little pyridine, dried, and crystallised from ethyl acetate, giving *2′ : 4′-dihydroxy-3 : 7-dimethoxy-4-benzoylcoumarin* in bright yellow rhombic prisms (2·1 g.), m. p. above 300° (Found : C, 63·0; H, 4·2%; *M*, 348·6. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%; *M*, 342·0). This keto-coumarin is sparingly soluble in cold alcohol, acetic acid, or benzene and gives an intense bottle-green ferric reaction in alcohol. Prepared by pyridine–acetic anhydride, the *diacetate* separated from acetic acid in long needles or from ethyl acetate in sharp prisms, m. p. 264°, having a negative ferric reaction (Found : C, 61·7; H, 4·5. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·2%).

7 : 7′-Dihydroxychromono(2′ : 3′-3 : 4)coumarin (VIII).—(*a*) The foregoing benzoylcoumarin (1 g.) was heated under reflux with a mixture of hydrobromic acid (20 ml.; sp. gr., 1·51) and acetic acid (10 ml.) for 2 hours and the resulting dark red solution diluted with water (100 ml.), neutralised with sodium hydrogen carbonate, and repeatedly extracted with ether (60 ml. × 10). Evaporation of the dried extracts left the *chromono(2′ : 3′-3 : 4)coumarin* (VIII) as a pale yellow solid which, on crystallisation from a little acetone or from aqueous dioxan, formed pale yellow, tiny, irregular plates (0·45 g.), m. p. above 320°, having a negative ferric reaction (Found : C, 65·1; H, 3·0. $C_{16}H_8O_6$ requires C, 64·9; H, 2·7%). This compound is sparingly soluble in the usual organic solvents except acetone, pyridine, or dioxan, and its solutions exhibit a blue fluorescence. The *dimethyl ether* was prepared by means of ethereal diazomethane and was crystallised from benzene, forming pale yellow, elongated flat prisms, m. p. 240° after slight sintering at 222°, soluble in acetone, ethyl acetate, chloroform, or alcohol (Found : C, 66·6; H, 4·0. $C_{18}H_{12}O_6$ requires C, 66·7; H, 3·7%). With concentrated sulphuric acid the parent chromono-coumarin forms an intense red solution which is unchanged on the addition of concentrated nitric acid. With sulphuric acid the methyl ether gives a red solution which becomes purple on the addition of concentrated nitric acid. With concentrated nitric acid the ether forms a bright green solution.

(*b*) Interaction of the acid chloride (VI; R = Cl) of 3-chloro-7-methoxycoumarin-4-carboxylic acid (Part XVI, *loc. cit.*) (prepared by the phosphorus pentachloride–chloroform method from 5 g. of acid) with resorcinol (4·3 g.) and aluminium bromide (12·5 g.) in nitrobenzene (50 ml.) at 65° for 6 hours gave a dark reaction mixture which was poured on ice and hydrochloric acid. The mixture was extracted with ether (80 ml. × 12), the ethereal extracts evaporated, the residue mixed with light petroleum (b. p. 40—60°) (300 ml.), and the resulting precipitate crystallised from dioxan, giving 7 : 7′-dihydroxy-chromono(2′ : 3′-3 : 4)coumarin in characteristic minute, pale yellow prisms, (0·3 g.), m. p. above 320°, identical with a specimen prepared by method (*a*).

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