438. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XVI. The Synthesis of Abutic Acid and its Analogues.*

By G. W. Holton, G. Parker, and Alexander Robertson.

Application of the Perkin transformation to esters of 3-chlorocoumarin-4-carboxylic acids and to their methyl ethers of type (IV), derived from resorcinol, phloroglucinol, and pyrogallol, gave satisfactory yields of the corresponding coumarone-2 : 3-dicarboxylic acids type (VI). By this procedure abutic acid (VIII), a degradation product of rotenononic acid, has been synthesised from 4-hydroxyveratrole.

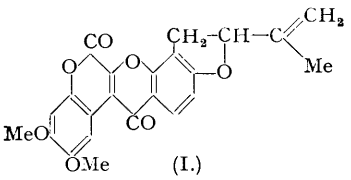
It has also been shown that on being heated with alkali the esters of 3-methoxycoumarin-4-carboxylic acids of type (IX), derived from resorcinol and phloroglucinol, are also readily converted into the corresponding coumarone-2 : 3-dicarboxylic acids, a process which affords a close analogy to the mechanism postulated for the rotenonone–rotenononic acid change (La Forge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1091).

When rotenone is oxidised with nitrous acid or chromic acid (Butenandt, *Annalen*, 1928, **464**, 255; Takei, *Biochem. Z.*, 1925, **157**, 1) the group $O{\cdot}CH_2{\cdot}C<$ is converted into a lactone system with the formation of the compound rotenonone $C_{23}H_{18}O_7$, for which the structure (I) has been proposed. Under the influence of warm 5% aqueous potassium hydroxide this lactone is hydrolysed and the resulting product (II) subsequently undergoes rearrangement with the formation of rotenononic acid to which the structure (III) has been allocated. The latter formula was deduced from the behaviour of the acid on oxidation with hydrogen peroxide whereby there is formed tubaic acid along with a dibasic acid, abutic acid, for which Takei (*Ber.*, 1932, **65**, 1049) has proposed formula (VIII). In this connection it may be noted that the mechanism postulated for the formation of rotenononic acid from rotenonone finds a close analogy in the well known Perkin transformation of a 3-halogen-substituted coumarin into the corresponding coumarone-2-carboxylic acid (*J.*, 1870, **8**, 368; 1871, **9**, 37), a reaction which has been extensively investigated. As a first step in attempting to confirm the formula proposed for rotenononic acid the synthesis of abutic acid was undertaken and the present communication deals with this topic.

As far as we have been able to learn from the literature, three routes have been employed for the synthesis of coumarone-2 : 3-dicarboxylic acids : (*a*) from isatin (Titanoff *et al.*, *Helv. Chim. Acta*, 1937, **20**, 883; Huntress and Hearson, *J. Amer. Chem. Soc.*, 1941, **63**, 2762), (*b*) by the cyclisation of oxalophenoxyacetate (Koelsch and Whitney, *ibid.*, p. 1762; Huntress and Olsen, *ibid.*, 1948, **70**, 2856), and (*c*) by the application of the Perkin transformation to 3-chloro-4-carbethoxycoumarins (Dey, *J.*, 1915, **107**, 1606), *e.g.*, conversion of type (IV) into type (VI) by way of (V). Although the only examples of procedure (*c*) described by Dey are the transformations of the ethyl 3-chloro-7-methyl- and 6 : 7-dimethyl-coumarin-4-carboxylate into the corresponding coumarone-2 : 3-dicarboxylic acids, this route appeared to us to be a flexible one, especially in the case of derivatives of *m*-dihydroxyphenols where the requisite 3-chlorocoumarins are readily accessible by means of the von Pechmann reaction or a modification of it. Further, it seemed likely that this method would afford a means of preparing hydroxy-derivatives of coumarone-2 : 3-dicarboxylic acids.

Accordingly, in conjunction with the synthesis of abutic acid by this procedure we have also applied the reaction to a series of 3-chlorocoumarins type (IV) derived from resorcinol, phloroglucinol, and pyrogallol. For example, the condensation of resorcinol with ethyl β-chloro-β-carbethoxypyruvate by the alcohol–hydrogen chloride method (modified von Pechmann method) gave an excellent yield of *ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate* (IV; R = H, R′ = Et), which on methylation furnished the *methyl ether* (IV; R = Me; R′ = Et) identical with the product formed directly when resorcinol is replaced by resorcinol monomethyl ether in the von Pechmann reaction. When heated under reflux with 5% aqueous potassium hydroxide the carbethoxycoumarin (IV; R = H, R′ = Et) was almost quantitatively converted into 6-*hydroxycoumarone-2 : 3-dicarboxylic acid* (VI; R = R′ = H). When the methyl ether (IV; R = Me, R′ = Et) of this coumarin was warmed with 5% aqueous potassium hydroxide on the steam-bath, the carbethoxy-group was hydrolysed without the Perkin transformation being effected and 3-*chloro-7-methoxycoumarin-4-carboxylic acid* (IV; R = Me, R′ = H) was obtained, identical with a specimen prepared by hydrolysis of the ester with boiling 40% sulphuric acid. The structure of this acid was confirmed by its reconversion into the original ethyl ester by the ethyl iodide–silver salt method. When heated under reflux with 10% aqueous potassium hydroxide or with 20% methanolic potassium hydroxide ethyl 3-chloro-7-methoxycoumarin-4-carboxylate was transformed almost quantitatively into 6-*methoxycoumarone-2 : 3-dicarboxylic*

acid, identical with the acid prepared by methylation of 6-hydroxycoumarone-2 : 3-dicarboxylic acid with diazomethane and subsequent hydrolysis of the resulting *methyl* 6-*methoxycoumarone*-2 : 3-*dicarboxylate*.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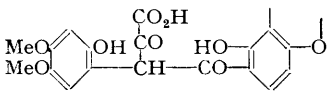
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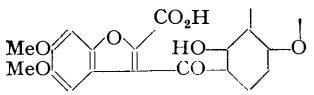
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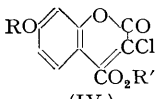
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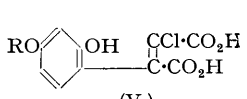
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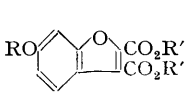
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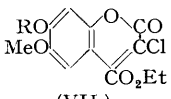
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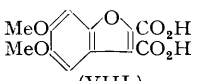
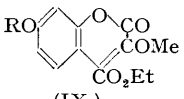

(VIII.)


(IX.)

For the synthesis of abutic acid *ethyl* 3-*chloro*-7-*hydroxy*-6-*methoxycoumarin*-4-*carboxylate* (VII; R = H) was prepared from 2 : 4-dihydroxyanisole by the modified von Pechmann method and on methylation furnished *ethyl* 3-*chloro*-6 : 7-*dimethoxycoumarin*-4-*carboxylate* (VII; R = Me), identical with a specimen prepared directly from 4-hydroxyveratrole by the general method. On being boiled with 10% aqueous sodium hydroxide the latter coumarin was converted into abutic acid having properties identical with those of the natural derivative. In this case the yield of the crude conversion product was satisfactory but that of the purified material was considerably reduced owing to losses incurred in removing small amounts of dark impurities.

As a closer analogy to the rotenonone–rotenononic acid change than is afforded by the conversion of 3-chlorocoumarins into the corresponding coumarone-2 : 3-dicarboxylic acids, we have examined the behaviour of 3-methoxycoumarins of type (IX), derived from resorcinol and phloroglucinol, towards warm alkalis. *Ethyl* 7-*hydroxy*-3-*methoxycoumarin*-4-*carboxylate* (IX; R = H) has been prepared by the interaction of resorcinol and the sodio-derivative of *ethyl* β-*methoxy*-β-*carbomethoxypyruvate* in boiling alcohol, and on treatment with boiling methanolic potassium hydroxide is converted into 6-hydroxycoumarone-2 : 3- dicarboxylic acid (VI; R = R′ = H). Likewise the methyl ether (IX; R = Me), which is obtained from the phenol (IX; R = H) by the methyl iodide–potassium carbonate or diazomethane method, gives 6-methoxycoumarone-2 : 3-dicarboxylic acid under similar conditions. Similarly, *ethyl* 3 : 5 : 7-*trimethoxycoumarin*-4-*carboxylate* was prepared from phloroglucinol dimethyl ether and with hot alkali gave 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid identical with a specimen obtained from the analogous 3-chlorocoumarin. These results serve to support the conclusion of La Forge and Smith (*J. Amer. Chem. Soc.*, 1930, **52**, 1091) regarding the mechanism of the rotenonone–rotenononic acid change and the structure of the resulting rotenononic acid.

Experimental.

Ethyl β-*Chloro*-β-*carbethoxypyruvate*.—The following recipe was employed for the preparation of this compound (cf. Wislicenus, *Ber.*, 1910, **43**, 3529). Ethyl chloroacetate (122 g.) was added dropwise in the course of 3 hours to a frequently agitated mixture of ethyl oxalate (146 g.) and ether (400 ml.) containing alcohol-free sodium ethoxide (from 23 g. of sodium) at room temperature. 24 Hours later the yellow sodio-derivative was dissolved in ice-cold water (200 ml.), the mixture was acidified (Congo-red) with dilute hydrochloric acid, the ethereal layer was separated, the residue was extracted with ether (100 ml.), and the combined ethereal solutions were dried and evaporated. Distillation of the product in a vacuum gave the ester as a pale yellow liquid (120 g.), b. p. 139—142°/12 mm. We have found that the preparation of this compound by the chlorination of ethyl oxaloacetate with sulphuryl chloride as described by Peratoner (*Gazzetta*, 1892, **22**, No. 11, 38) is troublesome and gives lower yields of a product which is difficult to purify.

The interaction of pulverised sodium (5·8 g.), methyl oxalate (29·5 g.), and methyl chloroacetate (30 ml., added dropwise with continued stirring) in ether (100 ml.) gave rise to the sodio-derivative of *methyl* β-*chloro*-β-*carbomethoxypyruvate* in the course of 2 days. Decomposition of this solid by means of dilute acetic acid, followed by isolation with ether, gave the ester (20·5 g.), as a mobile pale yellow oil, b. p. 113—115°/0·3 mm., having a violet-red ferric reaction in alcohol (Found : C, 36·6; H, 3·9; Cl, 18·8. $C_8H_7O_5Cl$ requires C, 37·0; H, 3·6; Cl, 18·3%).

Ethyl β-Carbomethoxy-β-methoxypyruvate.—Methyl methoxyacetate (23 g.) was added dropwise to a mixture of ethyl oxalate (22 ml.) and ether (200 ml.) containing pulverised sodium (4·6 g.), and 2 days later the solvent was distilled off, leaving a product which consisted mainly of the sodio-derivative of *ethyl β-carbomethoxy-β-methoxypyruvate* and was sufficiently pure to be used directly in the preparation of coumarins of type (IX). Treatment of the ethereal reaction mixture with acetic acid (26 g. in 85 ml. of water) and then N-sulphuric acid (120 ml.), followed by extraction of the aqueous layer with a further quantity of ether (100 ml. × 6) and evaporation of the dried extracts, gave the keto-ester which was purified by distillation in a vacuum and obtained as a pale yellow oil (12 g.), b. p. 75—78°/0·05 mm. (Found : C, 47·3; H, 6·0. $C_8H_{12}O_6$ requires C, 47·1; H, 5·9%). This compound gives a violet-red ferric reaction in alcohol, rapidly decolorises aqueous potassium permanganate, readily reduces Fehling's solution and ammoniacal silver nitrate, and forms a green copper complex with copper acetate solution.

Ethyl 3-Chloro-7-hydroxycoumarin-4-carboxylate (IV; R = H, R′ = Et).—A solution of resorcinol (4·6 g.) and ethyl β-chloro-β-carbethoxypyruvate in alcohol (50 ml.) was saturated with hydrogen chloride at room temperature in the course of 2 hours, and 24 hours later the *ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate* was collected, and recrystallised from alcohol or acetic acid, forming pale yellow prisms (7·6 g.), m. p. 234°, insoluble in aqueous sodium hydrogen carbonate and forming a yellow solution in warm aqueous sodium hydroxide [Found : C, 53·9; H, 3·5; Cl, 13·8; *M* (Rast), 267. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·4; Cl, 13·2%; *M*, 268]. Methylation of this compound (3 g.) with excess of methyl iodide and potassium carbonate in boiling acetone (50 ml.) during 3 hours gave rise to *ethyl 3-chloro-7-methoxycoumarin-4-carboxylate* which separated from methanol in pale yellow rhombic plates (2·4 g.), m. p. 119°, identical with a specimen prepared in almost quantitative yield by the action of excess of ethereal diazomethane on ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate, and having a negative ferric reaction (Found : C, 55·0; H, 4·0. $C_{13}H_{11}O_5Cl$ requires C, 55·2; H, 3·9%). This compound (0·6 g.) was also prepared by the condensation of ethyl β-chloro-β-carbethoxypyruvate (4·5 g.) and resorcinol monomethyl ether (2·5 g.) in alcohol (25 ml.) with excess of hydrogen chloride during 24 hours and isolated by evaporation of most of the solvent in a vacuum.

When methyl β-chloro-β-carbomethoxypyruvate (3·5 g.) was employed in place of the ethyl ester in the condensation with resorcinol (2 g.) in methanol (10 ml.) saturated with hydrogen chloride, *methyl 3-chloro-7-hydroxycoumarin-4-carboxylate* (IV; R = H, R′ = Me) (2·8 g.) was obtained and on crystallisation from methanol formed elongated yellow prisms, m. p. 212—214°, readily soluble in acetone and moderately soluble in acetic acid (Found : C, 51·8; H, 2·8; Cl, 14·2. $C_{11}H_7O_5Cl$ requires C, 51·9; H, 2·8; Cl, 14·0%). Methylation of this compound (4 g.) in boiling acetone (50 ml.) by the methyl iodide–potassium carbonate method gave *methyl 3-chloro-7-methoxycoumarin-4-carboxylate* (IV; R = Me, R′ = Me) which formed pale greenish-yellow prisms (3 g.), m. p. 152—153°, from a little acetone and then benzene or methanol (Found : C, 53·4; H, 3·3; Cl, 12·7. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·3; Cl, 13·2%).

Hydrolysis of ethyl 3-chloro-7-methoxycoumarin-4-carboxylate (1 g.) with boiling sulphuric acid (from 20 ml. of concentrated acid and 50 ml. of water) gave *3-chloro-7-methoxycoumarin-4-carboxylic acid* (IV; R = Me, R′ = H) which was isolated with ether (50 ml. × 5) and separated from unchanged ester (0·3 g.) by means of aqueous sodium hydrogen carbonate. Crystallised from alcohol or acetic acid this acid formed stellate clusters of needles (0·3 g.), m. p. 272° (decomp.; after sintering at 262°) [Found : C, 51·7; H, 3·0; *M* (by titration), 247. $C_{11}H_7O_5Cl$ requires C, 52·0; H, 2·8%; *M*, 254·5]. Esterification of this acid by the silver salt–ethyl iodide method re-formed the carbethoxycoumarin, m. p. and mixed m. p. 119°. Prepared from the acid (1 g.) by means of phosphorus pentachloride (0·85 g.) in chloroform (50 ml.), the acid chloride was treated with aniline, giving rise to the *anilide* which formed colourless rectangular plates (1·1 g.), m. p. 245°, from alcohol or ethyl acetate (Found : C, 61·9; H, 3·7. $C_{17}H_{12}O_4NCl$ requires C, 61·9; H, 3·6%).

6-Hydroxycoumarone-2 : 3-dicarboxylic Acid (VI; R = R′ = H).—A solution of ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate (1·5 g.) in 5% aqueous potassium hydroxide was heated on the steam-bath for 1 hour and on acidification with concentrated hydrochloric acid the filtered red reaction mixture, which had a green fluorescence, gave the *acid* which formed almost colourless needles (1·1 g.), m. p. 277° (decomp.), from dilute hydrochloric acid, acetic acid–hydrochloric acid, or ethyl acetate–light petroleum (b. p. 60—80°) (Found, in specimen dried in a high vacuum at 100° : C, 54·0; H, 3·0. $C_{10}H_6O_6$ requires C, 54·1; H, 2·7%). This acid was also obtained from the corresponding carbomethoxycoumarin (IV; R = H, R′ = Me) by the same procedure.

6-Methoxycoumarone-2 : 3-dicarboxylic Acid (VI; R = Me, R′ = H).—Prepared by the action of boiling 10% aqueous sodium hydroxide (20 ml.) on ethyl 3-chloro-7-methoxycoumarin-4-carboxylate (5 g.) during 40 minutes, this *acid* formed elongated pale yellow needles (3·4 g.), m. p. 219° (decomp.), from warm dilute hydrochloric acid or from a little ethyl acetate [Found : C, 56·0; H, 3·5; equiv. (by titration), 120·1. $C_{11}H_8O_6$ requires C, 55·9; H, 3·4%; equiv., 118]. The acid, which was also formed by the action of boiling 10% aqueous potassium hydroxide on the corresponding carbomethoxycoumarin, was readily soluble in water and in the usual solvents except light petroleum. On esterification with diazomethane the compound gave the *methyl* ester, forming pale yellow needles, m. p. 115°, from ethyl acetate–light petroleum (b. p. 60—80°) and then methanol (Found : C, 59·0; H, 4·5. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·5%).

6-Methoxycoumarone-2 : 3-dicarboxylic acid (2 g.) in chloroform (50 ml.) was treated with thionyl chloride (10 ml.), and 30 minutes later the solvent and excess of thionyl chloride were removed by distillation in a vacuum, leaving the acid chloride as a light-brown solid which reacted with aniline (10 ml.) on the steam-bath to give the *dianilide*. This derivative formed pale yellow needles (2·4 g.), m. p. 192°, from alcohol or dilute acetic acid (Found : N, 7·2. $C_{23}H_{18}O_4N_2$ requires N, 7·3%).

Ethyl 7-Hydroxy-3-methoxycoumarin-4-carboxylate (IX; R = H).—A mixture of resorcinol (80 g.), the sodio-derivative of ethyl β-methoxy-β-carbomethoxypyruvate (from 40 ml. of ester), and alcohol (250 ml.) was heated under reflux for 2 hours, cooled, and poured into dilute sulphuric acid (50 ml. of concentrated sulphuric acid and 2·5 l. of water). Next day the precipitate was collected, washed, and crystallised from dilute alcohol or acetic acid, giving *ethyl 7-hydroxy-3-methoxycoumarin-4-carboxylate* in

elongated plates (26 g.), m. p. 184°, readily soluble in acetone or ethyl acetate and sparingly soluble in benzene (Found: C, 59·3; H, 4·6; OMe, 11·9. $C_{12}H_9O_5$·OMe requires C, 59·1; H, 4·5; OMe, 11·7%). Methylation of this compound by means of diazomethane or by the methyl iodide–potassium carbonate method gave *ethyl* 3 : 7-*dimethoxycoumarin*-4-*carboxylate* which separated from light petroleum in colourless prisms, m. p. 83·5—84° (Found: C, 60·2; H, 4·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%).

Ethyl 7-hydroxy-3-methoxycoumarin-4-carboxylate (1 g.) was heated under reflux with methanolic potassium hydroxide (from 8 g. of potassium hydroxide, 5 ml. of water, and 35 ml. of methanol) on the steam-bath for 3 hours, and after about half of the methanol had been distilled off the residue was diluted with water (20 ml.), filtered, and acidified with excess of concentrated hydrochloric acid. 6-Hydroxycoumarone-2 : 3-dicarboxylic acid was isolated by extraction of the acidic liquor with ether, and on purification from dilute hydrochloric acid formed needles, m. p. 277°, identical with a specimen obtained from the corresponding 3-chlorocoumarin. Treated with an excess of diazomethane this acid gave methyl 6-methoxycoumarone-2 : 3-dicarboxylate, m. p. 113°, undepressed on admixture with an authentic specimen, m. p. 115°.

When ethyl 3 : 7-dimethoxycoumarin-4-carboxylate (0·5 g.) was heated under reflux with 20% methanolic potassium hydroxide (20 ml.), and part of the alcohol removed by evaporation in a vacuum, the residue on acidification gave 6-methoxycoumarone-2 : 3-dicarboxylic acid (0·3 g.), m. p. and mixed m. p. 217—218°, after purification.

Ethyl 3-*Chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate*.—The condensation of anhydrous phloroglucinol (6 g.) and ethyl β-chloro-β-carbethoxypyruvate (12 g.), dissolved in alcohol (45 ml.), with excess of hydrogen chloride in the course of 2 hours gave *ethyl* 3-*chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate* which separated from ethyl acetate or acetic acid in pale yellow squat prisms and from aqueous acetone or alcohol in needles (3·75 g.), m. p. 257° (rapid heating) (Found, in a specimen dried in a high vacuum at 80°: C, 50·4; H, 3·3. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2%). The crystal habit of this compound appears to depend somewhat on the solvent used. On being warmed the pale yellow solution of the coumarin in concentrated sulphuric acid becomes cherry-red. When methyl β-chloro-β-carbomethoxypyruvate was employed in place of the ethyl ester, *methyl* 3-*chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate* was obtained, forming pale yellow prisms, m. p. 255—258°; yield, 2·5 g. from 2·5 g. of phloroglucinol and 4 g. of ester (Found: C, 59·1; H, 2·5; Cl, 13·0. $C_{11}H_7O_6Cl$ requires C, 48·8; H, 2·6; Cl, 13·1%).

Methylation of ethyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate by the methyl iodide–potassium carbonate method or by means of an excess of diazomethane gave rise to *ethyl* 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylate*, forming pale yellow plates, m. p. 155—156°, from ethyl acetate, identical with a specimen prepared by the condensation of phloroglucinol dimethyl ether and ethyl β-chloro-β-carbethoxypyruvate with an excess of alcoholic hydrogen chloride (Found: C, 53·5; H, 4·3; Cl, 11·3. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2; Cl, 11·4%). This ester exhibits dimorphism. The unstable form is sometimes obtained by the direct condensation method and may be purified from methanol or alcohol, forming pale yellow needles, m. p. 141—143°, which, on being kept in contact with the solvent or on recrystallisation from benzene, ethyl acetate, or acetone change into the stable form, m. p. 155—156°.

Hydrolysis of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate (2·3 g.) with a boiling mixture of sulphuric acid (100 ml.) and water (100 ml.) for 45 minutes gave 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylic acid* which on isolation with ether was obtained as a pale yellow solid (2 g.), readily soluble in water, alcohol or acetone. Recrystallised from ethyl acetate, acetic acid, or methanol this coumarin formed colourless needles (1·8 g.), m. p. 270—272° and decomposing at 277° with effervescence (Found: C, 50·4; H, 3·2; Cl, 12·0. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2; Cl, 12·5%). The hydrolysis of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate with 5% aqueous potassium hydroxide (120 ml.) on the steam-bath for 20 minutes, followed by extraction of the acidified hydrolysate with ether, gave the same acid (1·3 g.), m. p. 270—272°, after purification. Esterification of this acid by the silver salt–ethyl iodide method regenerated the ethyl ester, m. p. 154—155°, undepressed on admixture with an authentic specimen.

Methylation of methyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate with an excess of diazomethane or esterification of 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylic acid with the same reagent gave rise to *methyl* 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylate* which formed minute cream-coloured needles, m. p. 171° (Found: C, 51·9; H, 3·7; Cl, 11·8. $C_{13}H_{11}O_6Cl$ requires C, 52·3; H, 3·7; Cl, 11·9%).

4 : 6-*Dimethoxycoumarone*-2 : 3-*dicarboxylic Acid*.—A solution of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate (3 g.) in methanol (50 ml.) was mixed with 20% methanolic potassium hydroxide (25 ml.), the solution was boiled under reflux for 2 hours, and next day about half of the methanol was evaporated off. After the addition of water (50 ml.) the mixture was acidified with hydrochloric acid, and 4 : 6-*dimethoxycoumarone*-2 : 3-*dicarboxylic acid* was isolated with ether and crystallised from ethyl acetate or acetic acid, forming colourless prisms, m. p. 219°, and giving a green fluorescein reaction with resorcinol (Found: C, 54·0; H, 4·0. $C_{12}H_{10}O_7$ requires C, 54·3; H, 3·8%). On warming, the pale yellow colour of the solution of this compound in concentrated sulphuric acid changes to green. The rearrangement of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate was also effected with boiling 10% aqueous potassium hydroxide in the course of 75 minutes. Esterification of 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid (1 g.) with an excess of diazomethane gave the *methyl* ester which formed colourless rectangular prisms (0·85 g.), m. p. 169°, from methanol (Found: C, 57·0; H, 5·0. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%). Hydrolysis of this ester with 15% aqueous sodium hydroxide regenerated the parent acid, m. p. and mixed m. p. 218° after purification.

On being heated with 10% aqueous potassium hydroxide on the steam-bath for 45 minutes ethyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate (3 g.) yielded 4 : 6-dihydroxycoumarone-2 : 3-dicarboxylic acid which was extracted from the cooled acidified reaction mixture with ether. Recrystallised from formic acid this coumarone formed tiny needles, m. p. 252°, and on treatment with excess of diazomethane gave methyl 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylate, m. p. and mixed m. p. 169°.

Ethyl 3 : 5 : 7-*trimethoxycoumarin*-4-*carboxylate* was prepared in poor yield by the condensation of

phloroglucinol dimethyl ether (2·8 g.) and ethyl β-methoxy-β-carbomethoxypyruvate (2 g.) in alcoholic hydrogen chloride. After 8 days the crystalline product (0·4 g.), m. p. 110—120°, which had separated, was collected and the filtrate then diluted with water, neutralised with sodium hydrogen carbonate, and extracted with ether. Evaporation of the combined extracts, followed by crystallisation of the residue from alcohol, gave rosettes of plates (0·4 g.), m. p. 117—120°. Recrystallisation of the combined specimens several times, alternately from alcohol and acetone, gave the *trimethoxy*-ester in tiny clusters of plates, m. p. 131—132° (Found : C, 58·7; H, 5·3. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%). Attempts to improve the yields of this compound by interaction of the sodio-derivative of ethyl β-methoxy-β-carbomethoxypyruvate with phloroglucinol dimethyl ether, and by the condensation of phloroglucinol dimethyl ether and the ester with the aid of ethereal concentrated sulphuric acid or of phosphoric oxide in place of hydrogen chloride in the von Pechmann reaction, were unsuccessful; in each case only minute yields of the required trimethoxycoumarin, m. p. and mixed m. p. 131—132° after purification, were obtained.

When ethyl 3 : 5 : 7-trimethoxycoumarin-4-carboxylate (0·35 g.) was boiled with 20% methanolic potassium hydroxide for 2 hours and the cooled mixture kept for 24 hours, a potassium salt of 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid separated. Decomposition of this compound gave the parent acid, m. p. 217—218°, identified by comparison with an authentic specimen, m. p. 219°.

Ethyl 3-Chloro-7 : 8-dihydroxycoumarin-4-carboxylate.—Prepared from pyrogallol (6 g.) and ethyl β-chloro-β-carbethoxypyruvate (10·6 g.) in alcohol (45 ml.) with excess of hydrogen chloride in the course of 3 days, this *coumarin* separated from acetic acid in clusters of minute prisms (11·5 g.), m. p. 232—234°, readily soluble in alcohol, ethyl acetate, or acetone and giving an olive-green ferric reaction in alcohol which changes to a deep wine-red on the addition of a little alkali (Found : C, 50·9; H, 3·3; Cl, 11·8. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2; Cl, 12·5%). Treatment of the coumarin (3·8 g.), dissolved in ether, with an excess of ethereal diazomethane gave rise to *ethyl 3-chloro-7 : 8-dimethoxycoumarin-4-carboxylate* which formed clusters of needles, m. p. 116—117°, from aqueous acetic acid, benzene, or alcohol (Found : C, 53·6; H, 4·0; Cl, 10·0. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2; Cl, 11·4%). This ether was identical with a specimen prepared by methylating the dihydroxycoumarin with methyl iodide and potassium carbonate in boiling acetone.

6 : 7-*Dimethoxycoumarone-2 : 3-dicarboxylic Acid.*—Oxygen-free 10% aqueous potassium hydroxide (120 ml.) was added to ethyl 3-chloro-7 : 8-dihydroxycoumarin-4-carboxylate (3 g.) in an atmosphere of nitrogen, and the mixture heated on the steam-bath for 45 minutes and acidified with concentrated hydrochloric acid. Crystallised from acetone and then from dilute hydrochloric acid, the resulting 6 : 7-*dihydroxycoumarone-2 : 3-dicarboxylic acid* (2 g.) formed pale yellow prisms, m. p. above 300° (Found : C, 50·3; H, 2·7. $C_{10}H_6O_7$ requires C, 50·4; H, 2·5%). Treatment of this acid (2 g.) with an excess of ethereal diazomethane gave *methyl* 6 : 7-*dimethoxycoumarone-2 : 3-dicarboxylate* which separated from methanol, benzene, or aqueous acetone in colourless needles (1·2 g.), m. p. 97° (Found : C, 56·9; H, 4·7. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

On being heated under reflux with 10% aqueous potassium hydroxide (50 ml.) for 1·5 hours ethyl 3-chloro-7 : 8-dimethoxycoumarin-4-carboxylate (1·5 g.) gave 6 : 7-*dimethoxycoumarone-2 : 3-dicarboxylic acid* (1·1 g.) which crystallised from ethyl acetate and then acetic acid in yellow needles, m.p. 252° (decomp.), identical with a specimen prepared by the hydrolysis of methyl 6 : 7-dimethoxycoumarone-2 : 3-dicarboxylate (0·2 g.) with boiling 2N-aqueous sodium hydroxide for 20 minutes (Found, in specimen dried in high vacuum at 100° : C, 54·0; H, 3·9. $C_{12}H_{10}O_7$ requires C, 54·1; H, 3·7%).

Ethyl 3-Chloro-6 : 7-dimethoxycoumarin-4-carboxylate (VII; R = Me).—Interaction of 2 : 4-dihydroxyanisole (Head and Robertson, *J.*, 1931, 1241) (2 g.) and ethyl β-chloro-β-carbethoxypyruvate (3 g.) in alcohol (15 ml.) with hydrogen chloride at 0° for 24 hours gave *ethyl 3-chloro-7-hydroxy-6-methoxycoumarin-4-carboxylate* (VII; R = H) which crystallised from acetic acid in pale yellow prisms (0·8 g.), m. p. 220°, soluble in alcohol or acetone and sparingly soluble in ethyl acetate or benzene (Found : C, 52·1; H, 4·0. $C_{13}H_{11}O_6Cl$ requires C, 52·3; H, 3·7%). By the same procedure 4-hydroxyveratrole was converted into *ethyl 3-chloro-6 : 7-dimethoxycoumarin-4-carboxylate* (VII; R = Me) which separated from benzene or ethyl acetate in pale yellow needles, m. p. 174—176° after sintering at 170°, identical in every way with a specimen prepared by the methylation of the foregoing 7-hydroxycoumarin (VII; R = H) with excess of ethereal diazomethane [Found : C, 53·5; H, 4·4; *M* (Rast), 320. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2%; *M*, 312].

5 : 6-*Dimethoxycoumarone-2 : 3-dicarboxylic Acid* (*Abutic Acid*) (VIII).—Ethyl 3-chloro-6 : 7-dimethoxycoumarin-4-carboxylate (2 g.) was gently boiled with 10% aqueous sodium hydroxide (40 ml.) for 35 minutes, and the cooled red solution acidified with hydrochloric acid and extracted with ether (50 ml. × 8). The residue left on evaporation of the combined dried extracts was dissolved in the minimum amount of hot water, and the solution boiled for a few minutes with a little charcoal, filtered, and treated with several drops of concentrated hydrochloric acid. When cooled, the filtered liquor deposited abutic acid, m. p. about 242° (decomp.), which was purified from the minimum amount of ethyl acetate and finally obtained in almost colourless prisms (0·3 g.), m. p. 262° (decomp.), identical in every way with the natural compound and giving an intense fluorescein reaction with resorcinol (Found : C, 53·8; H, 3·9. Calc. for $C_{12}H_{10}O_7$: C, 54·1; H, 3·8%). Esterification of this acid with diazomethane gave the *methyl* ester, forming colourless prisms, m. p. 156°, from methanol (Found : C, 57·0; H, 4·9. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

Ethyl 3-Chloro-7-methylcoumarin-4-carboxylate.—The ethyl ester of this coumarin (2 g.) was prepared from *m*-cresol (3 g.) and ethyl β-chloro-β-carbethoxypyruvate (6 g.) by the alcoholic hydrogen chloride method and formed colourless needles from acetic acid, m. p. 150°, identical with a specimen prepared by the sulphuric acid procedure, the yield from which was considerably inferior (compare Dey, *J.*, 1915, **107**, 1649, who gives m. p. 154°). On being hydrolysed with a mixture of concentrated sulphuric acid (100 ml.) and water (100 ml.) for 4 hours this ester (3·7 g.) gave the corresponding *3-chloro-7-methylcoumarin-4-carboxylic acid* (2·8 g.), forming colourless needles, m. p. 268—269°, from acetic acid, ethyl acetate, or dilute alcohol (Found : C, 55·5; H, 3·3; Cl, 15·7. $C_{11}H_7O_3Cl$ requires C, 55·4; H, 2·9; Cl, 14·9%). By means of boiling 10% aqueous-alcoholic potassium hydroxide ethyl 3-chloro-7-methylcoumarin-4-

carboxylate was converted into 6-methylcoumarone-2 : 3-dicarboxylic acid, m. p. 231—232° after purification from ethyl acetate; the melting point of the pure compound appears to be somewhat variable, dropping to 220—221° after recrystallisation several times from dilute alcohol, a phenomenon observed by Dey (*loc. cit.*). Esterified with diazomethane the acid gave *methyl 6-methylcoumarone-2 : 3-dicarboxylate*, forming as needles (from methanol), m. p. 64°, soluble in benzene or light petroleum (Found : C, 62·7; H, 4·6. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

Ethyl 3-chloro-6-methylcoumarin-4-carboxylate was prepared from *p*-cresol (6 g.) by the alcoholic hydrogen chloride method, forming colourless plates (2·4 g.), m. p. 150° from acetic acid and then alcohol (Found : C, 58·4; H, 4·3. $C_{13}H_{11}O_4Cl$ requires C, 58·5; H, 4·2%). When sulphuric acid or sulphuric acid monohydrate was employed as the condensing agent at 0° for 3 days, there was obtained a second unstable form which, on being crystallised from ether or acetone by slow evaporation of the solvent, formed colourless needles, m. p. 161—162°. Recrystallised from alcohol, this product reverted to the stable form, plates, m. p. and mixed m. p. 148—149°. Hydrolysis of this ester with boiling 50% sulphuric acid during 3·5 hours gave the *coumarin-4-carboxylic acid* which separated from acetic acid in needles, m. p. 282—283°, identical with a specimen obtained when the hydrolysis was effected with 5% aqueous potassium hydroxide on the steam-bath for 45 minutes (Found : C, 55·8; H, 3·2; Cl, 15·0. $C_{11}H_7O_4Cl$ requires C, 55·4; H, 2·9; Cl, 14·9%).

When ethyl 3-chloro-6-methylcoumarin-4-carboxylate (5 g.) was heated under reflux with 10% alcoholic potassium hydroxide (150 ml.) for 2 hours a good yield of *5-methylcoumarone-2 : 3-dicarboxylic acid* was obtained, which formed colourless prisms (4 g.), m. p. 288—290° (decomp.), from dilute hydrochloric acid (Found : C, 60·0; H, 3·7. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). Prepared by means of an excess of diazomethane, the *dimethyl* ester of this acid separated from aqueous methanol in needles, m. p. 63—64° (Found : C, 63·0; H, 4·5. $C_{13}H_{12}O_3$ requires C, 62·9; H, 4·8%).

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