Chebulinic Acid. Part III. Oxidation of Ellagic and Flavellagic Acids and the Synthesis of Some* isoCoumarin *Derivatives.*

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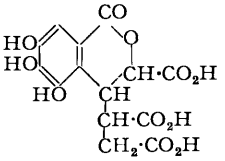
[Reprint Order No. 5462.]

Whilst the oxidation of ellagic acid with hydrogen peroxide yields simple aliphatic compounds, flavellagic acid gives 20% yields of 5 : 6 : 7-trihydroxy-4-*iso*coumarinylacetic acid (III; R = R′ = H). Decarboxylation of the trimethyl ether afforded 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin, which was identified by comparison with a synthetic product. Although a synthesis of the 4-acetic acid (III; R = R′ = H) has not been realised, a number of synthetic 5 : 6 : 7-trimethoxy*iso*coumarin derivatives substituted in the 3- and the 4-position, and related to chebulic acid, flavellagic acid, and galloflavin, have been prepared.

Schmidt and Mayer (*Annalen*, 1951, **571**, 1) suggested that chebulic acid (I) represented an oxidation product of ellagic acid (II; R = H), and the present paper is a result of experiments aiming at the oxidative disruption of one of the phenolic nuclei of ellagic acid by means of hydrogen peroxide. Difficulties were encountered in the reactions; at room temperature little or no oxidation occurred and at higher temperatures a very complex mixture of relatively simple aliphatic acids resulted, which gave no clue to the nature of the break-down. The acid mixtures were methylated, and fractional distillation of the esters and subsequent hydrolysis of the fractions gave oxalic, malonic, succinic, and ethane-1 : 2 : 2-tricarboxylic acid, and intractable oils. In view of the difficulty of isolating phenolic acid oxidation products our attention was diverted to the peroxide oxidation of flavellagic acid (II; R = OH). This proceeded smoothly in alkaline solution at room

* Part II, preceding paper.

temperature, giving 20% yields of a phenolic acid, $C_{11}H_8O_7$, which was subsequently shown to be 5 : 6 : 7-trihydroxy-4-*iso*coumarinylacetic acid (III; R = R′ = H). Methylation with diazomethane yielded the dimorphous ether-ester (III; R = R′ = Me) and thence the ether-acid (III; R = Me, R′ = H) on hydrolysis and a 3 : 4-dihydro-derivative on catalytic reduction. The acid (III; R = Me, R′ = H) titrated in the cold as a monobasic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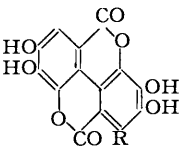
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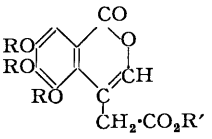
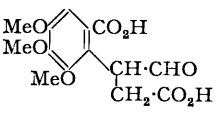

(III)

acid, but the lactone ring was ruptured by warm alkali and acidification then yielded β-(6-carboxy-2 : 3 : 4-trimethoxyphenyl)-β-formylpropionic acid (IV), a dibasic acid which was reconverted into 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) only after prolonged boiling with mineral acids. The dibasic acid (IV) was oxidised by potassium ferricyanide to 3 : 4 : 5-trimethoxyphthalic acid, thus proving that the pyrogallol nucleus of the flavellagic acid (II; R = OH) remained intact during the oxidation, and on methylation with diazomethane it was converted into either the dimethyl ester or the *O*-enol ether (V) according to the conditions; both derivatives yielded the same 2 : 4-dinitrophenylhydrazone. This evidence for a carbonyl group was confirmed by the production of a 2 : 4-dinitrophenylhydrazone, of structure (VI), from the dibasic acid (IV). Sublimation of the dibasic acid (IV) yielded a dilactone (VII) which was stable to boiling water or alcohol and unattacked by diazomethane or ketonic reagents, and was reconverted into the dibasic acid (IV) by hydrolysis with sodium hydroxide.

5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) was decarboxyl-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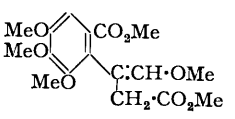
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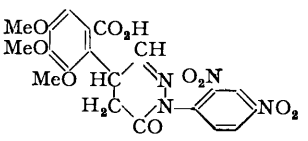
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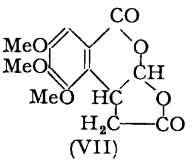
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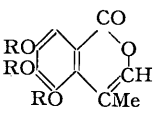
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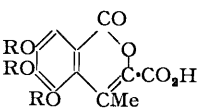
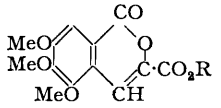

(IX)

ated by copper at 300°, and the product was identified by a comparison with a synthetic specimen as 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin (VIII; R = Me). A synthesis of 5 : 6 : 7-trihydroxy-4-methyl*iso*coumarin (VIII; R = H) has been reported by Fritsch (*Ber.*, 1893, **26**, 421) but the analytical results given are poor. Chloroacetone reacted with potassium gallate, and the resulting acetonyl gallate (gallacetol) was converted by 80% sulphuric acid into 5 : 6 : 7-trihydroxy-4-methyl*iso*coumarin (VIII; R = H) which gave the trimethyl ether (VIII; R = Me) with diazomethane. Acetonyl 3 : 4 : 5-trimethoxybenzoate, which was obtained from chloroacetone and 3 : 4 : 5-trimethoxybenzoic acid, could, however, not be cyclised to (VIII; R = Me). The isolation of 4-methyl*iso*coumarin (VIII; R = Me) can be accounted for on the basis of structure (III) or (IX) for the oxidation product of flavellagic acid. Of these, only (III) provides a satisfactory explanation of the reactions summarised above, and (IX) is also excluded by spectroscopic evidence. The ultra-violet absorption curves of 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H) and 5 : 6 : 7-trimethoxy-4-methyl*iso*coumarin (VIII; R = Me) were almost superposable with peaks at 2450 (log ε 4·48) and 3300 Å (log ε 3·50), whilst the maximum for 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), synthe-

sised by the method described on p. 3620, at 2580 Å (log ε 4·52), indicated the presence of a more conjugated chromophoric system in the latter acid.

Although the structure of the oxidation product of flavellagic acid is firmly established as (III; R = R′ = H) from the evidence outlined above, synthetical evidence has been sought, but, so far, without success. Ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) was prepared from 4 : 5 : 6-trimethoxy-3-trichloromethylphthalide (Alimchandani, *J.*, 1924, **125**, 540) by Meldrum and Parikh's method (*J. Proc. Ind. Acad. Sci.*, 1934—1935, **1**, 430), and with ethyl formate in presence of potassium ethoxide afforded, after cyclisation, ethyl 5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylate (XII; R = Et).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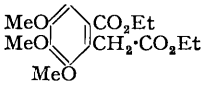
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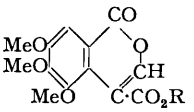
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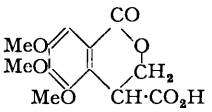
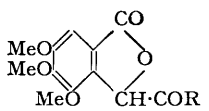

(XIII)

Hydrolysis to the acid (XII; R = H) could not be brought about with acids, alkalis, or boron trifluoride in acetic acid, and consequently Arndt–Eistert ascent to (III; R = Me, R′ = H) was excluded. As this difficulty in hydrolysis might have been due to the production of unstable β-aldehydic ester intermediate products, the ester (XII; R = Et) was reduced to its 3 : 4-dihydro-derivative which was readily hydrolysed by acids to 3 : 4-dihydro-5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylic acid (XIII) in which the lactone ring was readily ruptured by boiling water. Unfortunately the chloride of the acid (XIII) could not be prepared; reaction with thionyl chloride gave a sulphur-containing oil, which could not be converted into the methyl ester or the diazo-ketone by treatment with methyl alcohol or diazomethane respectively. This failure to prepare an acid chloride from (XII; R = H) or (XIII) is peculiar; as will be seen later (p. 3620) no such difficulties were encountered with the isomeric 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H) or its 3 : 4-dihydro-derivative, and 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid (XIV; R = OH) (Bargellini and Molina, *Atti R. Accad. Lincei*, 1912, **21**, II, 146) was readily converted *via* its acid chloride and diazo-ketone into 3-acetyl-4 : 5 : 6-trimethoxyphthalide (XIV; R = Me), identical with the compound prepared from galloflavin (Haworth and McLachlan, *J.*, 1952, 1583).

A synthesis of (III; R = Me, R′ = H) based on 2 : 3 : 4-trimethoxy-6-methoxycarbonylbenzyl cyanide (XV; R = CN) was envisaged but attempts to prepare this ester from methyl 2-chloromethyl-3 : 4 : 5-trimethoxybenzoate (XV; R = Cl) (Haworth, Moore, and Pauson, *J.*, 1949, 3278) gave results which showed that the product obtained by chloromethylation of methyl 3 : 4 : 5-trimethoxybenzoate was 7-chloromethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = Cl) and not (XV; R = Cl) as previously suggested. Thus treatment with potassium cyanide gave 7-cyanomethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = CN), which had lactonic properties and on alkaline hydrolysis gave the corresponding lactonic acid (XVI; R = CO_2H). In addition, alkaline hydrolysis of 7-chloromethylphthalide (XVI; R = Cl) gave, not 4 : 5 : 6-trimethoxyphthalide which would be expected from earlier theoretical views, but 7-hydroxymethylphthalide (XVI; R = OH) which contained a lactone ring and gave a positive Zerewitinoff test. The need for this structural revision was also proved by the preparation of 7-chloromethylphthalide (XVI; R = Cl) by the action of formaldehyde and hydrochloric acid on 4 : 5 : 6-trimethoxyphthalide.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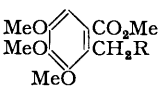
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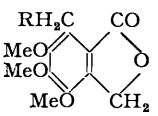
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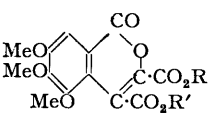
(XVII)

Attempts were also made to synthesise (III) or its derivatives by extensions of the *iso*coumarin synthesis used by Fritsch (*loc. cit.*; *Friedländer*, 1890—1894, **3**, 970). The first attempt failed because ethyl γ-chloroacetoacetate (Alexandrow, *Ber.*, 1913, **46**, 1022)

could not be condensed with potassium or silver gallate. A second scheme had for its objective the synthesis of 5 : 6 : 7-trihydroxy-4-propyl*iso*coumarin, which could probably have been made from (III). A convenient method of preparation of chloromethyl propyl ketone, from butyryl chloride *via* the corresponding diazo-ketone, is described in the Experimental section, but although satisfactory reaction with potassium gallate to 2-oxopentyl 3 : 4 : 5-trihydroxybenzoate was realised, we were unable to convert this ester into an *iso*coumarin derivative.

Condensation of the homophthalic ester (XI) with ethyl oxalate in presence of potassium ethoxide gave a product which readily cyclised to diethyl 5 : 6 : 7-trimethoxy*iso*coumarin-3 : 4-dicarboxylate (XVII; R = R′ = Et). This ester was hydrolysed by dilute sulphuric acid in acetic acid to 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), m. p. 262—264°. An acid ester, probably (XVII; R = H, R′ = Et), was isolated from some experiments, and converted into (X; R = H) by further treatment with acid. The decarboxylation observed during hydrolysis of the ester (XVII; R = R′ = Et) would be expected on theoretical grounds to result in the elimination of the 4-ethoxycarbonyl group, and Vorozhtsov and Bogusevich (*Zhur. Obshchey Khim.*, 1940, **10**, 2014) have shown that diethyl *iso*coumarin-3 : 4-dicarboxylate was converted into *iso*coumarin-3-carboxylic acid by hot concentrated hydrochloric acid. The constitution assigned to the trimethoxy*iso*coumarin-3-carboxylic acid was finally established by preparation of the ethyl ester, m. p. 118°, which differed from ethyl 5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylate (XII; R = Et), m. p. 106°, described previously. Tschitschibabin, Kirssanow, Korolew, and Woroschzow (*Annalen*, 1929, **469**, 93) prepared 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H) by oxidation of bergenin, but the melting point reported is 10° lower than that of the synthetic sample prepared as above, although the melting point of their ester is in good agreement with that of the ester prepared from our acid (X; R = H).

The identity of 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H) with the acid obtained by pyrolysis of trimethylchebulic acid (see previous paper, p. 3612) was established by direct comparison of the acids, acid chlorides, and methyl and ethyl esters, and of the 3 : 4-dihydro-acids and their ethyl esters. 5 : 6 : 7-Trimethoxy*iso*coumarin-3-carboxylic acid (X; R = H), unlike the 4-isomer, readily gave an acid chloride, which with diazomethane gave 3-diazoacetyl-5 : 6 : 7-trimethoxy*iso*coumarin. The diazo-compound was converted by Wolff rearrangement with silver oxide in methyl alcohol into methyl 5 : 6 : 7-trimethoxy-3-*iso*coumarinylacetate; the yields were poor, and the product, m. p. 127—128°, was not identical with either of the dimorphous forms of the 4-isomer (III; R = R′ = Me) prepared from flavellagic acid.

Experimental

Oxidation of Ellagic Acid (II; R = H).—Hydrogen peroxide (62·5 c.c. of 100-vol.) was added dropwise and with stirring to a solution of ellagic acid (10 g.) in water containing sodium hydroxide (7 g.) at 90—95°. The ice-cooled red solution was saturated with sulphur dioxide, and after 3 hr. unchanged ellagic acid (3 g.) was collected; the pale yellow filtrate, extracted continuously with ether for 2 days, gave a brown oil. This oil (17 g.; obtained from several experiments) was dissolved in acetone (100 c.c.) and mixed with ethereal diazomethane (from 60 g. of nitrosomethylurea), and after 18 hr. the residual brown oil (20 g.) was fractionated at 0·5 mm., yielding fractions, (1) (4·8 g.) b. p. 40—47°/0·5 mm., (2) (4·7 g.) b. p. 92—100°/0·5 mm., and (3) (3·1 g.), b. p. 120—130°/0·5 mm., and a residue.

Fraction (1) (2 g.) was hydrolysed for 2 hr. with warm methyl-alcoholic 10% potassium hydroxide (50 c.c.). Water (100 c.c.) was added, the alcohol was removed, and the acidified solution after continuous extraction with ether for 1 day gave a colourless oil which was taken up in a little water and treated with excess of calcium chloride solution. The precipitated calcium oxalate yielded hydrated oxalic acid, m. p. 100—101°. The filtrate from the calcium oxalate was extracted with ether for 1 day, yielding a solid, m. p. 120—130° (Found: equiv., 55), which when heated with benzaldehyde (2 c.c.), pyridine (5 c.c.), and piperidine (2 drops) gave cinnamic acid (1·1 g.), m. p. 133°. The filtrate therefrom was rendered alkaline, and the neutral and the basic products were removed with ether; acidification, continuous ether-extraction for 18 hr., and sublimation then yielded succinic anhydride, m. p. 119° (from benzene).

Fraction (2) was largely trimethyl ethane-1 : 2 : 2-tricarboxylate, b. p. 98—102°/0·5 mm. [Found : C, 45·8; H, 6·1; OMe, 40·5. $C_5H_3O_3(OMe)_3$ requires C, 46·5; H, 5·9; OMe, 45·5%]. Hydrolysis with methyl-alcoholic potassium hydroxide gave the acid, which was isolated with ether and crystallised from ethyl acetate in prisms, m. p. 156—157° (Found : equiv., 53·5; C, 37·4; H, 3·8%. Calc. for $C_5H_6O_6$: equiv., 54·0; C, 37·0; H, 3·7%), undepressed on admixture with a specimen prepared as described by Kay and Perkin (*J.*, 1906, **89**, 1643).

Fraction (3) (Found : C, 48·9; H, 5·1. Calc. for $C_{10}H_{12}O_7$: C, 49·2; H, 4·9%) gave an intractable hygroscopic oil on hydrolysis.

Flavellagic Acid (II; R = OH).—When prepared by persulphate oxidation of gallic acid as described by Perkin (*J.*, 1906, **89**, 251) and purified by hydrolysis of the penta-acetyl derivative, this had m. p. 317—319°.

Oxidation of Flavellagic Acid.—Hydrogen peroxide (15 c.c. of 100-vol.) was gradually added with stirring to a solution of flavellagic acid (16 g.) in 4% aqueous potassium hydroxide (600 c.c.). The temperature rose to 38°, after which oxidation was allowed to proceed, without stirring, at room temperature for 7 hr. The solution was acidified and after 2 hr. unchanged flavellagic acid (4 g.) was collected. The red filtrate gave, after continuous ether-extraction for 2 days, a red oil (5 g.) and a pale yellow solid (2·5 g.). The oil, with ethereal diazomethane, yielded an ester, b. p. <130°/0·2 mm., but was not investigated further. The solid was crystallised from hot water and gave the *monohydrate* of 5 : 6 : 7-*trihydroxy*-4-iso*coumarinylacetic acid* (III; R = R′ = H) as colourless needles (2·0 g.), m. p. 280—290° (decomp.) (Found, after drying in a vacuum for 1 day : C, 48·8; H, 3·7. $C_{11}H_8O_7,H_2O$ requires C, 48·8; H, 3·7%), which gave a deep blue ferric test. The *anhydrous acid* (III; R = R′ = H) was obtained by 6 hours' drying at 130°/0·2 mm. over phosphoric oxide (Found : C, 52·4; H, 3·5. $C_{11}H_8O_7$ requires C, 52·3; H, 3·2%).

Methyl 5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetate* (III; R = R′ = Me).—To an acetone solution of the phenolic acid (III; R = R′ = H) (2 g.) was added excess of ethereal diazomethane (from 20 g. of nitrosomethylurea), and removal of the solvent after 12 hr. gave an oil which crystallised from methyl alcohol. The crystals (2·2 g.) were dimorphous; rapid separation from hot methyl alcohol gave needles, m. p. 122—123°, and slow crystallisation afforded rhombic prisms, m. p. 125—126° [Found : C, 58·2; H, 5·2; OMe, 40·0. $C_{11}H_4O_3(OMe)_4$ requires C, 58·4; H, 5·2; OMe, 40·4%]. This ester gave a negative Zerewitinoff test.

5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetic Acid* (III; R = Me, R′ = H).—The foregoing ester (1 g.) was refluxed with concentrated hydrochloric acid (50 c.c.) and water (150 c.c.) for 1½ hr. The *acid* which separated on cooling crystallised from hot water or methyl alcohol in needles (0·8 g.), m. p. 210—211° (Found : equiv., 292; C, 57·3; H, 4·8%. $C_{14}H_{14}O_7$ requires equiv., 294; C, 57·1; H, 4·8%). The acid was reconverted into the methyl ester by refluxing with methyl alcohol and sulphuric acid. The *acid chloride*, prepared by refluxing with thionyl chloride (5 parts) for ½ hr., crystallised from benzene or toluene in prisms, m. p. 124—125° (Found : C, 53·7; H, 4·3. $C_{14}H_{13}O_6Cl$ requires C, 53·75; H, 4·3%). The *ethyl* ester (III; R = Me, R′ = Et), prepared from the chloride, separated from alcohol in needles, m. p. 138—139° (Found : C, 59·7; H, 5·7. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%. The *amide*, prepared by the action of dry ammonia on a benzene solution of the chloride, crystallised from water in needles, m. p. 230—231° (Found : C, 57·5; H, 5·2; N, 4·7. $C_{14}H_{15}O_6N$ requires C, 57·3; H, 5·1; N, 4·8%).

5 : 6 : 7-*Trimethoxy*iso*carbostyril*-4-*acetic Acid.*—The lactonic acid (III; R = Me, R′ = H) (0·65 g.) was treated in a sealed tube with a saturated solution (15 c.c.) of methyl-alcoholic ammonia for 18 hr. at 100°. Evaporation under reduced pressure gave a white solid which was taken up in water (10 c.c.) and acidified; the iso*carbostyril acid* crystallised from acetic acid in needles, m. p. 242—244° (Found : C, 57·0; H, 5·3; N, 4·8. $C_{14}H_{15}O_6N$ requires C, 57·3; H, 5·1; N, 4·8%).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*-4-iso*coumarinylacetic Acid.*—A solution of methyl 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetate (III; R = R′ = Me) (0·9 g.) in acetic acid (30 c.c.) was reduced in presence of 25% palladium–charcoal (0·90 g.) at 50°. After 6 hr., the filtered solution yielded a pale yellow oil, b. p. 215—220° (bath)/0·1 mm., which solidified and crystallised from methyl alcohol in prisms, m. p. 74—75° (Found : C, 58·2; H, 5·8. $C_{15}H_{18}O_7$ requires C, 58·1; H, 5·8%). Hydrolysis of this *methyl* ester with 6% aqueous potassium hydroxide (30 parts) for 2 hr. yielded the *acid*, which separated from hot water in prisms, m. p. 177—178° (Found : C, 56·6; H, 5·5. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%). Methylation with methyl alcohol and sulphuric acid gave the methyl ester, m. p. 74—75°.

β-(6-*Carboxy*-2 : 3 : 4-*trimethoxyphenyl*)-β-*formylpropionic Acid* (IV).—The ester (III;

R = R′ = Me) (1 g.) was refluxed for 2 hr. with methyl-alcoholic 5% potassium hydroxide (40 c.c.). After removal of the alcohol and acidification, the dibasic *acid* (IV) was collected and crystallised from hot water; rhombic prisms (0·7 g.), m. p. 167—169° (decomp.) [Found: equiv., C, 53·7; H, 5·1; OMe, 29·8%. $C_{11}H_7O_5(OMe)_3$ requires equiv., 156; C, 53·8; H, 5·1; OMe, 29·8%], were obtained. The dibasic acid (IV) was converted into 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid (III; R = Me, R′ = H), m. p. 210—211°, by 5 hours' heating with concentrated hydrochloric acid (14 parts) and water (46 parts). The acid (IV) was oxidised with potassium ferricyanide in the usual way; 3 : 4 : 5-trimethoxyphthalic acid was isolated and identified as the anhydride, m. p. 144°, and *N*-methylimide, m. p. 127°. The acid (IV) gave a 2 : 4-*dinitrophenylhydrazone* (VI) which crystallised from acetic acid in pale yellow needles, m. p. 281—282° (Found: C, 50·7; H, 3·8; N, 11·7. $C_{20}H_{18}O_{10}N_4$ requires C, 50·7; H, 3·8; N, 11·8%), and dissolved in cold sodium hydrogen carbonate solution. The *dimethyl* ester of the acid (IV), prepared by reaction with a small excess of ethereal diazomethane for ½ hr., was an oil, b. p. 220—225° (bath)/0·1 mm., yielding a 2 : 4-*dinitrophenylhydrazone*, which crystallised from methyl alcohol in deep yellow needles, m. p. 123° (Found: C, 51·0; H, 4·7; N, 10·7. $C_{22}H_{22}O_{11}N_4$ requires C, 51·0; H, 4·3; N, 10·8%). The *methyl ether* (V) of the enolic form of the above dimethyl ester, was obtained by treating the dibasic acid (IV) with excess of diazomethane for 24 hr.; it crystallised from methyl alcohol in stout prisms, m. p. 78—79° (Found: C, 57·3; H, 6·2. $C_{17}H_{22}O_8$ requires C, 57·6; H, 6·2%), which slowly reacted with 2 : 4-dinitrophenylhydrazine yielding the 2 : 4-dinitrophenylhydrazone of m. p. 123° described above.

The Dilactone (VII) *of* β-(6-*Carboxy*-2 : 3 : 4-*trimethoxyphenyl*)-β-*formylpropionic Acid.*—This was prepared by heating the acid (IV) either (*a*) at 175°/0·5 mm. or (*b*) with acetic anhydride (10 vol.) for 40 hr. The *dilactone* crystallised from hot water or benzene–light petroleum (b. p. 60—80°) in needles, m. p. 139—140° [Found: equiv., 145·5; C, 56·9; H, 4·8; OMe, 32·4%. $C_{11}H_5O_4(OMe)_3$ requires equiv., 147; C, 57·1; H, 4·8; OMe, 31·6%], which did not react with diazomethane but on alkaline hydrolysis regenerated the acid (IV), m. p. 167—169° (decomp.).

Decarboxylation of 5 : 6 : 7-*Trimethoxy*-4-iso*coumarinylacetic Acid* (IV; R = Me, R′ = H).—The lactonic acid (IV; R = Me, R′ = H) (1 g.) was heated for 1 hr. with copper powder at 280—300°. Distillation at 13 mm. yielded a small quantity of yellow oil, which gradually solidified and crystallised from methyl alcohol in colourless needles (0·1 g.), m. p. 93—94° (Found: C, 62·7; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%), undepressed on admixture with a synthetic specimen of 5 : 6 : 7-*trimethoxy*-4-*methyl*iso*coumarin* (VIII; R = Me) (see below).

Acetonyl Gallate (*Gallacetol*).—A mixture of chloroacetone (9·2 c.c.), gallic acid (18·8 g.), potassium carbonate (6·8 g.), water (140 c.c.), and sufficient methyl alcohol to produce a homogeneous solution was refluxed for 5 hr.; the product, isolated with ether, crystallised from benzene–light petroleum (b. p. 60—80°) in needles (11·5 g.), m. p. 155—156° (Fritzsch, *loc. cit.*, gives m. p. 155—156°).

5 : 6 : 7-*Trihydroxy*-4-*methyl*iso*coumarin* (VIII; R = H).—Gallacetol (2 g.) was kept in 80% sulphuric acid (40 c.c.) at 0° for 20 hr The mixture was decomposed with ice, and the precipitate was collected, washed with water, and crystallised from acetone; the *trihydroxymethyl*iso*coumarin* (VIII; R = H) separated in rhombic prisms which effloresced in air forming a powder, melting indefinitely between 260° and 280° (Found: C, 57·6; H, 4·2. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%).

The trihydroxy-derivative (1·1 g.) in methyl alcohol (25 c.c.) was allowed to react with ethereal diazomethane (from 20 g. of nitrosomethylurea). After 3 days, removal of solvent yielded the trimethyl ether (VIII; R = Me) which crystallised from methyl alcohol in needles (1·2 g.), m. p. 93—94°, identical with the compound obtained from flavellagic acid.

Acetonyl 3 : 4 : 5-*Trimethoxybenzoate.*—3 : 4 : 5-Trimethoxybenzoic acid (10·5 g.), potassium carbonate (3·4 g.), chloroacetone (4·6 c.c.), water (70 c.c.), and sufficient methyl alcohol to produce a clear solution were refluxed for 4 hr. The product, isolated with ether, crystallised from aqueous methyl alcohol in plates (7·2 g.), m. p. 83—84° (Found: C, 58·3; H, 6·3. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). This *ester* was recovered unchanged after treatment with 80% sulphuric acid (12 vol.) at 0° for 7 days.

Chloromethyl Propyl Ketone.—Butyryl chloride (5 g.) was added to ice-cold ethereal diazomethane (from 40 g. of nitrosomethylurea). After 6 hr. at room temperature, concentrated hydrochloric acid (100 c.c.) was added with stirring, and after a further ½ hr. the ether layer was separated, washed with water, dried, and evaporated. The residue was a colourless lachrymatory oil (4·8 g.), b. p. 153—155°/753 mm. (Levene and Haller, *J. Biol. Chem.*, 1928, **77**, 560,

give 154·5—156°). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow needles, m. p. 138—139° (Found : N, 18·7. $C_{11}H_{13}O_4N_4Cl$ requires N, 18·6%).

2-*Oxopentyl* 3 : 4 : 5-*Trihydroxybenzoate*.—A mixture of gallic acid (2·5 g.), chloromethyl propyl ketone (2·2 g.), potassium carbonate (0·9 g.), water (30 c.c.), and sufficient methyl alcohol to produce a homogeneous solution was refluxed for 4 hr. The *ester*, isolated with ether, separated from toluene as a microcrystalline powder (2·1 g.), m. p. 141—142° (Found : C, 56·5; H, 5·3. $C_{12}H_{14}O_8$ requires C, 56·7; H, 5·5%). It was recovered after treatment with 80% sulphuric acid at 0° for 7 days, and after 4 hours' refluxing in benzene with phosphoric oxide.

Ethyl 5 : 6 : 7-*Trimethoxy*iso*coumarin*-4-*carboxylate* (XII; R = Et).—A mixture of ethyl formate (21 c.c.) and ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) (28 g.) was added to potassium ethoxide [prepared from potassium (4·9 g.) and ethyl alcohol (7·2 c.c.)]. After 1 day, water was added and acidification of the red aqueous layer gave an oily formyl derivative which was isolated with ether and cyclised by 20 minutes' heating on a water-bath with concentrated hydrochloric acid (1 c.c.). *Ethyl* 5 : 6 : 7-*trimethoxy*iso*coumarin*-4-*carboxylate*, isolated with ether, crystallised from ethyl alcohol in needles (5 g.), m. p. 105—106° (Found : C, 58·5; H, 5·4. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*iso*coumarin*-4-*carboxylic Acid* (XIII).—The ethyl ester (XIII; R = Et) (0·77 g.) in acetic acid (50 c.c.) was shaken with 25% palladium–charcoal (0·08 g.) in hydrogen at 50°. After 10 days, removal of the catalyst and the solvent gave a yellow oil (A), which was hydrolysed by 4 hours' boiling with acetic acid (5 c.c.), concentrated hydrochloric acid (2 c.c.), and water (6 c.c.). Dilution with water (40 c.c.) and continuous ether-extraction for 18 hr. yielded a brown oily *acid* which slowly solidified and crystallised from 50% aqueous acetic acid in colourless prisms (0·4 g.), m. p. 160—161° (decomp.) (Found : C, 55·1; H, 5·2. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%).

Methyl β-*Hydroxy*-α-(2 : 3 : 4-*trimethoxy*-6-*methoxycarbonylphenyl*)*propionate*.—(*a*) 3 : 4-Dihydro-5 : 6 : 7-trimethoxy*iso*coumarin-4-carboxylic acid was dissolved in hot water. On cooling, an oil separated and slowly solidified; this was taken up in ether, dried, and mixed with excess of ethereal diazomethane. (*b*) The yellow oil produced as in the preceding paragraph was hydrolysed with hot 6% potassium hydroxide solution. Acidification and extraction with ether gave a white solid, which was allowed to react with excess of ethereal diazomethane for 2 hr. In both cases removal of the ether gave *methyl* β-*hydroxy*-α-(2 : 3 : 4-*trimethoxy*-6-*methoxycarbonylphenyl*)*propionate*, prisms (methyl alcohol), m. p. 110° (decomp.) (Found : C, 54·6; H, 5·8. $C_{15}H_{20}O_8$ requires C, 54·9; H, 6·1%).

7-*Cyanomethyl*-4 : 5 : 6-*trimethoxyphthalide* (XVI; R = CN).—A solution of 7-chloromethyl-4 : 5 : 6-trimethoxyphthalide (XVI; R = Cl) (4·7 g.; Haworth, Moore, and Pauson, *loc. cit.*) in alcohol (30 c.c.) was added to a solution of sodium cyanide (1·7 g.) in water (10 c.c.). After boiling for 3 hr., the mixture was cooled, then poured into an equal volume of dilute hydrochloric acid, and the brown solid was collected; crystallisation from methyl alcohol gave 7-*cyanomethyl*-4 : 5 : 6-*trimethoxyphthalide* as colourless prisms (3·6 g.), m. p. 105—106° (Found : C, 59·2; H, 4·9; N, 5·2. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 4·9; N, 5·3%). The nitrile was soluble in warm dilute sodium hydroxide, and was recovered by acidification.

7-*Carboxymethyl*-4 : 5 : 6-*trimethoxyphthalide*.—The nitrile (XVI; R = CN) (1 g.) was refluxed with 20% aqueous potassium hydroxide (10 c.c.) until evolution of ammonia ceased. Acidification then yielded the *acid* (XVI; R = CO_2H) which crystallised from hot water in prisms (0·9 g.), m. p. 124—125° [Found : equiv. (cold), 281; (hot), 142·5; C, 55·2; H, 4·9%. $C_{13}H_{14}O_7$ requires equiv. (cold), 282; (hot), 141; C, 55·3; H, 5·0%].

7-*Hydroxymethyl*-4 : 5 : 6-*trimethoxyphthalide* (XVI; R = OH).—The chloromethylphthalide (XVI; R = Cl) (1·5 g.) was boiled with 5% aqueous sodium hydroxide (50 c.c.) for 3 hr. Acidification and extraction with ether gave the *hydroxymethylphthalide* which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (0·8 g.), m. p. 87—88° (Found : C, 56·9; H, 5·9. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%), depressed to 78—80° on admixture with the starting material and giving a positive Zerewitinoff test.

Chloromethylation of 4 : 5 : 6-*Trimethoxyphthalide*.—5 : 4 : 6-Trimethoxyphthalide (1 g.), 40% aqueous formaldehyde (0·7 c.c.), and concentrated hydrochloric acid (4 c.c.) were warmed on a steam-bath for 1 hr. The product crystallised from light petroleum (b. p. 60—80°) in needles (0·3 g.), m. p. 83—84°, undepressed on admixture with the product obtained by Haworth, Moore, and Pauson (*loc. cit.*) by chloromethylation of methyl 3 : 4 : 5-trimethoxybenzoate.

3-*Diazoacetyl*-4 : 5 : 6-*trimethoxyphthalide* (XIV; R = CHN_2).—4 : 5 : 6-Trimethoxyphthalide-3-carboxylic acid (Bargellini and Molina, *loc. cit.*) (1 g.) was refluxed for 1 hr. with excess of thionyl chloride. Evaporation then yielded the oily chloride (XIV; R = Cl) which

with ethereal diazomethane (from 2·5 g. of nitrosomethylurea) during 10 hr. gave the *diazo*-ketone, pale yellow needles (0·3 g.) (from methyl alcohol), m. p. 104—105° (decomp.) (Found: C, 53·5; H, 4·2; N, 9·6. $C_{13}H_{12}O_6N_2$ requires C, 53·4; H, 4·1; N, 9·6%).

3-*Acetyl*-4 : 5 : 6-*trimethoxyphthalide* (XIV; R = Me).—The diazo-ketone (XIV; R = CHN_2) (0·5 g.) was treated in chloroform (30 c.c.) at 50° with 50% hydriodic acid (10 c.c.). When nitrogen evolution had ceased, the chloroform layer was washed with water and sodium thiosulphate solution, and dried. Removal of the solvent gave a brown solid, which crystallised from methyl alcohol (charcoal) in colourless needles (0·2 g.), m. p. 75—76°, undepressed on admixture with 3-acetyl-4 : 5 : 6-trimethoxyphthalide prepared from galloflavin (Haworth and McLachlan, *loc. cit.*).

The following experiments were carried out by Dr. P. R. Jefferies.

Diethyl 5 : 6 : 7-*Trimethoxy*iso*coumarin*-3 : 4-*dicarboxylate* (XVII; R = R′ = Et).—A mixture of diethyl oxalate (2·0 g.) and ethyl 6-ethoxycarbonyl-2 : 3 : 4-trimethoxyphenylacetate (XI) (3·0 g.) was added to potassium ethoxide (from 0·8 g. of potassium) in ether (50 c.c.). After 1 day at room temperature, water was added, the red aqueous layer was acidified, and the product, isolated with ether as a brown oil, was cyclised by 3 hours' heating at 140°. The dicarboxylic ester (XVII; R = R′ = Et) crystallised from ethyl alcohol in needles (1·9 g.), m. p. 159—162° (Found: C, 56·7; H, 5·7. $C_{18}H_{20}O_9$ requires C, 56·9; H, 5·3%).

5 : 6 : 7-*Trimethoxy*iso*coumarin*-3-*carboxylic Acid* (X; R = H).—The ester (XVII; R = R′ = Et) (0·5 g.) was refluxed with dilute sulphuric acid (20 c.c.) and acetic acid (5 c.c.) for 2 days. The product (X; R = H) separated on cooling and crystallised from ethyl alcohol in slender needles (0·35 g.), m. p. 262—264° (Found: C, 55·9; H, 4·6. Calc. for $C_{13}H_{12}O_7$: C, 55·7; H, 4·3%), undepressed on admixture with a specimen prepared by pyrolysis of trimethylchebulic acid as described in the preceding paper (p. 3616). Tschitschibabin *et al.*, *loc. cit.* give m. p. 254°.

When this hydrolysis was interrupted after 10 hr., some acid (X; R = H) was obtained but dilution of the alcoholic mother-liquors with water gave an *acid ester*, probably (XVIII; R = H; R′ = Et), which crystallised from 50% aqueous alcohol in prisms, m. p. 174—175° (Found: C, 54·2; H, 4·8. $C_{16}H_{18}O_9$ requires C, 54·2; H, 5·0%).

Methyl 5 : 6 : 7-*Trimethoxy*iso*coumarin*-3-*carboxylate* (X; R = Me).—This ester, prepared with ethereal diazomethane, separated from methyl alcohol in needles, m. p. 154—155° (Found: C, 57·4; H, 4·9. Calc. for $C_{14}H_{14}O_7$: C, 57·1; H, 6·8%) undepressed on admixture with the specimen described in the preceding paper (p. 3616). The acid chloride, prepared by use of refluxing thionyl chloride (5 parts) for 3 hr., separated from benzene in long prisms, m. p. 163—164° (Found: C, 52·6; H, 3·7. Calc. for $C_{13}H_{11}O_6Cl$: C, 52·3; H, 3·7%), identical with the chloride described in the preceding paper (p. 3616). The ethyl ester, prepared from the acid chloride and alcohol, crystallised from alcohol in needles, m. p. 118° (Found: C, 58·5; H, 5·5. Calc. for $C_{15}H_{16}O_7$: C, 58·4; H, 5·2%), undepressed on admixture with the specimen prepared in the preceding paper (p. 3616).

3-*Diazoacetyl*-5 : 6 : 7-*trimethoxy*iso*coumarin*.—The acid chloride, m. p. 163—164° (0·9 g.), described above, was added in small portions to ethereal diazomethane (from 3 g. of nitrosomethylurea), and after 15 hr. the yellow precipitate was collected and crystallised from benzene; 3-*diazoacetyl*-5 : 6 : 7-*trimethoxy*iso*coumarin* was obtained as pale yellow needles (0·55 g.), m. p. 158—159° (decomp.) (Found: N, 8·9. $C_{14}H_{12}O_6N_2$ requires N, 9·2%).

Methyl 5 : 6 : 7-*Trimethoxy*-3-iso*coumarinylacetate*.—The diazoketone (0·4 g.) in methyl alcohol (15 c.c.) was heated at 50° and dry silver oxide (0·1 g.) added; a further quantity of silver oxide (0·15 g.) was added in five portions at intervals of 10 min. The mixture was refluxed for 2 hr., filtered, and evaporated, and the resulting yellow oil was chromatographed in benzene (5 c.c.) on alumina (10 g.). Elution with the same solvent gave a solid fraction which yielded *methyl* 5 : 6 : 7-*trimethoxy*-3-iso*coumarinylacetate* as colourless prisms (0·06 g.), m. p. 127—128° (Found: C, 58·7; H, 5·2. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%) after crystallisation from benzene–light petroleum (b. p. 60—80°).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxy*iso*coumarin*-3-*carboxylic Acid*.—Ethyl 5 : 6 : 7-trimethoxy-*iso*coumarin-3-carboxylate (X; R = Et) (4·4 g.) in acetic acid (125 c.c.) was reduced in presence of 25% palladium–charcoal (0·5 g.) at 50°. After 2 days the catalyst and solvent were removed and the 3 : 4-dihydro-ester was distilled at 250° (bath)/0·1 mm. It crystallised from alcohol as prisms (3·7 g.), m. p. 84—85° (Found: C, 57·8; H, 5·7. Calc. for $C_{15}H_{18}O_7$: C, 58·1; H, 5·8%), undepressed on admixture with a specimen obtained as described in the preceding paper (p. 3616). Hydrolysis for 2 hr. with boiling hydrochloric acid (10 vol.) and water (30 vol.) gave the *acid*, which crystallised from hot water in needles, m. p. 166—167° (Found: C, 55·2; H, 5·1. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%).

Our thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant to H. K. P., to the University of Western Australia for a Hackett Research Studentship to P. R. J., and to the Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of this research.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, June 12th*, 1954.]