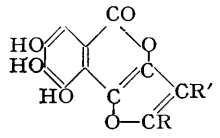
83. *Galloflavin. Part III.* The Position of the Carboxyl Group in* iso*Galloflavin and a Synthesis of Trimethylbrevifolin.*

By James Grimshaw and Robert D. Haworth.

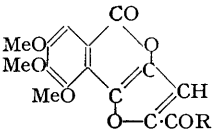
The correctness of structure (I) for *iso*galloflavin has been proved by conversion of trimethyl*iso*galloflavin into 5 : 6 : 7-trimethoxy-5′-*n*-propylfurano-(3′ : 2′-3 : 4)*iso*coumarin, which yielded 3-acetyl-4 : 5 : 6-trimethoxyphthalide, 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid, methyl *n*-propyl ketone, and *n*-butyric acid.

A synthesis of tri-*O*-methylbrevifolin from 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid has also been realised.

Previous work * led to the conclusion that *iso*galloflavin, obtained by the action of alkali on galloflavin, had either structure (I) or structure (II); experiments now reported have enabled a decision to be made in favour of structure (I). These involved conversion of the carboxyl group of tri-*O*-methyl*iso*galloflavin (III; R = OH) into an *n*-propyl group. The product (IV) proved, as expected, unstable to alkali and identification of the hydrolysis products revealed the structure of *iso*galloflavin.



(I) : R = CO_2H, R′ = H
(II) : R = H, R′ = CO_2H



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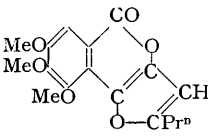


(IV)

The relatively large amounts of tri-*O*-methyl*iso*galloflavin were obtained, without recourse to diazomethane, by methylating the methyl ester with methyl sulphate and potassium carbonate in acetophenone and then hydrolysing the ester group. Galloflavin was similarly tetramethylated in xylene, although Herzig and Wachsler [1] found that methylation in aqueous alkali caused formation of tri- and tetra-methyl derivatives of *iso*galloflavin as well as partial rupture of the *iso*coumarin ring.

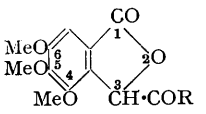
After an unsuccessful attempt to reduce the exocyclic ester but not the lactone group of tetramethyl*iso*galloflavin (III; R = OMe) with lithium aluminium hydride, attention was turned to the acid chloride (III; R = Cl) which was readily formed from trimethyl*iso*galloflavin by thionyl chloride. This chloride did not undergo the Friedel–Crafts reaction with anisole or veratrole, and the derived amide could not be dehydrated. However the chloride was normally hydrolysed to the acid by aqueous acetic acid, and converted into esters and thiolesters by the usual reactions. With diethylcadmium in ether it gave variable yields of 5 : 6 : 7-trimethoxy-5′-propionylfurano(3′ : 2′-3 : 4)*iso*coumarin (III; R = Et), and on one occasion tri-*O*-methyl*iso*galloflavin ethyl ester (III; R = OEt) was

* Parts I and II, *J.*, 1952, 1583; 1955, 833.

[1] Herzig and Wachsler, *Monatsh.*, 1914, **35**, 77.

the major product, presumably owing to reaction of the chloride with the solvent. Results were however satisfactory when benzene was the solvent.[2]

Clemmensen reduction of the ketone (III; R = Et) afforded the 5′-*n*-propyl derivative (IV), and the low yields obtained were presumably due to the instability of the product to the acidic conditions. The *n*-propyl compound was more stable to alkali than was the decarboxy-compound derived [3] from (I), but when boiled in 5% aqueous-methanolic potassium hydroxide for 4 hr. yielded 3-acetyl-4 : 5 : 6-trimethoxyphthalide (V; R = Me), 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid (V; R = OH), methyl *n*-propyl ketone, and butyric acid. The formation of the last two products shows that the propyl group must be attached to a carbon atom which bears oxygen. All four products are expected if the propylfurano*iso*coumarin has formula (IV), whence it follows that the intermediate ketone is (III; R = Et) and that *iso*galloflavin has structure (I). On the other hand, the propyl derivative corresponding to the alternative *iso*galloflavin formula (II) would be expected to yield 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid, 4 : 5 : 6-trimethoxy-3-*n*-valerylphthalide, *n*-valeraldehyde, and formic acid. Herzig's earlier formula [3] (VI) for *iso*galloflavin, previously considered erroneous on the basis of negative evidence and theoretical objections,[4] also fails to account for this new evidence. As a result of this



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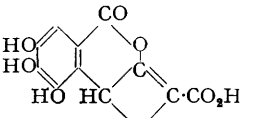
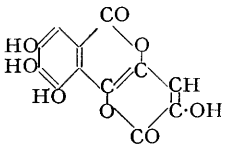


(VI)

proof of the *iso*galloflavin formula (I) it may be deduced [4] that galloflavin is represented by (VII); a scheme for its formation from gallic acid has previously [5] been proposed. Gilman and Wright [6] have show that the carboxyl group of α- but not of β-furoic acids is replaced by the mercurichloride group when the potassium salt is warmed with mercuric chloride. Tri-*O*-methyl*iso*galloflavin undergoes a similar replacement thus providing additional proof that the carboxyl group occupies an α-position in *iso*galloflavin.

Discussion of the mechanism of the formation of galloflavin led to our interpreting the degradative work of Schmidt and Bernauer [7] on brevifolincarboxylic acid, the major crystalline component of *Algarobilla* tannin, in terms of structure (VIII; R = H, R′ = CO_2H) not previously considered. We have now confirmed the formula proposed by these workers for the derived tri-*O*-methylbrevifolin (VIII; R = Me, R′ = H), by synthesis briefly reported elsewhere.[8] Schmidt and Bernauer [9] have also described a synthesis of tri-*O*-methylbrevifolin by an entirely different route.



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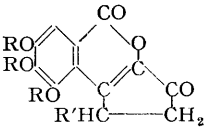
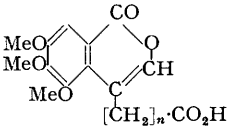


(VIII)



(IX)

5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetic acid (IX; $n = 1$) [10] gave a diazo-ketone which was rearranged by silver benzoate–triethylamine [11] in methanol to methyl β-(5 : 6 : 7-trimethoxy-4-*iso*coumarinyl)propionate. Acid hydrolysis afforded the corresponding acid (IX; $n = 2$) which was cyclised with phosphorus pentoxide in boiling benzene (cf. Plattner

[2] Cf. Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46.
[3] Herzig, *Annalen*, 1920, **421**, 247.
[4] Part I, *J.*, 1952, 1583.
[5] Part II, *J.*, 1955, 833.
[6] Gilman and Wright, *J. Amer. Chem. Soc.*, 1933, **55**, 3302.
[7] Schmidt and Bernauer, *Annalen*, 1954, **588**, 211.
[8] Grimshaw and Haworth, *Chem. and Ind.*, 1955, 199.
[9] Schmidt and Bernauer, *Annalen*, 1955, **591**, 133.
[10] Haworth, Pindred, and Jefferies, *J.*, 1954, 3617.
[11] Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

and Pfau [12]) to give good yields of tri-*O*-methylbrevifolin. This and its 2:4-dinitrophenylhydrazone were identical with specimens derived from natural sources, kindly supplied by Professor Otto Th. Schmidt.

Experimental

Tetra-O-methylgalloflavin.—Galloflavin (0·5 g.) and anhydrous potassium carbonate (4 g.) were suspended in xylene (20 ml.), and methyl sulphate (1·5 ml.) was added. The mixture was stirred and refluxed gently for 4 hr., then further methyl sulphate (1·5 ml.) was added and the mixture refluxed overnight, cooled, and poured into dilute hydrochloric acid. The xylene was removed in steam, and the residual solid collected and crystallised from acetic acid, giving tetra-*O*-methylgalloflavin (0·3 g.), m. p. and mixed m. p. 236—237°.

Tetra-O-methylisogalloflavin.—*iso*Galloflavin with boiling methanol (100 parts) containing 1% of sulphuric acid gave the methyl ester, needles, m. p. 300—305° (decomp.) (Herzig [3] gives m. p. 300—305°). This ester (5 g.), anhydrous potassium carbonate (30 g.), acetophenone (130 ml.), and methyl sulphate (15 ml.) were stirred and heated under reflux at 130—140°. Further methyl sulphate (15 ml.) was added after 4 hr. and the mixture heated for a total of 10 hr., cooled, poured into dilute hydrochloric acid, diluted with light petroleum (b. p. 80—120°) (50 ml.), and filtered. The residue of almost pure tetra-*O*-methyl*iso*galloflavin (4 g.) crystallised from toluene as needles, m. p. 231—232° (Found : C, 57·6; H, 4·3. Calc. for $C_{16}H_{14}O_8$: C, 57·5; H, 4·2%). Alkaline hydrolysis (cf. Herzig and Wachsler [1]) afforded tri-*O*-methyl*iso*galloflavin as needles, m. p. 264—265° (from 50% acetic acid) (Found : C, 56·7; H, 3·7. Calc. for $C_{15}H_{12}O_8$: C, 56·3; H, 3·8%). Decarboxylation then gave the compound, m. p. 130—132° (Part I) (Found : C, 61·3; H, 4·7. Calc. for $C_{14}H_{12}O_6$: C, 60·9; H, 4·3%). The m. p. of these compounds were undepressed on admixture with those prepared by using diazomethane for the methylation of *iso*galloflavin.

Tri-O-methylisogalloflavin Acid Chloride.—Tri-*O*-methyl*iso*galloflavin, refluxed with thionyl chloride (20 parts) for 2 hr., yielded the *acid chloride*, yellow needles, m. p. 217—218° (from toluene) (Found : C, 53·6; H, 3·6. $C_{15}H_{11}O_7Cl$ requires C, 53·2; H, 3·3%). The acid chloride was dissolved in hot acetic acid and water added at the b. p. until precipitation commenced; trimethyl*iso*galloflavin, m. p. and mixed m. p. 264—265°, which separated was converted by ethereal diazomethane into tetra-*O*-methyl*iso*galloflavin, m. p. and mixed m. p. 231—232°. Decomposition of the acid chloride with methanol furnished the same methyl ester, m. p. and mixed m. p. 231—232° (Found : C, 57·7; H, 4·0%).

The acid chloride with aqueous ammonia (*d* 0·88) gave the *amide* (III; R = NH_2), needles (from 50% acetic acid), m. p. 258—259° (Found : C, 56·5; H, 4·1; N, 4·1. $C_{15}H_{13}O_7N$ requires C, 56·4; H, 4·0; N, 4·4%). This was recovered unchanged after 4 hours' refluxing with thionyl chloride. Phosphoric oxide in toluene (8 hr.) caused much charring and only unchanged amide was recovered.

The acid chloride, dissolved in a minimum of hot ethanol, gave, on cooling, the *ethyl ester* which recrystallised from ethanol in needles, m. p. 170—171° (Found : C, 58·9; H, 4·8. $C_{17}H_{16}O_8$ requires C, 58·7; H, 4·7%). The n-*butyl ester* was similarly prepared with, and crystallised from, *n*-butanol, forming needles, m. p. 129—130° (Found : C, 60·8; H, 5·45. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·3%).

The chloride from tri-*O*-methyl*iso*galloflavin (0·2 g.), in dioxan (20 ml.), was treated with trimethylamine (10 drops) and ethanethiol (10 drops). During 8 hr. a precipitate was formed. The mixture was then poured into water. The resulting precipitate was dried, dissolved in hot benzene, and filtered. Addition of hot light petroleum (b. p. 60—80°) yielded the *ethyl thiolester* which recrystallised from benzene–light petroleum (b. p. 60—80°) as pale yellow needles, m. p. 166—167° (Found : C, 56·4; H, 4·6. $C_{17}H_{16}O_7S$ requires C, 56·1; H, 4·4%).

5 : 6 : 7-*Trimethoxy-5'-propionylfurano*(3' : 2'-3 : 4)iso*coumarin* (III; R = Et).—Anhydrous cadmium chloride (4·7 g.) was added to the ice-cold reagent from magnesium (1·2 g.) and ethyl bromide (5·5 g.) in ether (50 ml.) (cf. Gilman and Nelson [13]) and stirred for 0·5 hr. The ether was then removed under nitrogen and thiophen-free benzene (40 ml.) added to the residue which was again distilled almost to dryness. Further benzene (40 ml.) was added and the residual cake thoroughly extracted by refluxing and stirring under nitrogen. Half the resulting diethylcadmium solution was added to tri-*O*-methyl*iso*galloflavin acid chloride (3·5 g.) in hot benzene (150 ml.) and after the initial reaction had subsided the mixture was stirred and refluxed under

[12] Plattner and Pfau, *Helv. Chim. Acta*, 1937, **20**, 1474.
[13] Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518.

nitrogen for 2 hr. On cooling, the bright red mixture was decomposed with ice and dilute hydrochloric acid and diluted with chloroform, and the organic layer was separated and dried. Evaporation of the solvents left a red solid which was refluxed with acetone (80 ml.) and water (40 ml.) for 1 hr.; then water was added and the acetone removed. The residue was extracted with chloroform, and the chloroform extract washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Evaporation left an oil which crystallised on dilution with methanol. This crystalline *ketone* recrystallised from butan-1-ol as needles (0·75 g.), m. p. 201—203°, raised to m. p. 207—208° after several recrystallisations from ethanol (Found: C, 61·0; H, 5·0. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·8%). Acidification of the carbonate extract gave tri-*O*-methyl*iso*galloflavin (0·5 g.). The ketone in hot methanol gave an insoluble deep red precipitate with Brady's reagent. The p-*nitrophenylhydrazone* crystallised from acetic acid as orange plates, m. p. 281—282° (decomp.) (Found: C, 59·7; H, 4·55; H, 9·35. $C_{23}H_{21}O_8N_3$ requires C, 59·1; H, 4·5; N, 9·0%).

5 : 6 : 7-*Trimethoxy*-5′-n-*propylfurano*(3′ : 2′-3 : 4)iso*coumarin* (IV).—The above ketone (0·7 g.) was dissolved in toluene (15 ml.) and refluxed with amalgamated zinc needles (5 g.), water (15 ml.), and concentrated hydrochloric acid (1·5 ml.), further acid (1 ml.) being added every hour. After 10 hr., the mixture was diluted with chloroform and water, and the separated organic layer was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated, finally under reduced pressure. The residual oil gave no reaction with Brady's reagent and was distilled at 190° (bath)/0·05 mm., the distillate solidifying (0·13 g.). The resulting *propyl compound* crystallised from methanol as colourless needles, m. p. 135—136° (Found: C, 63·9; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%), depressed on admixture with decarboxylated trimethyl*iso*galloflavin, m. p. 130—132°.

Action of Alkali on the Propyl Compound (IV).—The compound (0·09 g.) was heated in methanol (2 ml.) and 10% aqueous potassium hydroxide (2 ml.) for 4 hr., becoming bright red. The mixture was then acidified with dilute sulphuric acid and distilled, about half its volume being collected (distillate A). The residue was diluted with water and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution (extract B) and water and dried (Na_2SO_4). Evaporation of the ether left an oil (0·02 g.), which crystallised under methanol. The solid was dissolved in methanol and Brady's reagent added, to give a yellow precipitate, m. p. 198—200°, crystallising from ethanol as yellow needles, m. p. 202—203° (Found: C, 51·5; H, 3·8. Calc. for $C_{19}H_{18}O_9N_4$: C, 51·1; H, 4·0%) undepressed on admixture with 3-acetyl-4 : 5 : 6-trimethoxyphthalide 2 : 4-dinitrophenylhydrazone, m. p. 202—203° (lit., m. p. 202—203°). Extract B was acidified and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated, leaving an oily solid (0·03 g.) which was esterified with ethereal diazomethane. Evaporation of the solvent left an oil which was taken up in benzene (5 ml.) and filtered through alumina (1 g.). Elution with benzene and evaporation of the solvent left a colourless oil (0·02 g.) which slowly solidified and crystallised from *cyclo*hexane in needles, m. p. 118—119° undepressed on admixture with methyl 4 : 5 : 6-trimethoxyphthalide-3-carboxylate, m. p. 119—120° (lit., m. p. 118—120°). Distillate A had a strong odour of butyric acid. It was made alkaline with ammonia and about half the solution was distilled over (distillate C). The residue was chromatographed on paper, markers of formic, *n*-butyric, and *n*-valeric acid being used, with 95% ethanol containing a little ammonia as developing solvent.[14] One spot only, corresponding to *n*-butyric acid, was detected. The residue did not reduce ammoniacal silver nitrate solution, even on boiling. Distillate C was acidified with hydrochloric acid and added to a solution of 2 : 4-dinitrophenylhydrazine (0·03 g.) in dilute hydrochloric acid. The resulting precipitate was collected after 1 day and crystallised from dilute ethanol as orange needles, m. p. 137—138° undepressed by methyl *n*-propyl ketone 2 : 4-dinitrophenylhydrazone, m. p. 137—138° (lit., m. p. 141°).

*Action of Mercuric Chloride on Tri-O-methyl*iso*galloflavin.*—Mercuric chloride (0·57 g.) in water (15 ml.) was added to tri-*O*-methyl*iso*galloflavin (0·6 g.) and potassium hydrogen carbonate (0·21 g.) in water (20 ml.) and warmed on the steam-bath for 3 hr. The yellow *chloromercuri-derivative* which gradually separated was collected, dried (Found: C, 33·2; H, 2·7. $C_{14}H_{11}O_6ClHg$ requires C, 32·9; H, 2·2%), and crystallised from dimethylformamide as pale yellow needles, decomp. 255° (Found: C, 34·6; H, 2·6. $C_{14}H_{11}O_6ClHg,\frac{1}{2}C_3H_7ON$ requires C, 34·3; H, 2·7%). This derivative was converted into 5 : 6 : 7-trimethoxyfurano(3′ : 2′-3 : 4)*iso*coumarin, m. p. 130—132°, by boiling with 2N-hydrochloric acid (25 parts) and methanol (25 parts).

[14] Kennedy and Barker, *Analyt. Chem.*, 1951, **23**, 1033.

4-(3-*Diazo*-2-*oxopropyl*)-5 : 6 : 7-*tri*-O-*methoxy*isocoumarin.—5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetyl chloride [10] (1·5 g.) was finely powdered and slowly added to 3 mols. of diazomethane in ether (*ca.* 60 ml.). A vigorous effervescence resulted and the pure *diazo-ketone* crystallised as buff needles (1·3 g.), m. p. 140—141° (decomp.), recrystallisable from benzene–light petroleum (b. p. 60—80°) (Found: N, 8·8. $C_{15}H_{14}O_6N_2$ requires N, 8·8%).

Methyl β-(5 : 6 : 7-*Trimethoxy*-4-iso*coumarinyl*)*propionate*.—The above diazo-ketone (1·2 g.), dissolved in cold methanol (70 ml.), was treated with a filtered solution of silver benzoate (0·5 g.) in triethylamine (4 ml.) during 90 min., set aside for 60 min., and then refluxed with charcoal and a little formic acid, filtered, and evaporated somewhat. Dilution of the residue with water precipitated the product which was extracted with ether. The ethereal solution was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated, yielding the *methyl ester* (0·69 g.), needles (from methanol), m. p. 97—98° (Found: C, 59·3; H, 5·7. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%).

Refluxing the ester (0·5 g.) for 2 hr. with concentrated hydrochloric acid (4 ml.), acetic acid (1 ml.), and water (1 ml.), gave the *acid*, needles (0·35 g.) (from benzene), m. p. 179—180° (Found: C, 58·0; H, 5·3. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

5 : 6 : 7-*Trimethoxy*-5′-*oxo*-3 : 4-cyclo*penteno*iso*coumarin* (VIII; R = Me, R′ = H).—The above acid (0·2 g.) was refluxed with phosphoric oxide (1 g.) in benzene (20 ml.) for 1 hr., then poured on ice, and the organic layer was separated. The aqueous layer, containing charred material, was washed with chloroform, and the combined organic extracts were washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Removal of the solvents left the *ketone*, crystallising from methanol (in a freezing mixture) as pale yellow needles (0·12 g.), m. p. 212—213° (Found: C, 61·6; H, 5·0. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·9%) undepressed on admixture with tri-*O*-methylbrevifolin, m. p. 213—214°, kindly supplied by Professor Schmidt. The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate as red needles, m. p. and mixed m. p. 294—296° (decomp.). The p-*nitrophenylhydrazone*, prepared in acetic acid, crystallised from anisole as deep red rhombs, m. p. 284—286° (decomp.) (Found: N, 10·3. $C_{21}H_{19}O_7N_3$ requires N, 9·9%).

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