

The constitution of scopoletin / by Charles W. Moore.

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Publication/Creation

London : Wellcome Chemical Research Laboratories, 1911.

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THE CONSTITUTION
OF
SCOPOLETIN

BY

CHARLES W. MOORE, PH.D.

(From the Transactions of the Chemical Society, Vol. 99, 1911)

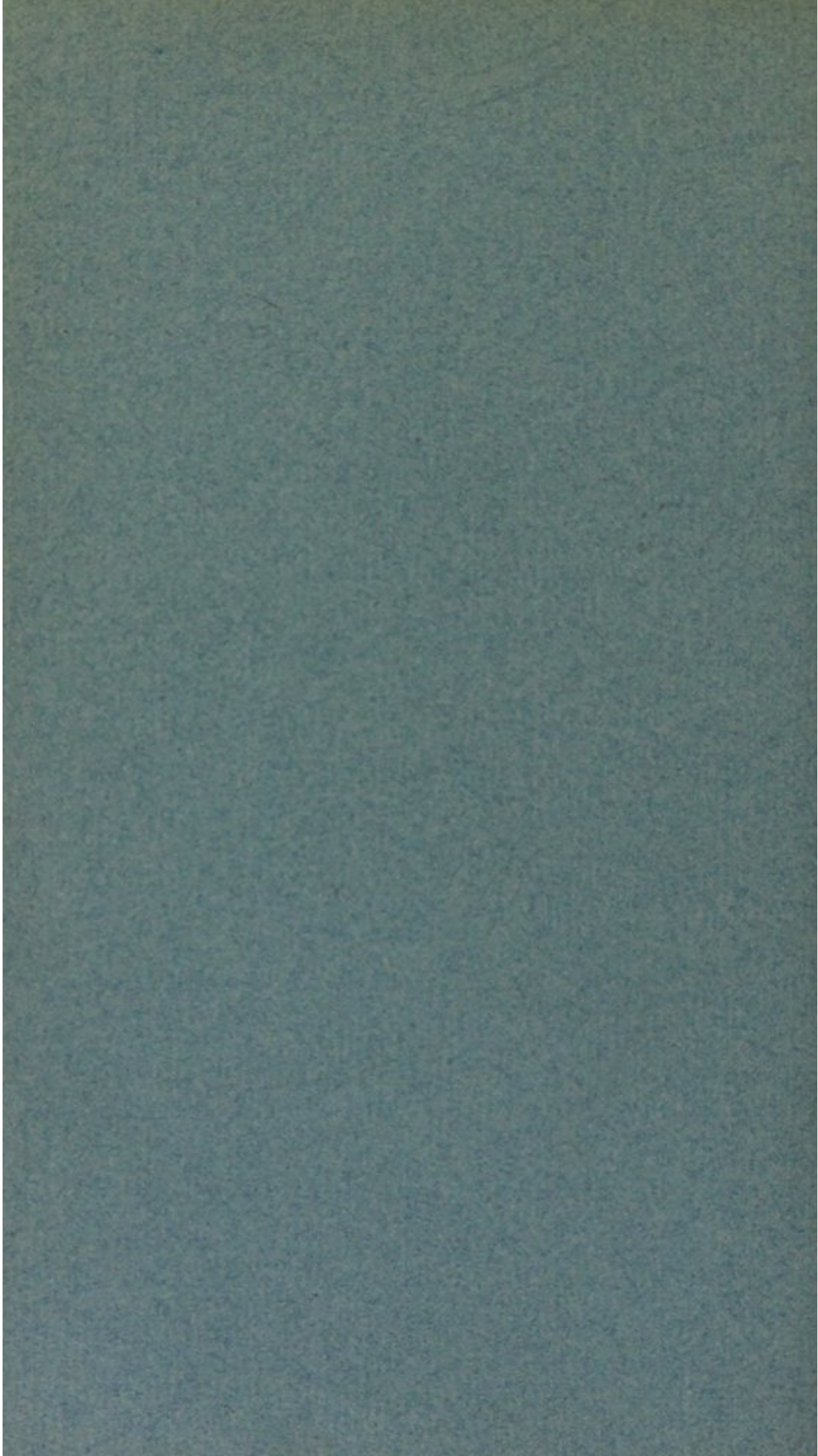


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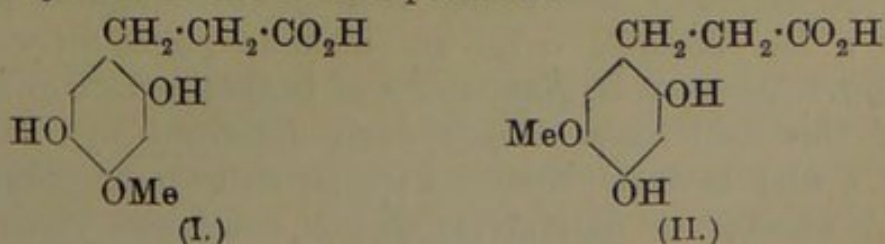
CIX.—*The Constitution of Scopoletin.*

By CHARLES WATSON MOORE.

Two monomethyl ethers of aesculetin (4:5-dihydroxycoumarin) are known, which melt at 184° and 204° respectively. One of these (m. p. 204°) was designated as scopoletin by Eykman (*Rec. trav. chim.*, 1884, **3**, 171), who first isolated it from the rhizome of *Scopolia japonica*. This substance also occurs in *Atropa Belladonna* (Kunz-Krause, *Arch. Pharm.*, 1885, **223**, 701), in *Gelsemium* (Wormley, *Amer. J. Pharm.*, 1870, **42**, 1; and Moore, *Trans.*, 1910, **98**, 2223), in the bark of *Prunus serotina* (Power and Moore, *Trans.*, 1909, **95**, 243), and in jalap (Power and Rogerson, *J. Amer. Chem. Soc.*, 1910, **32**, 93). On account of its occurrence in different plants, scopoletin has been variously referred to as "gelseminic acid," "chrysotropic acid," and " β -methylaesculetin," but the latter designation is particularly inappropriate for reasons which have previously been noted (*Trans.*, 1910, **98**, 2224), and it is therefore considered desirable to retain the original name, scopoletin, for the above-mentioned compound.

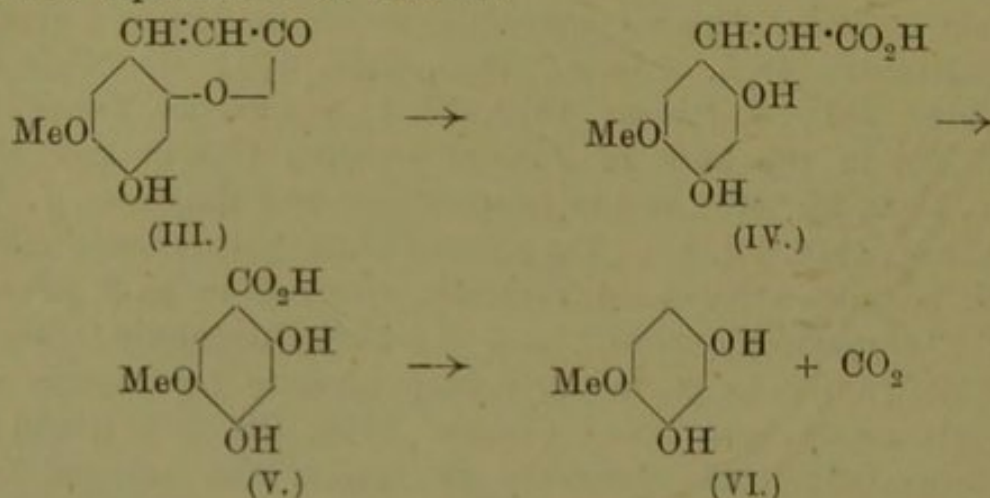
Although scopoletin is known to be a monomethyl ether of aesculetin (Schmidt, *Arch. Pharm.*, 1898, **236**, 236), the position of the methyl group does not appear to have been determined. Kunz-Krause (*Ber.*, 1893, **31**, 1189) refers to this substance as 4-hydroxy-5-methoxycoumarin, but this was apparently only an assumption, as no evidence is cited in support of his statement. A quantity of scopoletin being available, it therefore appeared of interest to ascertain the position of the methyl group in this substance, and thus determine the orientation of both the monomethyl ethers of aesculetin.

On hydrolysis, scopoletin should be converted into the corresponding coumaric acid, from which a dihydroxymethoxyphenylpropionic acid would be formed on reduction. The latter acid would be represented by formula I or II, according as to whether scopoletin were methylated in the 4- or 5-position:



In the former case the two hydroxyl groups would be in the para-position with respect to each other, and it should therefore be possible to obtain the corresponding quinone by oxidation.

On attempting to prepare the substituted coumaric acid from scopoletin by the prolonged action of aqueous potassium hydroxide on the latter, it was found that oxidation took place, with the production of a dihydroxymethoxybenzene. Only two possibilities can here exist, and the product of the reaction must be either 2:5- or 2:4-dihydroxyanisole, according as scopoletin is the 4- or 5-methyl ether of aesculetin. As the phenol obtained was found to be the 2:4-dihydroxy-compound, its formation from scopoletin must be represented as follows:



Scopoletin must, therefore, be 4-hydroxy-5-methoxycoumarin, whilst the other monomethyl ether of aesculetin, melting at 184°, which has only been obtained synthetically, will be 5-hydroxy-4-methoxycoumarin.

The identification of the above-mentioned 2:4-dihydroxyanisole was effected by means of its analysis and melting point, and by the preparation of its *diacetyl* derivative, which melts 30° lower than 2:5-*diacetoxyanisole*.

Attempts to isolate the 2:4-dihydroxy-5-methoxybenzoic acid (V), which must be formed as an intermediate product, were unsuccessful, and it appears probable that this substance, when liberated from its salts, loses carbon dioxide with the formation of the corresponding dihydroxyanisole.

Although the prolonged action of aqueous potassium hydroxide on scopoletin had been found to result only in the formation of a phenol, it has been ascertained that if the alkali is allowed to act for a few minutes only, an almost quantitative yield of 2:4-dihydroxy-5-methoxycinnamic acid is obtained. Sodium derivatives of this acid have already been described by Kunz-Krause (*loc. cit.*), who, however, does not appear to have prepared the free acid. A number of derivatives of this substance have now been prepared, which are described in this paper.

The ease with which scopoletin is hydrolysed is remarkable, as coumarin is only very slowly converted into *o*-coumaric acid by

prolonged boiling with aqueous potassium hydroxide, and the dimethyl ether of aesculetin shows a similar stability.

EXPERIMENTAL.

The scopoletin employed was obtained from the rhizome of *Elesemium sempervirens*, Aiton (Trans., 1910, **97**, 2223), in which it occurs to the extent of about 0.05 per cent. It forms yellow needles, melting at 204°, and in alkaline solution shows a fine blue fluorescence.

Action of Potassium Hydroxide on Scopoletin.

(1) *Formation of 2:4-Dihydroxyanisole.*

With the endeavour to obtain the coumaric acid corresponding with scopoletin, a quantity (4 grams) of the latter was boiled for nine hours with 50 c.c. of a 45 per cent. aqueous solution of potassium hydroxide. The resulting dark-coloured aqueous solution was acidified, and extracted with ether. The ethereal extract was dried, and the solvent removed, when a dark brown, syrupy liquid was obtained, which showed no tendency to crystallise. The product was therefore distilled under diminished pressure, when the greater part of it passed over as an almost colourless, viscid liquid, which, when dissolved in dry benzene, separated, on keeping, in glistening prisms (1.5 grams), melting at 66—68°. (Found, C=59.8; H=5.9; OMe=22.0. Calc., C=60.0; H=5.7; OMe=22.1 per cent.).

The compound is therefore a dihydroxyanisole, and from its melting point must be 2:4-dihydroxyanisole, the only possible alternative being the 2:5-dihydroxy-compound, which, however, melts at 84°. For the purpose of comparison, a small quantity of the latter was prepared by the reduction of the corresponding quinone, as described by Witt (*Ber.*, 1888, **21**, 605). Methoxyquinone was found to melt at 145°, instead of 140°, as recorded (*loc. cit.*), and possesses no quinone-like odour. On reduction it yields 2:5-dihydroxyanisole, which crystallises from benzene in glistening prisms, melting at 84°, as recorded in the literature (*loc. cit.*).

Further confirmation as to the identity of the above-described compound with 2:4-dihydroxyanisole was obtained by preparing its *diacetyl* derivative, and comparing this with 2:5-*diacetoxyanisole*.

2:4-Diacetoxyanisole.—2:4-Dihydroxyanisole was boiled for a few minutes with acetic anhydride in the presence of a trace of *d*-camphorsulphonic acid. The solution was then poured into water, when, after a time, a crystalline precipitate separated. This

was collected, and recrystallised from methyl alcohol, when it formed glistening prisms, melting at 62—64°:

0.1468 gave 0.3180 CO₂ and 0.0725 H₂O. C=59.0; H=5.5.

0.2142 „ 0.2225 AgI. OMe=13.7.

C₁₀H₉O₄·OMe requires C=58.9; H=5.3; OMe=13.8 per cent.

2:5-Diacetoxyanisole.—This was prepared by the action of acetic anhydride on 2:5-dihydroxyanisole, as in the preceding case. *2:5-Diacetoxyanisole* crystallises from methyl alcohol in glistening, prismatic needles, melting at 93—94°:

0.1258 gave 0.2720 CO₂ and 0.0605 H₂O. C=58.9; H=5.3.

C₁₁H₁₂O₅ requires C=58.9; H=5.3 per cent.

It is therefore evident that the product of the prolonged action of boiling aqueous potassium hydroxide on scopoletin is 2:4-dihydroxyanisole, and the formation of this compound is only possible, as already indicated, if scopoletin is 4-hydroxy-5-methoxycoumarin. Attempts to isolate the corresponding 2:4-dihydroxy-5-methoxybenzoic acid, which must be formed as an intermediate product, were unsuccessful.

(2) *Formation of 2:4-Dihydroxy-5-methoxycinnamic Acid.*

If scopoletin is dissolved in 10—20 per cent. aqueous potassium hydroxide, and the solution boiled for a few minutes, the lactone grouping is hydrolysed, and the liquid then shows no fluorescence.

A quantity (10 grams) of scopoletin was added to 100 c.c. of boiling 20 per cent. aqueous potassium hydroxide, and the solution boiled for four minutes. The alkaline liquid was then at once cooled, ice added, and acidified by the addition of 40 c.c. of concentrated hydrochloric acid, mixed with an equal volume of ice, the temperature being kept below 10°. After a short time, a yellow, crystalline precipitate separated, which was collected, well washed with ice-water, and dried in a desiccator. The product so obtained amounted to 9 grams. It crystallised from hot water in bright yellow needles, melting and decomposing at 178—180°:

0.5778,* on heating at 110°, lost 0.0468 H₂O. H₂O=8.1.

0.1426 † gave 0.2995 CO₂ and 0.0650 H₂O. C=57.3; H=5.0.

0.1628 † „ 0.1780 AgI. OMe=14.4.

C₁₀H₁₀O₅·H₂O requires H₂O=8.0 per cent.

C₉H₇O₄·OMe requires C=57.1; H=4.8; OMe=14.7 per cent.

The substance is therefore the coumaric acid corresponding with scopoletin, or *2:4-dihydroxy-5-methoxycinnamic acid*, sodium derivatives of which were obtained by Kunz-Krause (*Ber.*, 1898, 31, 1192).

* Air-dried.

† Anhydrous substance.

2:4-Dihydroxy-5-methoxycinnamic acid is sparingly soluble in ether and cold water, but dissolves readily in hot water. It rapidly decomposes on boiling with dilute acids, more slowly with hot water, with loss of carbon dioxide. On heating with acetic anhydride, it loses water, and is converted into acetylscopoletin.

2:4:5-Trimethoxycinnamic Acid.—Ten grams of 2:4-dihydroxy-5-methoxycinnamic acid were dissolved in 100 c.c. of alcohol, and to the solution were added 10 grams of methyl sulphate and then excess of concentrated aqueous potassium hydroxide. The solution was then boiled, acidified, and extracted with ether, the ethereal extracts being subsequently extracted with aqueous ammonium carbonate. The alkaline liquids thus obtained were acidified, extracted with ether, and the ethereal solution concentrated to a small volume, when a substance separated in small, yellow needles. This was collected, and recrystallised from dilute alcohol, when it formed a crystalline mass, melting at 163—165°:

0.1336 gave 0.2970 CO₂ and 0.0725 H₂O. C=60.6; H=5.9.

C₁₂H₁₄O₅ requires C=60.6; H=5.9 per cent.

The substance is thus 2:4:5-trimethoxycinnamic acid, and on oxidation it yielded asarylaldehyde (2:4:5-trimethoxybenzaldehyde) and the corresponding asaronic acid.

Reduction of 2:4-Dihydroxy-5-methoxycinnamic Acid.

Formation of 2:4-Dihydroxy-5-methoxy-β-phenylpropionic Acid.

A quantity (5 grams) of 2:4-dihydroxy-5-methoxycinnamic acid was dissolved in about 150 c.c. of aqueous methyl alcohol, and twice the theoretical amount of 3 per cent. sodium amalgam gradually introduced, the mixture being kept acid by the frequent addition of acetic acid. When the reduction was finished, hydrochloric acid, in slight excess, was added, and the solution boiled to remove the excess of methyl alcohol. The aqueous liquid was then extracted with ether, which removed a quantity (3 grams) of a crystalline substance. The latter, on recrystallisation from water, formed small, glistening needles, which melted, when dried in the air, at 68—69°:

0.1158 * gave 0.2216 CO₂ and 0.0640 H₂O. C=52.2; H=6.1.

C₁₀H₁₂O₅, H₂O requires C=52.2; H=6.1 per cent.

This substance is therefore 2:4-dihydroxy-5-methoxy-β-phenylpropionic acid, and, as the analysis shows, it crystallises from its aqueous solution with one molecule of water of crystallisation.

Lactone of 2:4-Dihydroxy-5-methoxy-β-phenylpropionic Acid.—

* Air-dried.

On distilling 2:4-dihydroxy-5-methoxy- β -phenylpropionic acid under diminished pressure, it loses one molecule of water, and is converted into its lactone, which crystallises from water in colourless needles, melting at 155°:

0.1442 gave 0.3280 CO₂ and 0.0695 H₂O. C=62.0; H=5.3.

C₁₀H₁₀O₄ requires C=61.9; H=5.2 per cent.

Lactone of 2-Hydroxy-4-acetoxy-5-methoxy- β -phenylpropionic Acid.—This substance is obtained by the action of acetic anhydride on either 2:4-dihydroxy-5-methoxy- β -phenylpropionic acid, or the corresponding lactone. It crystallises from methyl alcohol in glistening plates, melting at 135°:

0.1180 gave 0.2644 CO₂ and 0.0570 H₂O. C=61.1; H=5.4.

C₁₂H₁₂O₅ requires C=61.0; H=5.1 per cent.

2:4:5-*Trimethoxy- β -phenylpropionic acid* was obtained by the action of methyl sulphate and potassium hydroxide on 2:4-dihydroxy-5-methoxy- β -phenylpropionic acid, as in the case of the corresponding 2:4:5-trimethoxycinnamic acid. It crystallises from its aqueous solution in small, glistening needles, containing one molecule of water of crystallisation, and melts at 74—76°. On drying in a vacuum, the water of crystallisation is lost, and the substance then melts at 95—96°:

0.1710,* on heating at 110°, lost 0.0124 H₂O. H₂O=7.2.

0.1604 † gave 0.3520 CO₂ and 0.0970 H₂O. C=59.8; H=6.7.

C₁₂H₁₆O₅, H₂O requires H₂O=7.0 per cent.

C₁₂H₁₆O₅ requires C=60.0; H=6.7 per cent.

Methyl 2:4:5-trimethoxy- β -phenylpropionate was formed on saturating a methyl-alcoholic solution of 2:4:5-trimethoxy- β -phenylpropionic acid with hydrogen chloride. It crystallises from water or methyl alcohol in small, colourless needles, melting at 54°:

0.1312 gave 0.2944 CO₂ and 0.0854 H₂O. C=61.2; H=7.2.

C₁₃H₁₈O₅ requires C=61.4; H=7.1 per cent.

* Air-dried.

† Anhydrous substance.

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