862. *The Coumarins of* Ammi visnaga *L. Part I. Their Reactions with Benzene, Toluene, and Anisole in Presence of Aluminium Chloride: Isolation of Minor Constituents of* Ammi visnaga.

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Visnadin, dihydrosamidin, and khellactone diacetate react with benzene and anisole in presence of anhydrous aluminium chloride to give the corresponding 4′-aryl-substituted derivatives (I). Under similar conditions visnadin reacts with toluene to give the 4′-tolyl derivative.

Khellactone reacts with acetyl or isovaleryl chloride to give the 4′-ester.

From the aqueous mother-liquor derived from the alcoholic extract of the seeds of *Ammi visnaga*, seven minor constituents have been isolated.

THE infrared spectra of visnadin (Ia) and dihydrosamidin (If), isolated in the present investigation from *Ammi visnaga* L., did not show the band at 1656 cm.$^{-1}$ (in Nujol, CCl_4, or KBr) which was reported by Schroeder, Bencze, Halpern, and Schmid [1] for samidin (In). It appears, therefore, that this band belongs, not to the pyrone double bond, but to that in the senecate ester group, $CMe_2{:}CH{\cdot}CO{\cdot}O$, which is present only in samidin.

The ultraviolet spectrum of dihydrosamidin in methanol (Fig. 1, curve A) is very similar to that of coumarin and to that reported.[2] However, in cyclohexane solution more fine structure develops (Fig. 1, curve B).

When exposed to sunlight, visnadin (Ia) and dihydrosamidin (If) give dimers, a reaction characteristic of some coumarins.[3] The hypsochromic shift in the ultraviolet spectrum of the dimer of dihydrosamidin (Fig. 1, curve C) indicates disappearance of the α-pyrone double bond.

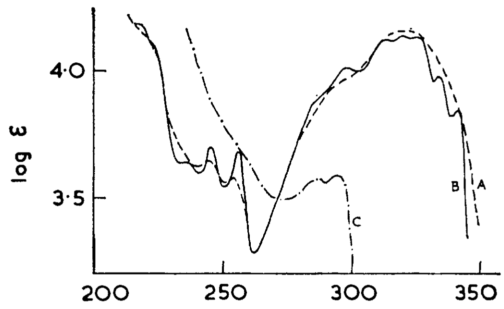

FIG. 1. Ultraviolet absorption spectra of dihydrosamidin (A) in methanol and (B) in cyclohexane, and (C) of its dimer in methanol.

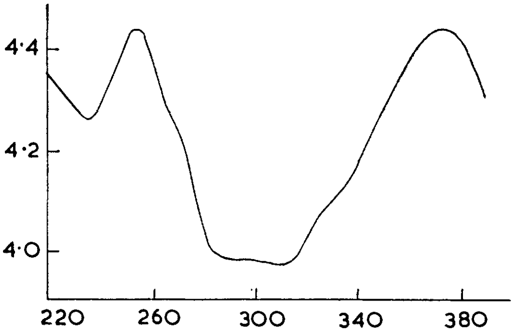

FIG. 2. Ultraviolet absorption spectrum of the trihydroxymethoxyflavone (III) in ethanol.

When visnadin (Ia) was treated with anhydrous aluminium chloride in benzene, toluene, or anisole, the 4′-acetate group was replaced by an aryl group, giving compounds (Ib, c, and d, respectively). The first of these was converted into the alcohol (Ie) on alkaline hydrolysis. When dihydrosamidin (If) was similarly treated with aluminium chloride in benzene or anisole, it gave rise to the aryl derivatives (Ig and h, respectively). On re-esterification, the alcohol (Ie) gave its acetate (Ij) and isovalerate (Ig).

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[1] Schroeder, Bencze, Halpern, and Schmid, *Chem. Ber.*, 1959, **92**, 2338.

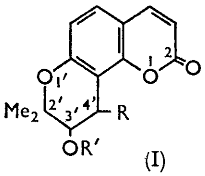
[2] Smith, Hosansky, Bywater, and Tamelen, *J. Amer. Chem. Soc.*, 1957, **79**, 3534.

[3] Wessely and Plaichinger, *Ber.*, 1942, **75**, 971.

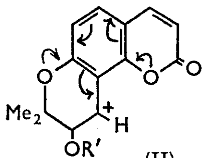
When khellactone diacetate (Ii) was similarly treated with benzene and anisole, it gave rise to the compounds (Ij and k, respectively).

The Friedel–Crafts reactions with visnadin and dihydrosamidin appear to proceed by intermediate formation of a 4′-carbonium ion (II),[1] which attacks the substrate with resultant substitution. This is supported by the following fact: khellactone diacetate is a mixture of *cis*- and *trans*-isomers, but by reaction with aluminium chloride in benzene, it gives compound (Ij), identical in optical rotation and melting point with that obtained from visnadin (which is a pure *cis*-isomer [1]) by similar reaction to give (Ib), followed by hydrolysis and acetylation. The ease of formation of the 4′-carbonium ion (see II) is attributed to stabilisation by resonance with the benzene nucleus, the ether-oxygen atom, and the oxygen of the pyrone ring.

	R	R′		R	R′
a	OAc	CO·Bu^s	i	OAc	Ac
b	Ph	CO·Bu^s	j	Ph	Ac
c	p-C_6H_4Me	CO·Bu^s	k	p-C_6H_4·OMe	Ac
d	p-C_6H_4·OMe	CO·Bu^s	l	OAc	H
e	Ph	H	m	O·CO·Bu^i	H
f	OAc	CO·Bu^i	n	OAc	CO·CH:CMe_2
g	Ph	CO·Bu^i	o	O·CO·Bu^i	Ac
h	p-C_6H_4·OMe	CO·Bu^i			



(I)

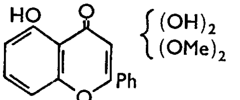


(II)

Refluxing khellactone with acetyl chloride or isovaleryl chloride in benzene gave the 4′-acetate (Il) and 4′-isovalerate (Im), respectively, both containing a free 3′-hydroxy-group and affording, with acetic anhydride in pyridine, the diesters (Ii and o, respectively). That it is the 4′-hydroxyl group which is selectively esterified by the acid chloride is inferred from the reaction of the diester (Io) with benzene in presence of aluminium chloride to give the 4′-acetyl-3′-phenyl compound (Ij).

Minor Constituents of Ammi visnaga *L.*—When the constituents of *Ammi visnaga* soluble in 70% ethanol, and insoluble in chloroform (see Experimental section), were heated with 2N-hydrochloric acid and then chromatographed on alumina, two fractions (A) and (B) were obtained. Fraction (A) afforded four substances, which were identified as marmesin,[4] (+)-khellactone, (−)-khellactone, and visamminol.[5] The ultraviolet spectrum of the last compound in ethanol [$\lambda_{max.}$ 299 mμ (log ε 4·04) and $\lambda_{min.}$ 270 mμ (log ε 3·55)], is characteristic of dihydrofuranochromones.[6]

Fraction (B) afforded ammiol,[7a] 8-hydroxy-5-methoxypsoralen,[8] and a trihydroxydimethoxyflavone (III). The flavone structure assigned to the last compound was inferred from the following evidence. (1) Its ultraviolet spectrum (in ethanol), which showed maxima at 254 (log ε 4·44) and 372 mμ (log ε 4·43) (cf. Fig. 2), which are characteristic of flavones.[9] In the presence of anhydrous aluminium chloride these bands are shifted to longer wavelengths: the band at 254 mμ is shifted to 266 mμ, and that at 372 mμ to 427 mμ. According to Swain,[10] this shift is due to the chelating effect of the aluminium atom with an o-hydroxy-ketone. (2) Its infrared spectrum (in KBr) showed absorption bands at 1656 (carbonyl group of flavones [11]) and 3533 and 3325 (OH) cm.$^{-1}$. The latter band is characteristic of chelated OH group.[11]



(III)

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[4] Starkovsky and Badran, *J. Org. Chem.*, 1958, **23**, 1818.

[5] Bencze, Eisenbeiss, and Schmid, *Helv. Chim. Acta*, 1956, **39**, 923.

[6] Davies and Norris, *J.*, 1950, 3195; Davies, McCrea, Norris, and Ramage, *J.*, 1950, 3206.

[7] Mustafa, Starkovsky, and Salama, *J. Org. Chem.*, 1961, **26**, (*a*) 886, (*b*) 896.

[8] (*a*) Noguchi and Kawanami, *Ber.*, 1938, **71**, 344, 1428; (*b*) Kincl, Romo, Rosenkranz, and Sondheimer, *J.*, 1956, 4163.

[9] Geissman, "Modern Methods of Plant Analysis," Vol. III, Peach and Tracey, Berlin, 1955, p. 485.

[10] Swain, *Chem. and Ind.*, 1954, 1480.

[11] Shaw and Simpson, *J.*, 1955, 655; Hergert and Kurth, *J. Amer. Chem. Soc.*, 1953, **75**, 1622.

(3) A positive boric–oxalic acid reaction, which is given only by 5-hydroxyflavones.[12] This excludes also any isoflavone or flavanone structure.[12] Further support for the presence of a hydroxyl group in position 5 is provided by positive reactions with antimony trichloride [13] and uranyl acetate.[14]

EXPERIMENTAL

Infrared and ultraviolet spectra were run on a Perkin-Elmer infracord 137 and a Spectracord 4000A spectrophotometer, respectively. Light petroleum used in this investigation had b. p. 60—80°, unless otherwise specified.

Isolation of Visnadin (Ia) *and Dihydrosamidin* (If) *from the Umbels of* Ammi visnaga.—The syrup (300 ml.), remaining after concentration of the alcoholic extract (7 l.; 85%) of the powdered umbels (1000 g.), was extracted with chloroform (2 × 200 ml.). Removal of chloroform left a residue which was re-extracted 10 times (200 ml. each) at 40—50° with light petroleum (b. p. 70—90°), then concentrated to 50 ml. and left at 0° for 3 days.

The precipitated material (10 g.) was extracted with 50% aqueous sodium benzoate (20 ml.), and the insoluble part (6 g.) was twice crystallised from 7 : 1 light petroleum–propylene glycol monolaurate (2·4 g.) and repeatedly from light petroleum, to give visnadin in needles, m. p. 85—88°, $[\alpha]_D^{20}$ +9·2° (*c* 1·0 in EtOH), $[\alpha]_D^{30}$ +42·5° (*c* 2·0 in dioxan) {lit.,[2] m. p. 84—86°, $[\alpha]_D$ +9° (*c* 2·0 in EtOH) +38° (*c* 1·0 in dioxan)} (Found: C, 64·9; H, 6·55. Calc. for $C_{21}H_{24}O_7$: C, 64·9; H, 6·2%), $\nu_{max.}$ 1754—1740 cm.$^{-1}$ (C=O of esters and α-pyrones).

The mother-liquor from the first crop of crude visnadin was cooled to −10°, and the precipitated crude dihydrosamidin (1·2 g.) was repeatedly crystallised from ether–light petroleum, affording prisms, m. p. 117—119° (1·0 g.), $[\alpha]_D^{20}$ +63·5° (*c* 1·0 in dioxan), $[\alpha]_D^{30}$ +17° (*c* 1·2 in EtOH) (Found: C, 65·05; H, 6·3. Calc. for $C_{21}H_{24}O_7$: C, 64·9; H, 6·2%) {lit.,[2] $[\alpha]_D$ +63° (*c* 1·0 in dioxan)}, $\nu_{max.}$ 1754—1740 cm.$^{-1}$.

The sodium benzoate solution contained khellin (0·6 g.) and visnagin (0·6 g.).

These yields are low compared with the reported furanochromones content of the inflorescence of *Ammi visnaga* grown in central Germany, namely, 2·34%.[15]

Dimerisation of Visnadin and Dihydrosamidin.—A solution of the monomer (1 g.) in benzene (20 ml.) was exposed to direct sunlight for a month (October). The product was digested with boiling light petroleum, then crystallised from benzene–light petroleum, to give the dimer of visnadin (0·185 g.), needles, m. p. 258—260°, $[\alpha]_D^{28}$ +85° (Found: C, 65·0; H, 6·25%), and of dihydrosamidin (0·066 g.), m. p. 222—224° (Found: C, 64·8; H, 6·3%). Both had $\nu_{max.}$ 1754—1740 cm.$^{-1}$.

Reactions with Benzene, Toluene, and Anisole in presence of Aluminium Chloride.—(i) *With benzene and anisole.* A solution of visnadin (Ia), dihydrosamidin (If), and khellactone diacetate (Ii) in benzene was treated at room temperature with anhydrous aluminium chloride, stirred for 40 min., and worked up as usual. The crude products were crystallised from suitable solvents, to give the *α-methylbutyrate* (Ib), *isovalerate* (Ig), and *acetate* (Ij), respectively, of *3′,4′-dihydro-3′-hydroxy-4′-phenylseselin.* Crude products obtained similarly by reaction with anisole were extracted with benzene, precipitated with light petroleum, and crystallised from suitable solvents, to give the *α-methylbutyrate* (Id), *isovalerate* (Ih), and *acetate* (Ik), respectively, of *3′,4′-dihydro-3′-hydroxy-4′-*p*-methoxyphenylseselin.*

(ii) A similar reaction of visnadin with toluene gave *3′,4′-dihydro-3′-α-methylbutyryloxy-4′-*p*-tolylseselin* (Ic). Details are recorded in the Table.

Hydrolysis of the α-Methylbutyrate (Ib).—This ester (2·0 g.) was refluxed with N-ethanolic sodium hydroxide (40 ml.) for 40 min. The acidified solution was extracted with chloroform and worked up as usual, to give *3′,4′-dihydro-3′-hydroxy-4′-phenylseselin* (0·5 g.) (Ie) in needles (from ether–light petroleum), m. p. 144—145°, $[\alpha]_D^{30}$ −186° (*c* 1·5 in $CHCl_3$) (Found: C, 74·8; H, 5·8. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%).

4′-Acetoxy-3′,4′-dihydro-3′-hydroxyseselin (Il).—A suspension of khellactone (a mixture of *cis*- and *trans*-isomers prepared by acid hydrolysis of visnadin [7b]) (1·0 g.) in dry benzene (10 ml.) was refluxed with acetyl chloride (0·36 g.) for 1 hr. The product which separated on dilution with

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[12] Taubock, *Naturwiss.*, 1942, **30**, 439; Neelakantam, Row, and Venkateswarlu, *Proc. Indian Acad. Sci.*, 1943, **18**, *A*, 364.

[13] Neu and Hagedorn, *Naturwiss.*, 1953, **40**, 411.

[14] Mustafa, Starkovsky, and Zaki, *J. Org. Chem.*, 1960, **25**, 794.

[15] Geissner, *Pharmazie*, 1959, **14**, 629.

No.	Reactants	$AlCl_3$ (g.)	Product	Yield (g.)	Solvent for cryst.	M. p.	$[\alpha]_D$ (temp.) in EtOH
1	Ia (5 g.), C_6H_6 (15 ml.)	5	Ib	4·5 *	70% EtOH	164—165°	−206° (16°)
2	If (5 g.), C_6H_6 (15 ml.)	5	Ig †	4·3	,,	169—171	−187 (30)
3	Ii (0·5 g.), C_6H_6 (5 ml.)	1	Ij ‡	0·42	EtOH §	225—227	−254 (28)
4	Ia (5 g.), PhMe (5 ml.)	5	Ic	4·5	Aq. EtOH	132—133	—
5	Ia (0·2 g.), PhOMe (2 ml.)	0·25	Id	0·17	80% EtOH	172—173·5	—
6	If (0·2 g.), PhOMe (2 ml.)	0·25	Ih	0·17	Aq. EtOH	165—167	—
7	Ii (0·2 g.), PhOMe (2 ml.)	0·25	Ik	0·17	,,	216—217	—

	Found (%)				Required (%)		
No.	C	H	OMe	Formula	C	H	OMe
1	74·0	6·4	—	$C_{25}H_{26}O_5$	73·9	6·45	—
2	74·1	6·5	—	,,	,,	,,	—
3	72·9	5·6	—	$C_{22}H_{20}O_5$	72·5	5·5	—
4	74·7	6·8	—	$C_{26}H_{28}O_5$	74·3	6·7	—
5	71·0	6·4	7·1	$C_{26}H_{28}O_6$	71·5	6·5	7·1
6	70·9	6·4	7·3	,,	,,	,,	,,
7	69·7	5·6	7·6	$C_{23}H_{22}O_6$	70·0	5·6	7·9

* Crude. † The same product (m. p., $\nu_{max.}$) was obtained (0·45 g.) from compound (Ie) (0·5 g.) and isovaleryl chloride (5 ml.) with pyridine (2 drops) at the b. p. (0·5 hr.). ‡ The same product was obtained (i) from 3′,4′-dihydro-3′-hydroxy-4′-phenylseselin (Ie) (0·3 g.) and sodium acetate (0·8 g.) in boiling acetic anhydride (4 ml.) (1 hr.; yield, 0·3 g.), and (ii) from compound (Io) and aluminium chloride in benzene. § Then benzene–light petroleum (b. p. 60—80°).

light petroleum crystallised from acetone–water to give the *4′-acetate* (Il) (0·4 g.) m. p. 149—150°, $[\alpha]_D^{23}$ −49·5° (Found: C, 63·15; H, 5·2. $C_{16}H_{16}O_6$ requires C, 63·15; H, 5·3%).

This product (0·2 g.) was refluxed with acetic anhydride (2 ml.) and a few drops of pyridine for 1 hr., giving khellactone diacetate, m. p. 161—163° (from 50% ethanol), $[\alpha]_D^{19}$ −27° (*c* 1·0 in EtOH), identical with that obtained by direct acetylation of the khellactone mixture.[2]

3′,4′-Dihydro-3′-hydroxy- (Im) *and 3′-Acetoxy-3′,4′-dihydro-4′-isovaleroxyseselin* (Io).—Khellactone (1·0 g.) was treated with isovaleryl chloride (0·69 g.) instead of acetyl chloride as in the previous experiment. The product (Im) (0·64 g.) had m. p. 145—147° (from light petroleum) $[\alpha]_D^{25}$ −94 (*c* 0·6 in $CHCl_3$) (Found: C, 66·05; H, 6·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

When the isovalerate (Im) (0·05 g.) was treated with acetic anhydride (2 ml.) and a drop of pyridine as in the previous experiment, it gave the *diester* (Io) in plates, m. p. 194—197° (from benzene–light petroleum), $[\alpha]_D^{22}$ −31° (*c* 2·4 in dioxan) (Found: C, 64·8; H, 6·3. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%).

Isolation of Minor Constituents of Ammi visnaga L.—*Ammi visnaga* seeds (5 kg.) were percolated with 70% ethanol, the extract distilled, and the aqueous residue extracted with chloroform (2 × 0·5 l.). The aqueous layer was then refluxed with 2N-hydrochloric acid (2 l.) for 3 hr. It was then extracted with hot benzene (15 × 1 l.), and the combined extracts were concentrated to 100 ml. and chromatographed on alumina (Brockmann; 250 g.). Elution was with benzene (6 l.). The first 2 l. afforded material *A*, the remainder material *B*.

Material *A* was rechromatographed on alumina (200 g.) and eluted with 4 : 1 benzene–light petroleum (b. p. 50—70°) (3 l.), then with the same mixture to which benzene was added continuously, with benzene, and with chloroform–benzene containing increasing proportions of the former. The eluate was collected in 48 fractions (250 ml. each). These were examined by chromatography on Whatman No. 1 paper with water as the solvent (ascending method). Fractions containing the same constituents were collected and concentrated. Three different products crystallised on cooling, and were identified as follows. (i) Marmesin (*ca.* 0·41 g.), m. p. and mixed m. p. 188—189° (from benzene),[16] $[\alpha]_D^{30}$ +24·8° (*c* 1·2 in $CHCl_3$), R_F (28°) 0·64 {lit.,[4] m. p. 189—190°, $[\alpha]_D$ +25° (in $CHCl_3$), R_F 0·65} (Found: C, 68·3; H, 5·6. Calc. for $C_{14}H_{14}O_4$: C, 68·3; H, 5·7%) [monoacetate, m. p. 129—130° (lit.,[17] 130°)] (Found: C, 66·6; H, 5·3. Calc. for $C_{16}H_{16}O_5$: C, 66·7; H, 5·6%); on dehydration with boiling 50% sulphuric acid (3 hr.) it gave deoxyoreoselone, m. p. 139—140° (from dilute ethanol) (lit.,[17] 138—140°)

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[16] Abu-Mustafa, Badran, Fayez, and Starkovsky, *Nature*, 1958, **182**, 54.
[17] Chatterjee and Mitra, *J. Amer. Chem. Soc.*, 1949, **71**, 606.

(Found: C, 73·3; H, 5·2. Calc. for $C_{14}H_{12}O_3$: C, 73·7; H, 5·3%). (ii) (+)-3′,4′-Dihydro-3′,4′-dihydroxyseselin [(+)-khellactone] (*ca.* 0·08 g.), m. p. and mixed m. p.[1] 174—175° (from water), $[\alpha]_D^{25}$ +81° (*c* 1·0 in $CHCl_3$), R_F 0·69 (Found: C, 64·0; H, 5·45. Calc. for $C_{14}H_{14}O_5$: C, 64·1; H, 5·4%). (iii) (−)-3′,4′-Dihydro-3′,4′-dihydroxyseselin [(−)-khellactone] (*ca.* 0·65 g.) had m. p. and mixed m. p.[1] 187—188° (from water), $[\alpha]_D^{28}$ −17·5° (*c* 1·0 in $CHCl_3$), R_F 0·74 (Found: C, 63·8; H, 5·5. Calc. for $C_{14}H_{14}O_5$: C, 64·1; H, 5·4%). {lit.,[1] m. p. 186°, $[\alpha]_D$ −18° (in $CHCl_3$)}.

The combined mother-liquors were evaporated and the residue was extracted with hot 1 : 9 benzene–light petroleum (b. p. 50—70°). On cooling of the extract, there crystallised visamminol as needles, m. p. 160—161° (from benzene–light petroleum or aqueous ethanol), $[\alpha]_D^{28}$ +89° (*c* 0·8 in $CHCl_3$) (Found: C, 65·2; H, 5·8. Calc. for $C_{15}H_{16}O_5$: C, 65·2; H, 5·8%) {lit.,[5] m. p. 160—160·5°, $[\alpha]_D$ +92·7° ± 3°}.

Crystallisation of material *B* from benzene gave a mixture of yellow crystals, which were separated by each of the following procedures: (*a*) The mixture was extracted successively with hot water and 20%, then 95%, ethanol, from which ammiol, 8-hydroxy-5-methoxyfurano-(4′,5′-6,7)coumarin, and a *trihydroxydimethoxyflavone* (III), respectively, were isolated. (*b*) The mixture crystallised from chloroform to give the flavone, leaving the other two components in solution. The chloroform mother-liquor was evaporated and the residue crystallised from alcohol to give ammiol. The alcoholic mother-liquor precipitated the third component on dilution with water.

Ammiol was obtained in needles, m. p. and mixed m. p.[7a] 210—211° (from water or alcohol), R_F 0·49 (lit.,[7] 0·47) (Found: C, 60·8; H, 4·5; OMe, 21·9. Calc. for $C_{14}H_{12}O_6$: C, 60·9; H, 4·4; OMe, 22·5%).

8-Hydroxy-5-methoxyfurano(4′,5′-6,7)coumarin[8b] formed yellow crystals (from dilute ethanol), m. p. 222—223° (lit.,[8b] 223—224°) (Found: C, 62·0; H, 3·45; OMe, 13·95%; *M*, 225. Calc. for $C_{12}H_8O_5$: C, 62·1; H, 3·5; OMe, 13·35%; *M*, 232). Its acetyl derivative, pale yellow needles, had m. p. 179—181° (lit.,[8b] 181—182°) (from dilute ethanol) (Found: C, 61·2; H, 3·7. Calc. for $C_{14}H_{10}O_6$: C, 61·3; H, 3·7%). Oxidation of this hydroxycoumarin (10 mg.) with a few drops of concentrated nitric acid in acetone (4 ml.) converted it into psoralenquinone (bergaptenquinone), which was precipitated as the mixture, cooled, and had m. p. and mixed m. p. 253—255° (lit.,[8b] 251—253°).

The trihydroxydimethoxyflavone, yellow needles (from ethanol), m. p. 222—223° (Found: C, 61·9; H, 4·4; OMe, 18·4%; *M*, 350. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·3; 2OMe, 18·8%; *M*, 330), gave a brown colour with ferric chloride, a red colour with magnesium and hydrochloric acid in alcohol, and, on evaporation with boric and oxalic acid in acetone and dissolution of the residue in ether, a bright yellow solution with an intense blue fluorescence was obtained. Its chloroform solution gave, with antimony chloride in chloroform, a bright yellow colour with a green fluorescence when exposed to ultraviolet light. Its alcoholic solution gave with an aqueous solution of uranyl acetate a red colour, discharged on addition of concentrated hydrochloric acid.

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