Tetrahedron, 1965, Vol. 21, pp. 3237 to 3245. Pergamon Press Ltd. Printed in Northern Ireland

CHEMICAL INVESTIGATION OF *ANDROGRAPHIS WIGHTIANA*

ISOLATION AND STRUCTURE OF WIGHTIN, A NEW FLAVONE

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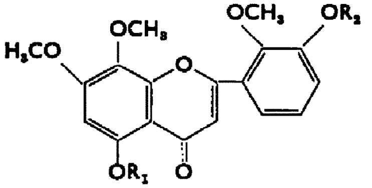
(*Received* 5 *April* 1965)

Abstract—The isolation of two new flavones, wightin and echioidinin, from *Andrographis wightiana* Arn. ex. Nees is reported. By a combination of spectral, degradative and synthetic evidence, wightin is shown to be 5,3′-dihydroxy-7,8,2′-trimethoxyflavone. Wightin appears to be the first example of a naturally occurring flavone with an unique 2′,3′-oxygenation pattern instead of the normal 3′, 4′-pattern.

Andographis wightiana Arn. ex. Nees (Acanthaceae) is a herb, widely distributed in the forests of Western Ghats, Anamalais and Hills of Travancore and Tinnevely.[1] Extraction of the leaves‡ with acetone gave a flavone and a small amount of a colourless crystalline bitter principle. The flavone was named "echioidinin" in view of its isolation in better yields from *Andrographis echioides* Nees and its structure is discussed in a separate communication. The bitter principle, which has been tentatively named "*wightionolide*", is different from andrographolide[2,3] and analysed for $C_{20}H_{32}O_5$, had an UV maximum at 214 mμ and exhibited bands in the IR at 2·94 μ (OH) and 5·72 μ (γ-lactone); owing to paucity of material no further work could be done.

Extraction of the stems and roots with acetone, on the other hand, afforded a yellow crystalline compound designated "*wightin*". Wightin is a new flavone and evidence is presented in this paper to show that it is 5,3′-dihydroxy-7,8,2′-trimethoxyflavone (Ia).



Ia: $R_1 = R_2 = H$
Ib: $R_1 = H$; $R_2 = CH_3$
Ic: $R_1 = R_2 = CH_3$
Id: $R_1 = R_2 = C_2H_5$

Wightin, purified through its acetate, forms golden yellow needles from methanol, m.p. 188°. It analyses for $C_{18}H_{16}O_7$ and has three methoxyl groups (Zeisel). It gives

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‡ The plant material was collected from Poringalkuthu (Kerala State) during December–January.

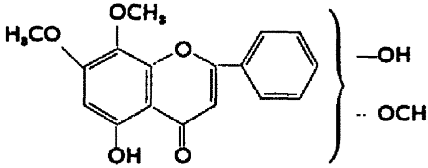
[1] Gamble, *The Flora of the Presidency of Madras* Vol. II, 734 (1956).

[2] D. Chakravarti and R. N. Chakravarti, *J. Chem. Soc.* 1697 (1952).

[3] M. P. Cava, W. R. Chan, L. J. Haynes, L. F. Johnson and B. Weinstein, *Tetrahedron* **18**, 397 (1962) and the Ref. cited therein.

a green colour with ferric chloride and forms a diacetate, dibenzoate and a di-O-methyl ether proving the presence of two phenolic hydroxyl groups. Indications of its flavonoid character were obtained by the usual reduction tests with magnesium–hydrochloric acid[4] (Orange–red) and sodium amalgam[5] (Orange–red). The IR spectrum of wightin (Fig. 1) exhibits bands at 2·8 μ (OH), 3·1–3·2 μ (chelated OH), 6·06 μ (C=O of γ-pyrone) and 6·2 μ (aromatic). The UV spectrum (Fig. 2) shows a sharp maximum at 272 mμ and an inflexion at 330–340 mμ, suggesting that wightin may be a flavone derivative unsubstituted in the 3-position.[6]

Only one of the two hydroxyl groups present in wightin, can be methylated by diazomethane. Mono-O-methylwightin (Ib) so obtained is sparingly soluble in dilute alkali, gives a green ferric reaction and a positive Wilson's boric acid test,[7] indicating the presence of a 5-hydroxyl group.[8] That the hydroxyl group in mono-O-methylwightin (Ib) is at C-5 is supported by the fact that no hydroxyl band in the 3 μ region is apparent in its IR spectrum (due to chelation).[9] The presence of a hydroxyl at 5-position was further confirmed by the bathochromic shifts of both the bands in the UV spectrum in the presence of aluminium chloride[10] (Fig. 2). The UV spectrum is not changed in the presence of sodium acetate–boric acid indicating that the two-hydroxyl groups in wightin are not in *o*-positions.[11] The spectrum is also not affected by the addition of fused sodium acetate suggesting the absence of a free hydroxyl at 7-position.[12] However, the presence of a well defined maxima at 306 mμ in the spectrum of di-O-acetylwightin indicates the presence of a 7-methoxyl group.[6] Another methoxyl is located at the 8-position based on the evidence that mono-O-methylwightin (Ib) gives a negative Gibbs test[13] and wightin (Ia) a negative Gossypetone test.[14] The partial structure (II) assigned to wightin, is supported by the NMR spectrum of di-O-methyl-wightin which exhibits two sharp singlets at 6·45 and 6·83 δ assignable to C_3 and C_6 protons.[15,16]



II

Hydrolysis of di-O-methylwightin (Ic) with 10% alcoholic potassium hydroxide gives in good yields a yellow crystalline phenolic compound, later shown to be III. This compound which has been named *wightinone*, analyses for $C_{20}H_{22}O_8$ and contains

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[4] J. Shinoda, *J. Pharm. Soc. Japan* **48**, 214 (1928).

[5] Y. Asahina and M. Inubuse, *Ber. Dtsch. Chem. bes.* **61**, 1646 (1928); *Ibid.* **64**, 1256 (1931).

[6] L. Jurd, *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman), p. 107. Pergamon Press Oxford (1962).

[7] C. W. Wilson, *J. Amer. Chem. Soc.* **61**, 2303 (1939).

[8] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3136 (1951).

[9] F. Sondheimer and A. Meisels, *Tetrahedron* **9**, 139 (1960) and the Refs. cited therein.

[10] T. Swain, *Chem. & Ind.* 1480 (1954).

[11] L. Jurd, *Arch. Biochem. Biophys.* **63**, 376 (1956).

[12] L. Jurd and R. M. Horowitz, *J. Org. Chem.* **22**, 1618 (1957).

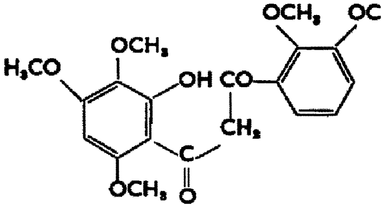
[13] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).

[14] A. G. Perkin, *J. Chem. Soc.* **103**, 657 (1913).

[15] J. Massicot and J. P. Morthé, *Bull. Soc. Chim. Fr.* 1962 (1962).

[16] T. J. Batterham and R. J. Highet, *Austr. J. Chem.* **17**, 428 (1964).

five methoxyl groups (Zeisel and NMR). A strong band at 6·22 μ in its IR spectrum suggests a β-diketone structure.[17] Indeed, the corresponding *o*-hydroxy-β-diketone regenerates di-O-methylwightin (Ic) on heating with sodium acetate and glacial acetic acid. It is surprisingly very resistant to further alkaline hydrolysis with alcoholic potassium hydroxide, but may be further degraded by oxidation with 30% alkaline hydrogen peroxide[18] which gives a mixture of two acids (TLC). These were separated by crystallization from absolute ether. One of these acids, m.p. 120–121° is identical with 2,3-dimethoxybenzoic acid,[19] thereby proving that di-O-methylwightin must be formulated as 5,7,8,2′,3′-pentamethoxyflavone (Ic) and consequently wightinone is 2-hydroxy-3,4,6,2′,3′-pentamethoxydibenzoylmethane (III).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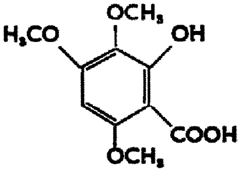
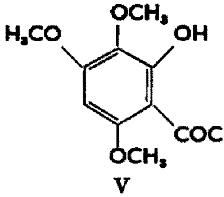

IV

The second acid obtained from the oxidation of wightinone (m.p. 148°) is a salicylic acid derivative. It analyses for $C_{10}H_{12}O_6$, gives a bluish-purple colour with ferric chloride and exhibits bands in the IR spectrum at 3·2 μ (chelated OH) and 6·06 μ (COOH). In view of structure Ic for di-O-methylwightin it must be formulated as 2-hydroxy-3,4,6-trimethoxybenzoic acid (IV). The above two acids are obtained from the alkaline hydrogen peroxide oxidation of di-O-methylwightin (Ic) itself.

Structures Ic for di-O-methylwightin and III for wightinone were confirmed by synthesis. 2-hydroxy-3,4,6-trimethoxyacetophenone[20] (V) was condensed with *o*-veratroyl chloride in presence of pyridine to give the ester (VI) which undergoes isomerization in the presence of pyridine-potassium hydroxide[21] to give 2-hydroxy-3,4,6,2′,3′-penthamethoxy-dibenzoylmethane (III) identical with wightinone. Cyclization of this β-diketone with acetic acid–sodium acetate gives 5,7,8,2′,3′-pentamethoxyflavone* identical with di-O-methyl-wightin (Ic). The constitution of di-O-methylwightin as Ic is thus rigidly established.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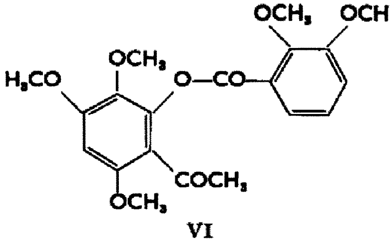
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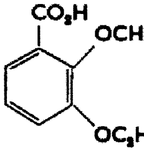
VII

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* A. Arcoleo, A. Bellinio, C. Casinovi and P. Venturella, *Ann. Chim. Rome* 47, 75 (1957) have described another independent synthesis.

[17] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 142. J. Wiley, New York (1958).

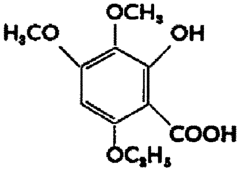
[18] D. Molho, *Bull. Soc. Chim. Fr.* 39 (1956).

[19] G. A. Edwards, W. H. Perkin and F. W. Stoyle, *J. Chem. Soc.* 127, 195 (1925).

[20] W. Baker, *J. Chem. Soc.* 662 (1941).

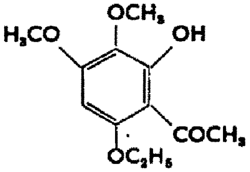
[21] W. Baker, *J. Chem. Soc.* 1381 (1933); K. Venkataraman and H. S. Mahal, *Ibid.* 1767 (1934).

The disposition of the second hydroxyl group in wightin was determined by oxidation of di-O-ethylwightin (Id) with 30% alkaline hydrogen peroxide which gives a mixture of two acids (TLC). These were separated by crystallization from absolute ether. One of the acids, m.p. 60° is identical with 3-ethoxy-2-methoxybenzoic acid (VII) synthesized from 3-hydroxy-2-methoxybenzoic acid.[22] This evidence together with the knowledge already gained establishes the structure of wightin as 5,3',-dihydroxy-7,8,2'-trimethoxyflavone (Ia) and that of di-O-ethylwightin as 5,3'-diethoxy-7,8,2'-trimethoxyflavone (Id). The second acid obtained from the oxidation of Id is a salicylic acid derivative, m.p. 146° (IR bands at 3·12 and 6·0 μ) and was insufficient for further characterization. In view of structure Id for di-O-ethylwightin it must be formulated as VIII.

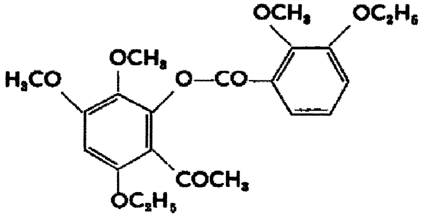


VIII

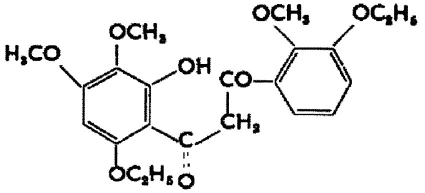
Finally, the synthesis of di-O-ethylwightin itself unequivocally established the constitution of wightin as Ia. Condensation of 2-hydroxy-6-ethoxy-3,4-dimethoxyacetophenone[23] (IX) with 3-ethoxy-2-methoxybenzoyl chloride in presence of pyridine gave the ester (X) which was isomerized to the β-diketone (XI) in the usual manner by treatment with pyridine and potassium hydroxide. Cyclization of this β-diketone by means of sodium acetate in acetic acid gave 5,3'-diethoxy-7,8,2'-trimethoxyflavone identical with di-O-ethylwightin.



IX



X



XI

The isolation of wightin from *Andrographis wightiana* is of biogenetic interest since it appears to be the first example of a naturally occurring flavone with a unique 2',3'-oxygenation pattern in the B-ring, except perhaps nepusidin (XII) an isoflavanone recently isolated from the roots of the leguminous plant *Neorautanenia pseudopachyrrhiza*

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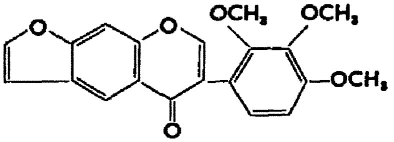
[22] F. E. King, J. H. Gilks and M. W. Partridge, *J. Chem. Soc.* 4206 (1955).

[23] S. Hattori, *Acta Phyto Chim.* **5**, 219 (1931).

Harms which incorporates the unique 2′,3′,4′-oxygenation pattern instead of the normal 3′,4′,5′-pattern.



XII

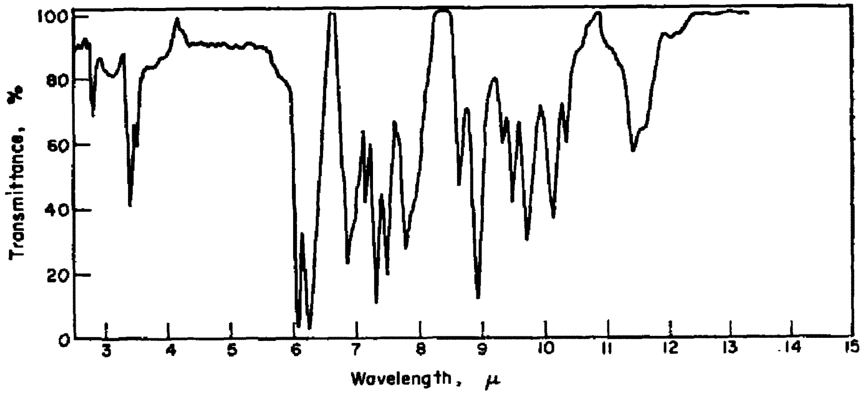


FIG. 1. IR spectrum of wightin in chloroform.

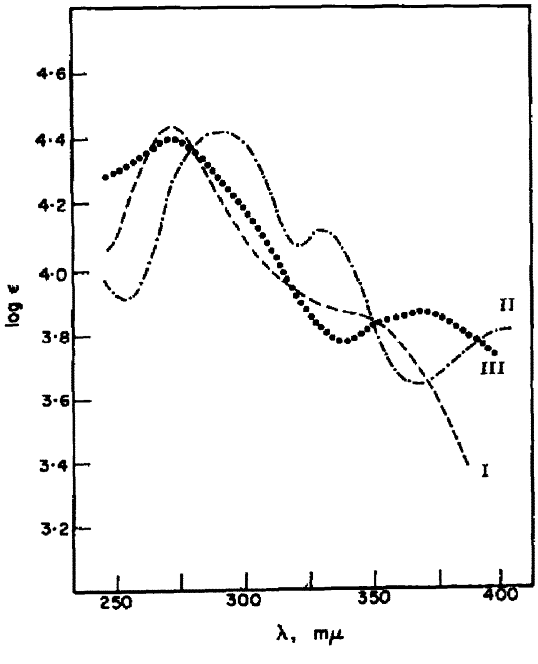


FIG. 2. UV spectrum of: I. Wightin in absolute ethanol. II. Wightin in ethanol plus aluminium chloride. III. Wightin in ethanol plus sodium ethoxide.

EXPERIMENTAL

1. *Extraction of* Andrographis wightiana

(a) *Stems and roots* (*isolation of wightin*). The stems and roots were separated from the leaves, air dried, powdered (1 kg) and extracted with acetone (4 l.) by cold percolation. The greenish residue obtained by distilling off the acetone was filtered, washed repeatedly with cold chloroform and dried (1·2 g). Wightin thus obtained was a pale yellow amorphous substance m.p. 160–170°. Purification of this crude material was effected by conversion to the acetyl derivative followed by hydrolysis (*vide infra*).

(b) *Leaves* (*isolation of echioidinin and the bitter principle*). Dried, powdered leaves (1·5 kg) were extracted thrice with acetone (3 l. each time) in the cold as above. Concentration of the extract resulted in the separation of a greenish solid residue which was filtered, washed thoroughly with cold chloroform and dried (0·5 g). This material, m.p. 243–251° was echioidinin.

The total mother liquors obtained above were concentrated to a small volume, decolourized with animal charcoal and filtered. The clear solution on leaving in the ice-chest for a few days deposited colourless crystals of the bitter principle (wightionolide), which after 3 crystallizations from ethyl acetate formed colourless needles (90 mg), m.p. 176–177°. $\lambda_{\max}^{\text{EtOH}}$ 214 mμ (log ε 3·96). (Found: C, 68·1, 68·2; H, 9·1, 9·1. $C_{20}H_{32}O_5$ requires: C, 68·2; H, 9·1%.)

2. *Purification of crude wightin through its acetyl derivative*

Crude wightin (1 g), dry pyridine (5 ml) and acetic anhydride (5 ml) were heated on a steam-bath for 2 hr, cooled and poured into ice-water. The resulting precipitate was collected, washed with water, dried and crystallized repeatedly from ethyl acetate–pet. ether (b.p. 40–60°), giving *di-O-acetylwightin* as colourless needles (0·7 g), m.p. 159–160°. It gave an orange-red colour with Mg–HCl aq, an orange colour with NaHg followed by acidification and no colour with $FeCl_3$. $\lambda_{\max}^{\text{EtOH}}$ 260, 306 mμ (log ε 4·43, 4·30). (Found: C, 61·3; H, 4·8. $C_{22}H_{20}O_9$ requires: C, 61·7; H, 4·7%.)

Pure wightin. Di-O-acetylwightin (0·8 g) was refluxed with alcoholic HCl (40 ml; 85% EtOH saturated with HCl) for 2 hr. Part of the alcohol was removed under red. press. and the yellow crystalline *wightin* which separated on cooling was collected, dried and recrystallized from MeOH; as slender yellow needles (0·42 g), m.p. 188–189° and gave a single spot in thin layer (silica) chromatography (benzene:methanol:n-butyl acetate—20:4:1). Wightin gave an orange colour with both Mg–HCl aq and NaHg followed by acidification, and no green colour with H_2SO_4 and alcoholic gallic acid. A green colour was obtained with alcoholic $FeCl_3$ and an intense yellow colour developed in the Wilson's boric acid test. With Gibb's reagent a bluish-green colour developed instantaneously and the indophenol chromophore had maximum absorption at 640 mμ. Paper chromatography (Whatman No. 1; upper phase of n-butanol:water—1:1), R_f 0·95. $\lambda_{\max}^{\text{EtOH}}$ 275, 330–340 (sh) mμ (log ε 4·39, 3·86). $\lambda_{\max}^{\text{EtOH-AlCl}_3}$ 290–95, 330, 400 mμ (log ε 4·40, 4·10, 3·81). $\lambda_{\max}^{\text{EtOH-NaOEt}}$ 270, 370 mμ (log ε 4·41, 3·87). (Found: C, 62·5; H, 4·5; OCH_3, 12·6. $C_{18}H_{16}O_7$ requires: C, 62·8; H, 4·7; $3OCH_3$, 13·1%.)

The benzoyl derivative prepared by the pyridine–benzoyl chloride method at 80°, crystallized from $CHCl_3$–MeOH, m.p. 221–223°. (Found: C, 69·6; H, 4·4. $C_{32}H_{24}O_9$ requires: C, 69·6; H, 4·4%.)

3. *Mono-O-methylwightin*

To a solution of wightin (0·1 g) in ether (20 ml) and MeOH (10 ml), was added an ethereal solution of diazomethane (from 2 g of nitrosomethylurea). After being kept at room temp for 12 hr the solvent was evaporated and the yellow residue crystallized from MeOH giving *mono-O-methylwightin* as yellow fibrous needles (60 mg), m.p. 156°. It was sparingly soluble in NaOH aq (1%) and its alcoholic solution gave a green colour with $FeCl_3$. It gave a positive Wilson's boric acid test and no colour with Gibb's reagent (there was no maximum in the region 500–700 mμ). $\lambda_{\max}^{\text{EtOH}}$ 270, 330–340 (sh) mμ (log ε 4·48, 3·85). (Found: C, 63·7; H, 4·9. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·0%.)

4. *Di-O-methylwightin*

A mixture of wightin (0·6 g), dimethyl sulphate (3·5 ml) and ignited K_2CO_3 (2 g) in absolute acetone (30 ml) was refluxed on a water-bath for 40 hr. Acetone was distilled off, the residue treated with water and extracted with $CHCl_3$. After washing with water, the $CHCl_3$ extract was dried

(Na_2SO_4) and the solvent distilled off. The residue was dissolved in benzene and chromatographed over alumina in the same solvent. Elution with $CHCl_3$ gave *di-O-methylwightin* (0·4 g), which after recrystallization from ethyl acetate formed pale brown cubes, m.p. 190–191°. It gave an orange-red colour with Mg-HCl aq, an orange colour with NaHg followed by acidification and no colour with $FeCl_3$. λ_{max}^{EtOH} 266, 325–330 (sh) mμ (log ε 4·54, 4·07). (Found: C, 64·5; H, 5·5; OCH_3, 20·1. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4; 5OCH_3, 20·2%.)

5. *Alkaline hydrolysis of di-O-methylwightin (isolation of wightinone)*

Di-O-methylwightin (0·3 g) was refluxed with alcoholic KOH aq (8%; 30 ml) for 9 hr in an atmosphere of N_2. Alcohol was removed under red. press. and the residue treated with water (25 ml). The well-cooled solution was acidified and taken up in ether (2 × 160 ml). The ether solution was washed with sat. $NaHCO_3$ (2 × 10 ml) and finally washed with water. Evaporation of ether after drying (Na_2SO_4) gave a yellow crystalline solid (wightinone), which after recrystallization from MeOH formed yellow fibrous needles (0·16 g), m.p. 134–136°. It gave a brown colour with $FeCl_3$. λ_{max}^{EtOH} 295, 370 mμ (log ε 4·52, 4·61). (Found: C, 61·7; H, 5·7; OCH_3, 19·1. $C_{20}H_{22}O_8$ requires: C, 61·5; H, 5·6; 5OCH_3 19·2%.)

The bicarbonate washings obtained above were acidified and extracted exhaustively with ether. The dried (Na_2SO_4) extract on removal of ether left no residue.

6. *Di-O-methylwightin from wightinone*

A mixture of wightinone (75 mg), glacial acetic acid (2 ml) and fused sodium acetate (200 mg) was refluxed gently (oil-bath, 150–155°) for 1 hr, cooled and carefully diluted with water. The resulting colourless crystalline precipitate was collected, washed, dried and recrystallized from ethyl acetate, giving *di-O-methylwightin* as tiny prisms, m.p. and mixed m.p. 190–191°.

7. *Attempted alkaline fission of wightinone*

Wightinone (100 mg) was refluxed with alcoholic KOH (30%; 6 ml) for 6 hr, in an atm. of N_2. The solvent was removed *in vacuo* and the residue treated with water (12 ml), acidified and taken up in ether. The ether solution was then examined for acid and phenolic components by extracting with $NaHCO_3$ aq. Acidification of the bicarbonate solution followed by thorough extraction with ether did not give any acid. Evaporation of the dried (Na_2SO_4) ether solution left after extraction with bicarbonate, gave yellow crystals of *wightinone*, which after recrystallization from MeOH (60 ml) had m.p. and mixed m.p. 134–135°.

8. *Alkaline hydrogen peroxide oxidation of wightinone*

Wightinone (450 mg) in MeOH (7 ml) was refluxed with a solution of NaOH (2 g) in water (12 ml). At the end of 4 hr, the reaction mixture was cooled and treated with water (10 ml). After extracting with ether, the aqueous layer was cooled to 15° and treated dropwise with H_2O_2 (30%; 14 ml). After standing overnight in the ice-chest, the colourless solution was evaporated to dryness *in vacuo*. The pale brown residue was dissolved in water (10 ml) and extracted with ether. The clear aqueous solution was well cooled, acidified and extracted exhaustively with ether (5 × 20 ml). The ether solution was washed with $NaHCO_3$ aq (10%, 3 × 4 ml), the bicarbonate solution acidified during strong cooling and reextracted with ether (5 × 20 ml). The combined ether extract was washed with ice-water (5 ml), dried (Na_2SO_4) and the solvent distilled off. The pale brown gummy residue (thin layer chromatography, silica; benzene:diethylamine:n-butyl acetate—25:1:1,2 spots) was crystallized from absolute ether to give two sharp melting acids. The acid from the more soluble fraction crystallized as colourless prisms, m.p. 120–121° and was identified as *o*-veratric acid by direct comparison with an authentic specimen (m.p. mixed m.p. and IR spectra). (Found: C, 59·3; H, 5·4. $C_9H_{10}O_4$ requires: C, 59·3; H, 5·5%.)

The other acid, obtained from the less soluble fraction crystallized as colourless needles m.p. 148–149°. It gave a blue colour with $FeCl_3$. (Found: C, 52·5; H, 5·4. $C_{10}H_{12}O_6$ requires: C, 52·6; H, 5·3%.)

9. *Alkaline hydrogen peroxide oxidation of di-O-methylwightin*

Di-O-methylwightin (225 mg) was oxidized with alkaline H_2O_2 as above. After working up, followed by crystallization, *o*-veratric acid, m.p. and mixed m.p. 120–121° and the second acid, m.p. 148–149° were obtained.

10. *Ethylation of wightin* (*di-O-ethylwightin*)

Wightin (222 mg) was refluxed with ethyl bromide (2 ml) and anhydrous K_2CO_3 (3 g) in dry acetone (25 ml) for 16 hr. The solvent was then distilled off and water added to the residue. The precipitate was collected, washed with dilute alkali (2%) and water, and then dried. Crystallization from alcohol afforded colourless needles of *di-O-ethylwightin* (160 mg) m.p. 136–137°. λ_{max}^{EtOH} 267, 320–330 (sh) mμ (log ε 4·48, 4·00). (Found: C, 66·3; H, 6·1. $C_{22}H_{24}O_7$ requires: C, 66·0; H, 6·0%.)

11. *Alkaline hydrogen peroxide oxidation of di-O-ethylwightin*

A mixture of di-O-ethylwightin (200 mg), alcohol (4 ml), NaOH (1 g) and water (5 ml) was refluxed gently for 6 hr. After being cooled, water (10 ml) was added and the mixture treated dropwise with H_2O_2 (30%; 5 ml). The reaction mixture was left overnight at room temp and after being worked up as in the case of wightinone, a gummy mixture of acids was obtained. The gummy residue was crystallized from absolute ether giving two sharp melting acids. One of these acids obtained from the more soluble part, m.p. 58–60° was identical in all respects (m.p., mixed m.p. and IR spectra) with an authentic specimen of 3-ethoxy-2-methoxybenzoic acid. (Found: C, 61·6; H, 6·2. $C_{10}H_{12}O_4$ requires: C, 61·2; H, 6·1%.)

The other acid, m.p. 145–146°, was sparingly soluble in ether but insufficient for analysis.

12. *Synthesis of* 3-*ethoxy*-2-*methoxybenzoic acid*

(a) *Ethyl*-3-*ethoxy*-2-*ethoxybenzoate*. 3-Hydroxy-2-methoxy-benzoic acid (3 g), dry acetone (60 ml), ethyl sulphate (6 ml) and ignited K_2CO_3 (6 g) were refluxed for 12 hr. After distilling off the acetone, the residue was treated with water and extracted with ether. The ether extract was washed first with cold NaOH aq (4%), then with water and dried (Na_2SO_4). The colourless residual sweet smelling liquid left after distilling off the ether, was distilled *in vacuo* (2·5 g), b.p. 106°/0·2 mm.

(b) 3-*Ethoxy*-2-*methoxybenzoic acid*. Ethyl 3-ethoxy-2-methoxybenzoate (2·5 g) was refluxed with alcoholic NaOH (10%; 75 ml) for 6 hr. The solvent was removed *in vacuo* and water (75 ml) added to the residue. The oily product obtained by acidification was extracted with ether (2 × 200 ml) and the ether solution washed with sat. $NaHCO_3$ aq (2 × 40 ml). Acidification of the bicarbonate solution during strong cooling gave the acid as an oil which solidified. It was isolated by extraction with ether and purified by crystallization from $CHCl_3$–pet. ether (b.p. 40–60°) giving 3-*ethoxy*-2-*methoxybenzoic acid* as colourless plates (1·8 g), m.p. 63°. Davies[24] who prepared this acid from ethoxysalicylaldehyde, reported m.p. 59°; Manske *et al.*[25] who also prepared it starting from ethoxysalicylaldehyde, have reported m.p. 64°. It was identical in all respects (m.p., mixed m.p. and IR spectra) with the degradation acid from di-O-ethylwightin.

13. *Synthesis of di-O-methylwightin*

(a) 2-O-*Veratroyloxy*-3,4,6-*trimethoxyacetophenone*. O-Veratroyl chloride was prepared by refluxing *o*-veratric acid (3 g) and $SOCl_2$ (12 ml) on a steam bath for 1 hr. After removing excess $SOCl_2$ *in vacuo*, the crude acid chloride was purified by distillation *in vacuo*, b.p. 146°/8 mm. The distillate solidified in the receiver (3 g). It was dissolved in dry pyridine (15 ml), well dried 2-hydroxy-3,4,6-trimethoxyacetophenone (2·2 g) added, and the mixture heated on a steam-bath for 1 hr. The product was poured into crushed ice containing conc. HCl (15 ml) and kept overnight in an ice-chest. The colourless sticky solid so obtained was extracted with ethyl acetate (2 × 150 ml) and the extract washed successively with dil. HCl aq (50 ml), NaOH aq (5%; 2 × 50 ml), and finally with water. After drying (Na_2SO_4), the solvent was distilled off, and the solid residue crystallized from dilute alcohol giving 2-*o*-*veratroyloxy*-3,4,6-*trimethoxyacetophenone* as stout colourless needles (2·4 g), m.p. 108–110°. (Found: C, 61·9; H, 5·6. $C_{20}H_{22}O_8$ requires: C, 61·5; H, 5·6%.)

(b) 2-*Hydroxy*-3,4,6,2′-3′-*pentamethoxydibenzoylmethane* (*wightinone*). A mixture of the foregoing ester (0·5 g), powdered dry KOH (0·3 g) and absolute pyridine (5 ml), was shaken vigorously at room temp in a microflask shaker. After shaking for 3 hr, it was acidified with ice-cold dilute acetic acid and kept overnight in the ice-chest. The resulting crystalline yellow solid was collected, washed and dried. Recrystallization from alcohol afforded yellow needles of 2-*hydroxy*-3,4,6,2′,3-*pentamethoxydibenzoylmethane* (0·42 g), m.p. 134–136°. It gave a brown colour with $FeCl_3$ and was

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[24] W. Davies, *J. Chem. Soc.* **123**, 1575 (1923).

[25] R. H. F. Manske, A. E. Ledingham and H. L. Holmes, *Canad. J. Res.* **22B**, 116 (1944).

identical in all respects (m.p., mixed m.p., and IR spectra), with *wightinone*. (Found: C, 61·5; H, 5·7; OCH_3, 18·7. $C_{20}H_{22}O_8$ requires: C, 61·5; H, 5·6; $5OCH_3$, 19·2%.)

(c) *5,7,8,2′,3′-Pentamethoxyflavone* (*di-O-methylwightin*). 2-Hydroxy-3,4,6,2′,3′-pentamethoxydibenzoylmethane (0·25 g), fused sodium acetate (0·3 g) and glacial acetic acid (5 ml) were refluxed gently in an oil-bath (150–155°) for 3 hr, cooled, diluted with water (5 ml) and the acid just neutralized with dilute alkali solution (5%). *5,7,8,2′,3′-Pentamethoxyflavone* separated as a colourless crystalline solid which was filtered, washed, dried and recrystallized from ethyl acetate giving colourless tiny prisms (0·18 g), m.p. 190–191° alone or when mixed with di-O-methylwightin. They had identical IR and UV spectra. (Found: C, 64·6; H, 5·6; OCH_3, 19·8. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4; $5OCH_3$, 20·2%.)

14. *Synthesis of di-O-ethylwightin*

(a) 2-(3-*Ethoxy-2-methoxybenzoyloxy*)-3,4-*dimethyl-6-ethoxyacetophenone*. 3-Ethoxy-2-methoxybenzoyl chloride (from 0·9 g acid and 3 ml $SOCl_2$) and 2-hydroxy-6-ethoxy-3,4-dimethoxy-acetophenone (0·65 g) in dry pyridine (4 ml) were heated on a steam-bath for 1 hr. After working up in the usual manner, the ester was finally purified by chromatography in benzene over aluminia. 2-(3-*Ethoxy-2-methoxybenzoyloxy*)-6-*ethoxy*-3,4-*dimethoxyacetophenone* crystallized from dilute alcohol as colourless needles (0·95 g), m.p. 109–110°. (Found: C, 63·0; H, 6·3. $C_{22}H_{26}O_8$ requires: C, 63·2; H, 6·2%.)

(b) 6,3′-*Diethoxy-2-hydroxy*-3,4,2′-*trimethoxydibenzoylmethane*. The foregoing ester (0·25 g) in dry pyridine (3 ml) was shaken with powdered KOH (175 mg) for 3 hr. Water (4 ml) was added and the mixture acidified with dilute acetic acid. A brown oil separated which solidified into a yellow solid on leaving in the ice-chest overnight. This was washed, dried and crystallized from dilute alcohol giving 6,3′-*diethoxy-2-hydroxy*-3,4,2′-*trimethoxydibenzoylmethane* as yellow needles (0·16 g), m.p. 100–101°. It gave a brown colour with alcoholic $FeCl_3$. (Found: C, 63·1; H, 6·4. $C_{22}H_{26}O_8$ requires: C, 63·2; H, 6·2%.)

(c) 5,3′-*Diethoxy*-7,8,2′-*trimethoxyflavone* (*di-O-ethylwightin*). A mixture of the above diketone (0·15 g), fused sodium acetate (0·25 g) and glacial acetic acid (3 ml) was refluxed gently for 2 hr. After being cooled, carefully diluted with water, the precipitated white solid was collected, washed and dried. Three crystallizations from benzene–pet. ether (b.p. 40–60°) afforded pure 5,3′-*diethoxy*-7,8,2′-*trimethoxyflavone* as colourless needles (90 mg), m.p. 136° alone or when mixed with *di-O-ethylwightin*. Their UV and IR spectra were identical. (Found: C, 65·9; H, 6·1. $C_{22}H_{24}O_7$ requires: C, 66·0; H, 6·0%.)

Acknowledgement—We are grateful to Prof. B. G. L. Swamy and Dr. Govindarajulu, for collection and identification of the plant material. We thank the Council of Scientific & Industrial Research for the award of a senior Research Fellowship to P. C. P. and to the Government of India and Messrs Amrutanjan Ltd., Madras for the award of scholarships to P. S. S. during the tenure of this work.