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THE SYNTHESES OF WIGHTIN AND ECHIOIDININ, TWO FLAVONES FROM *ANDROGRAPHIS WIGHTIANA*

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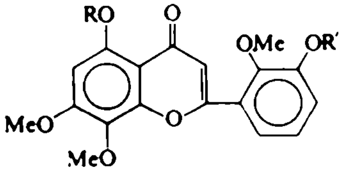
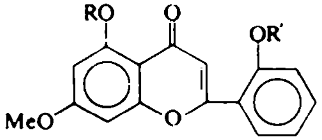
Abstract—The total synthesis of wightin and echioidinin, is reported.

There has been considerable controversy about the natural occurrence of 2′-substituted flavones. Lotoflavin was claimed to be a member of this group,[1] but later shown to be a mixture of quercetin and kaempferol.[2] Zapotin and zapotinin isolated from *Casimiroa edulis* Llave et Lex[3,4] were assigned the structures 2′,5,6,7-tetramethoxyflavone and 5-hydroxy-2′,6,7-trimethoxyflavone resp.[5] Unambiguous syntheses of both flavones demonstrated however, that the natural products can not be represented by their formulae.[6–8]

Recently two 2′-substituted flavones, wightin (Ia) and echioidinin (IIa)* have been isolated from *Andrographis wightiana* Arn. ex. Nees.[9]



Ia: R = R′ = H
Ib: R = R′ = Me
Ic: R = R′ = Et
Id: R = Me; R′, = H



IIa: R = R′ = H
IIb: R = Me; R′ = Benzyl
IIc: R = Me; R′ = OH

The oxygenation pattern of wightin (Ia) was proved by identification of its dimethyl ether with the already known 2′,3′,5,7,8-pentamethoxyflavone[11] (Ib); the position of the hydroxyls was demonstrated by alkaline degradation of both the parent compound and its diethyl ether (Ic) and by the synthesis of wightin diethyl ether.[9]

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* Echioidinin-2′-glucoside, echioidin is a constituent of the closely related *Andrographis echioides Nees.*[10]

[1] W. R. Dunstan and T. A. Henry, *Proc. Roy. Soc.* **68**, 374 (1901).

[2a] M. L. Deporto, K. M. Gallagher, I. E. Gowan, A. C. Hughes, E. M. Philbin, T. Swain and T. S. Wheeler, *J. Chem. Soc.* 4249 (1955); [b] W. B. Whalley, *J. Chem. Soc.* 1833 (1957).

[3] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956).

[4] F. A. Kincl, J. Iriarte, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).

[5] F. Sondheimer and A. Meisels, *Tetrahedron* **9**, 139 (1960).

[6] L. Farkas and M. Nógrádi, *Chem. Ber.* **98**, 164 (1965).

[7] V. V. S. Murti, P. V. Raman and T. R. Seshadri, *Curr. Sci.* **34**, 398 (1965).

[8] B. R. Pai, P. S. Subramanian, and V. Subramanian, *Tetrahedron* **21**, 3573 (1965).

[9] T. R. Govindichari, P. C. Parthasarathy, B. R. Pai and P. Subramanian, *Tetrahedron* **21**, 3237 (1965)

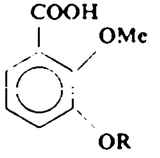
[10] T. R. Govindichari, P. C. Parthasarathy, B. R. Pai and P. S. Subramanian, *Tetrahedron* **21**, 2633 (1965).

[11] A. Arcoleo, A. Bellinio, C. Casinovi and P. Venturella, *Ann. Chim. Roma* **47**, 75 (1957).

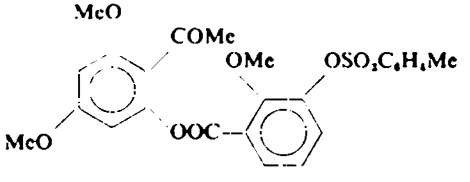
The constitution of echioidinin (IIa) has been elucidated by the analysis of its spectra, as well as by an unambigous synthesis via the chalcone route.[10]

The unique 2′,3′-oxygenation pattern in the B-ring of wightin and our interest in 2′-substituted flavones,[6] prompted the synthesis of both wightin and echioidinin.

The acid chloride of 2-methoxy-3-*p*-toluenesulphonyloxybenzoic acid (III)[12] reacted with 2-hydroxy-3,4,6-trimethoxyacetophenone,[14] to give 2-(2-methoxy-3-*p*-toluenesulphonyloxybenzoyloxy)-3,4,6-trimethoxyacetophenone (IV). Rearrangement of IV and elimination of the blocking group was performed in one step[15] and gave rise directly to 2,3′-dihydroxy-2′,3,4,6-tetramethoxy-dibenzoylmethane (V). Acid catalysed cyclization of V to 3′-hydroxy-2′,5,7,8-tetramethoxyflavone (Id) and selective demethylation completed the synthesis of 3′,5-dihydroxy-2′,7,8-trimethoxyflavone (Ia), identical in every respect with natural wightin.

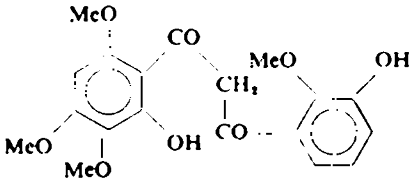


III: R = —SO$_2$C$_6$H$_4$CH$_3$

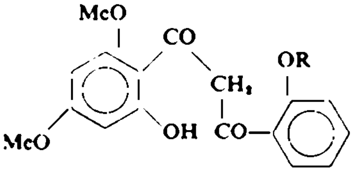


IV

The synthesis of echioidinin (IIa) was similar. Acylation of 2-hydroxy-4,6-dimethoxyacetophenone[16] afforded 2-(2-benzyloxybenzoyl)-4,6-dimethoxyacetophenone.



V



VI: R = Benzyl

This was rearranged[15] to 2′-benzyloxy-2-hydroxy-oxy-4,6-dimethoxydibenzoylmethane (VI) and cyclized to 2′-benzyloxy-5,7-dimethoxyflavone (IIb). Debenzylation and partial demethylation of IIb to echioidinin (IIa) was accomplished in one step.

EXPERIMENTAL

2-(2-*Methoxy*-3-p-*toluenesulphonyloxybenzoyloxy*)-3,4,6-*trimethoxyacetophenone* (IV). 2-methoxy-3-p-toluenesulphonyloxybenzoyl chloride[12] and 2-hydroxy-3,4,6-trimethoxy-acetophenon[17] (7 g) was heated in dry pyridine (35 ml) for 15 min at 110°. The reaction mixture was poured into dil. HCl, when a sticky oil separated. This was crystallized from aqueous MeOH and MeOH giving IV (4·1 g) as colorless needles of m.p. 111–113°. (Found: C 59·07; H 5·08. C$_{26}$H$_{26}$O$_{10}$S; (530·6) requires: C 58·89; H 4·94%.)

2,3′-*Dihydroxy*-2′,3,4,6-*tetramethoxydibenzoylmethane* (V). Compound IV (3·5 g) was stirred in dry pyridine (30 ml) with powdered KOH (3 g) at 50° for 3 hr. The resulting suspension was poured

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

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

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

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

[16] V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.* 23A, 261 (1946).

[17] A. Oliviero and E. Lugli, *Gazz. Chim. Ital.* 78, 16 (1948).

into 20% aqueous AcOH (300 ml), the ppt recrystallized from MeOH giving V (2·1 g), as bright yellow needles, m.p. 146–148°. It gives a dark green colour with methanolic $FeCl_3$. λ_{max}^{EtOH} 293, 367 mμ, (log 4·48, 4·57). (Found: C 60·95; H 5·76. $C_{19}H_{20}O_8$; (376·4) requires: C 60·63; H 5·36%.)

3′-*Hydroxy*-2′,5,7,8-*tetramethoxyflavone* (Id). A mixture of V, (1·5 g), fused AcONa (2·5 g) and AcOH (30 ml) was refluxed for 4 hr. The white solid, which precipitated on dilution with water (1·1 g) was recrystallized from MeOH as colorless needles of Id, m.p. 237–239°. λ_{max}^{EtOH} 268, 325 mμ (10 g 4·40, 4·09). (Found: C 63·95; H 5·60. $C_{19}H_{18}O_7$ (358·3) requires: C 63·68 H 5·06%.)

3′,5-*Dihydroxy*-2′,7,8-*trimethoxyflavone* (*wightin*) (Ia). A mixture of Id (0·26 g), anhyd $AlCl_3$ (0·5 g) and MeCN (10 ml) was refluxed for 3 hr. After removing the solvent *in vacuo* the complex was decomposed by with 1:1 HCl on the steam bath. The resulting yellow ppt was filtered off, washed thoroughly with water and recrystallized from MeOH giving rise to pure wightin (Ia, 0·20 g) as yellow needles, m.p. 187–189° (lit.[9] 188–189°, mixed m.p. with natural wightin 187–189°). It gives a green colour with methanolic $FeCl_3$.λ_{max}^{EtOH} 273, 338 mμ (10 g 4·38, 3·84). $\lambda_{max}^{EtOH-NaOEt}$ 269, 370 mμ (10 g 4·40, 3·86). $\lambda_{max}^{EtOH-AlCl_3}$ 292, 322, 403 mμ (10 g 4·38, 4·08, 3·79). Lit.[9] λ_{max}^{EtOH} 275, 330–340 mμ (10 g 4·39, 3·86) $\lambda_{max}^{EtOH-NaOEt}$ 270, 370, mμ (10 g 4·41, 3·87). $\lambda_{max}^{EtOH-AlCl_3}$ 290–295, 330, 400 mμ (10 g 4·40, 4·10, 3·81). (Found C 62·58; H 4·66. $C_{18}H_{16}O_7$ (344·3) requires: C 62·79; H 4·68%.)

Diacetate. Acetylation of synthetic wightin (0·15 g) (Ac_2O–AcONa) afforded 3′,5-diacetoxy-2′,7,8-trimethoxyflavone as colorless needles of m.p. 158–160° (MeOH). (Lit.[9] 159–160°). (Found: C 61·28; H 4·50. $C_{22}H_{20}O_9$ (428·4) requires: C 61·68 H 4·71%.)

Diethylether. Ethylation of synthetic wightin (0·15 g) with diethylsulphate (K_2CO_3, acetone) afforded 3′,5-diethoxy-2′,7,8-trimethoxyflavone as colorless needles, m.p. 136–137° (benzene–pet ether). (Lit.[9] m.p. 136°). (Found: C 65·77; H 6·19; $C_{22}H_{24}O_7$ (400·4) requires: C 65·99, H 6·04%.)

2-*Benzyloxybenzoic acid*. Salicylic acid (20 g), ignited K_2CO_3 (90), benzylchloride (58 g) and dimethylformamide was refluxed with stirring for 1 hr. Dilution with water afforded in quantitative yield *benzyl-2-benzyloxybenzoate* as a rapidly solidifying colorless oil. A small sample was recrystallized from MeOH to give colorless needles of m.p. 52–54°. (Found: C 79·00; H 5·53. $C_{21}H_{18}O_3$ (318·4) requires: C 79·22; H 5·70%.)

The crude ester was hydrolysed by refluxing with a mixture of MeOH (380 ml) and 40% NaOHaq (70 ml) for 2 hr. Dilution with water and acidification with HCl precipitated the acid, which recrystallized from MeOH, yield 16 g; m.p. 76–178° (lit.[10] 76–78°).

2-(2-*Benzyloxybenzoyloxy*)-4,6-*dimethoxyacetophenone*. A mixture of 2-benzyloxybenzoyl chloride (prepared from 14 g acid with $SOCl_2$), 2-hydroxy-4,6-dimethoxyacetophenone (10 g)[10] and dry pyridine was heated at 110° for 20 min. The reaction mixture was diluted with water and the oil crystallized by scratching. Recrystallization gave colorless needles (12 g), m.p. 94–96°. (Found C 73·20; H 5·49. $C_{24}H_{22}O_6$ (390·4) requires: C 73·83; H 5·68%.)

2′-*Benzyloxy*-2-*hydroxy*-4,6-*dimethoxydibenzoylmethane* (VI). 2-(2-benzyloxybenzoyloxy) 4,6-dimethoxyacetophenone (6·5 g) and powdered KOH (6 g) was stirred in dry pyridine (50 ml) at 50° for 3 hr. The reaction mixture was decomposed with 20% aqueous AcOH, when the diketone precipitated as an oil (60 g). This was dissolved in MeOH (60 ml) and added to a methanolic soln of cupric acetate (7·2 g in 60 ml). The Cu-complex precipitated as a reddish-brown solid, (5 g) which melted after recrystallization from dimethylformamide at 214–216°.

The Cu complex (5 g) was decomposed with a mixture of cold 5% HClaq (100 ml) and 100 ml ether. After separation, the organic phase was washed with sat. $NaHCO_3$aq and water. Evaporation of the solvent and repeated recrystallization from MeOH yielded pure crystalline diketone (3·2 g) as pale yellow needles, m.p. 108–111°. λ_{max}^{EtOH} 246 (sh), 292 and 378 mμ (10 g 4·03, 4·27, 4·07). (Found: C 70·70; H 5·28 $C_{24}H_{22}O_6$ (406·4) requires: C 70·92; H 5·46%.) With methanolic $FeCl_3$ sluggish development of brownish-green colour was observed.

2′-*Benzyloxy*-5,7-*dimethoxyflavone* (IIb). Ring closure of 2′-benzyloxy-2-hydroxy-4,6-dimethoxydibenzoylmethane (6·5 g) was effected as described with Id. Recrystallization of the crude product from benzene–pet. ether and EtOH afforded IIb (41 g) as colorless prisms, m.p. 139–141°, (lit.[10] 134–135°). λ_{max}^{EtOH} 262, 318 mμ (log 4·40, 4·20). Lit.[10] λ_{max}^{EtOH} 262, 320 m (10 g 4·41, 4·22). (Found: C 74·43; H 5·19. $C_{24}H_{20}O_5$ (388·40) requires: C 74·21; H 5·19%.)

2′,5-*Dihydroxy*-7-*methoxyflavone* (*echioidinin*) (IIa). Compound IIb (0·20 g), anhyd $AlCl_3$ (10 g) and 25 ml dry MeCM was refluxed for 6 hr. The solvent was evaporated *in vacuo* and the residue decomposed by heating with dil. HCl on a water bath. The product was recrystallized from acetone

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[10] B. Jones, *J. Chem. Soc.* 1831 (1935).

to give echioidinin (IIa, 0·11 g) as pale yellow needles, m.p. 262–264° (lit.[10] 262–264°). It gives a brown colour with methanolic $FeCl_3$. λ_{max}^{EtOH} 267, 340 mμ (log 4·48, 4·30). $\lambda_{max}^{EtOH-NaOEt}$ 264, 404 mμ (10 g 4·33. 4·20). $\lambda_{max}^{EtOH-AlCl_3}$ 278, 348, 370 mμ (log 4·41, 4·22, 4·03). Lit.[10] λ_{max}^{EtOH} 267, 340 mμ (10 g 4·50, 4·32); $\lambda_{max}^{EtOH-NaOEt}$ 265, 410–415 mμ (10 g 4·35, 4·22); $\lambda_{max}^{EtOH-AlCl_3}$ 255, 280, 350, 380–385 (i) mμ (10 g 4·15, 4·43, 4·24, 4·05). (Found: C 67·81; H 4·22. $C_{16}H_{12}O_5$ (282·3) requires: C 67·60; H 4·26%.)

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