The Synthesis of Tlatlancuayin and Some Related Compounds

By Kenji FUKUI, Takashi MATSUMOTO and Shigehiro NAKAMURA

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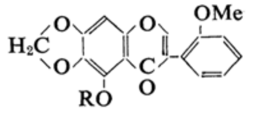
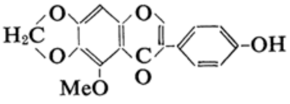
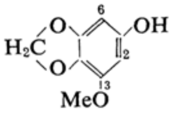
Tlatlancuayin was isolated from *Iresine celosioides L.* (*fam. Amarantaceae*) by Crabbé et al.[1] They established its structure as 2′, 5-dimethoxy-6, 7-methylenedioxyisoflavone (I) from analytical, spectroscopic and degradative studies. As an isoflavone it is a unique compound which has a fully-alkylated system, with a lone 2′-methoxyl in the side phenyl and a methylenedioxy group in the chromone nucleus. Two methods for the synthesis of the compound have been reported by Arora et al.[2] In previous papers the present authors have reported the synthesis of irisolone (4′-hydroxy-5-methoxy-6, 7-methylenedioxyisoflavone) (II),[3] one of the few naturally-occurring isoflavones containing a methylenedioxy substituent, and some 6, 7-methylenedioxyisoflavones.[4,5]



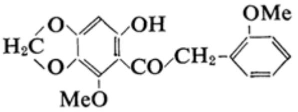
(I) R=Me (V) R=H



(II)



(III)



(IV)

The present paper will describe the synthesis of tlatlancuayin and some related compounds.

In previous papers,[3,6] the authors have shown that, in the Hoesch reaction, 3-methoxy-4, 5-methylenedioxyphenol (III)[7] was condensed with some acetonitriles at the 2-position (not at the 6-position). By a similar reaction with 2-methoxybenzyl cyanide, III yielded 2-hydroxy-4, 5-methylenedioxy-6-methoxyphenyl 2-methoxybenzyl ketone (IV) which had been obtained by the degradation[1] of natural tlatlancuayin with alkali. According to the method of Crabbé et al.,[1] IV was cyclized with ethyl formate to tlatlancuayin (I), whose identity with the natural substance was confirmed by mixed melting point determination and by ultraviolet and infrared spectral comparisons (Figs. 1 and 2). The synthetic substance, I, was converted into the known product, V, by demethylation.

By a similar reaction with benzyl cyanide, 3, 4-methylenedioxybenzyl cyanide and 3, 4-dimethoxybenzyl cyanide, III was derived to the respective ketones, VI, VII and VIII. These ketones were also cyclized with ethyl formate to the corresponding isoflavones (IX, X and XI). The treatment of IX and X with aluminum chloride in boiling ether gave the 5-demethyl derivatives (XII and XIII), which could also be methylated back into the parent isoflavones (IX and X), indicating that no

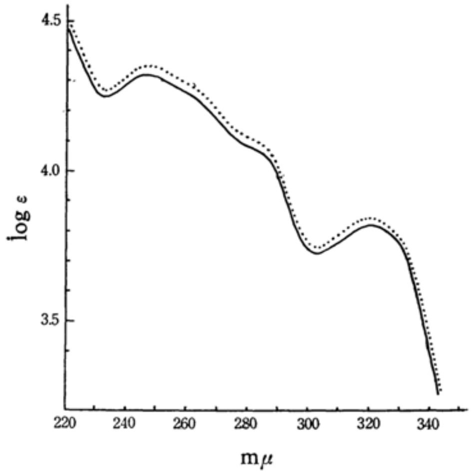


Fig. 1. Ultraviolet spectra of natural (……) and synthetic tlatlancuayin (——) in ethanol.

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[1] P. Crabbé, P. R. Leeming and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 5258 (1958).

[2] S. K. Arora, A. C. Jain and T. R. Seshadri, *Tetrahedron*, **18**, 559 (1962).

[3] K. Fukui and T. Matsumoto, This Bulletin, **38**, 887 (1965).

[4] K. Fukui and T. Matsumoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **85**, 793 (1964). to be published.

[5] K. Fukui and T. Matsumoto, This Bulletin, **38**, 612 (1965)

[6] K. Fukui and T. Matsumoto, ibid., **36**, 806 (1963).

[7] A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin and F. W. Holly, *J. Am. Chem. Soc.*, **81**, 4983 (1959).

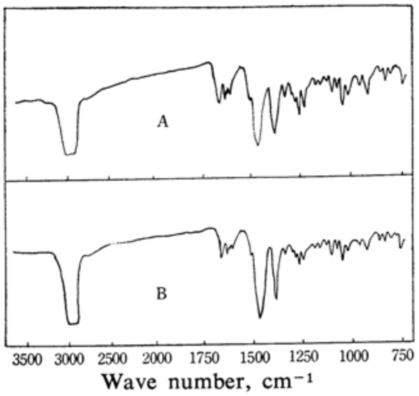
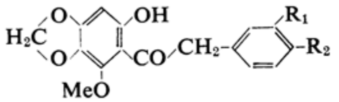
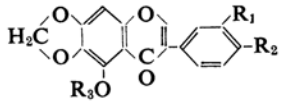


Fig. 2. Infrared spectra of natural (A) and synthetic tlatlancuayin (B) in Nujol.

isomerization occurs during the treatment with aluminum chloride.



(VI) $R_1=R_2=H$
(VII) R_1, R_2=O-CH_2-O
(VIII) $R_1=R_2$=OMe



(IX) $R_1=R_2=H$ R_3=Me
(X) R_1, R_2=O-CH_2-O R_3=Me
(XI) $R_1=R_2$=OMe R_3=Me
(XII) $R_1=R_2=R_3=H$
(XIII) R_1, R_2=O-CH_2-O R_3=H

Experimental[*1]

2-Hydroxy-4, 5-methylenedioxy-6-methoxyphenyl 2-Methoxybenzyl Ketone (IV).—3-Methoxy-4, 5-methylenedioxyphenol (III)7) (5.0 g.) and 2-methoxybenzyl cyanide8) (5.0 g.) were dissolved in dry ether (120 ml.), and then fused zinc chloride (1.5 g.) was added. The mixture was saturated with dry hydrogen chloride in an ice-bath and allowed to stand overnight. The ether solution was decanted from the ketimine hydrochloride - zinc chloride complex which had separated. The residue was washed with dry ether and heated on a steam bath with water (100 ml.) for 75 min. The oil which had separated on cooling was extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate and then with water. After the solvent had evaporated, the residue was distilled. The distillate (bath temperature 230—280°C/0.1 mmHg) was collected and crystallized from ether - petroleum ether to give IV as yellow needles; m. p. 115—116°C (reported m. p. 115—116°C1)); yield, 0.6 g. This gave a green ferric chloride reaction in ethanol. UV: $\lambda_{max}^{\mathrm{EtOH}}$ mμ (log ε); 243.5 (4.08), 284 (4.13), 351 (3.70). In all these properties it agreed with that substance obtained by Crabbé et al.1)

Found: C, 64.26; H, 5.07. Calcd. for $C_{17}H_{16}O_6$; C, 64.55; H, 5.10%.

Tlatlancuayin (2′, 5-Dimethoxy-6, 7-methylenedioxyisoflavone) (I).—According to the method of Crabbé et al.,1) the ketone IV (1.44 g.) by cyclization with sodium (3.0 g.) in ethyl formate (200 ml.) gave I (480 mg.) as colorless prisms, m. p. 147—148°C (reported m. p. 145—147°C,1) 147—148°C2)). This gave no ferric chloride reaction. This substance was found to be identical with the natural substance by mixed melting point measurement and by infrared and ultraviolet spectral comparisons. IR; 1645, 1614, 1603, 1589, 1016, 938 cm^{-1}. UV: $\lambda_{max}^{\mathrm{EtOH}}$ mμ (log ε); 246 (4.32), 281[*2] (4.08), 321 (3.82).

Found: C, 66.28; H, 4.37. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32%.

The Partial Demethylation of Tlatlancuayin (I).—According to the method of Crabbé et al.,1) I was demethylated with aluminum chloride to give 5-hydroxy-2′-methoxy-6, 7-methylenedioxyisoflavone (V) as yellow needles, m. p. 191—192°C (reported m. p. 192—193°C1)). This gave a green ferric chloride reaction in ethanol. UV: $\lambda_{max}^{\mathrm{EtOH}}$ mμ (log ε); 243.5 (4.25), 271.5 (4.27), 332[*2] (3.58).

Found: C, 65.21; H, 3.89. Calcd. for $C_{17}H_{12}O_6$; C, 65.38; H, 3.87%.

2-Hydroxy-4, 5-methylenedioxy-6-methoxyphenyl Benzyl Ketone (VI).—From the phenol III (5.0 g.), benzyl cyanide (4.0 g.), fused zinc chloride (1.5 g.) and dry ether (120 ml.), synthesis was carried out by a method similar to that used for IV. The product was recrystallized from methanol to give VI as yellow needles, m. p. 162—164°C, which gave a green ferric chloride reaction in ethanol; yield 2.0 g. UV: $\lambda_{max}^{\mathrm{EtOH}}$ mμ (log ε); 245.5 (4.06), 289 (4.12), 357 (3.68).

Found: C, 67.21: H, 4.69. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93%.

2-Hydroxy-4, 5-methylenedioxy-6-methoxyphenyl 3, 4-Methylenedioxybenzyl Ketone (VII).—From the phenol III (19.8 g.), 3, 4-methylenedioxybenzyl cyanide (21.0 g.), fused zinc chloride (6.0 g.) and dry ether (350 ml.), synthesis was carried out by a method similar to that used for IV. The product was recrystallized from chloroform-methanol to give VII as yellow needles, m. p. 153—154°C, which gave a green ferric chloride reaction in ethanol; yield 4.3 g. UV: $\lambda_{max}^{\mathrm{EtOH}}$ mμ (log ε); 241.5 (4.12), 289 (4.21), 355 (3.70).

Found: C, 61.58; H, 4.17. Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27%.

2-Hydroxy-4, 5-methylenedioxy-6-methoxyphenyl 3, 4-Dimethoxybenzyl Ketone (VIII).—From the phenol III (15.0 g.), 3, 4-dimethoxybenzyl cyanide (17.5 g.), fused zinc chloride (4.5 g.) and dry ether (1000 ml.), synthesis was carried out by a method

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[*1] All melting points are uncorrected; the infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in an ethanol solution.

8) J. B. Niederl and R. T. Roth, *J. Am. Chem. Soc.*, **60**, 2140 (1938); Z. Horii, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **77**, 252 (1957).

[*2] Inflection point.

similar to that used for IV. The product was distilled, and the distillate (bath temperature 300—330°C/0.05 mmHg) was collected and then crystallized from chloroform-methanol to give VIII as yellow needles, m. p. 121.5—122°C, which gave a green ferric chloride reaction in ethanol; yield 450 mg. UV: λ_{max}^{EtOH} mμ (log ε); 287.5 (4.18), 355 (3.72).

Found: C, 62.23; H, 5.23. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24%.

5-Methoxy-6, 7-methylenedioxyisoflavone (IX).—The ketone VI (1.0 g.) in freshly-distilled ethyl formate (60 ml.) was added slowly to sodium powder (2.0 g.) at −10°C. The reaction mixture was allowed to stand for 24 hr. at 0°C and then for 48 hr. at room temperature. Ice water containing hydrochloric acid was added, and the solution was extracted with ether. The ether solution was washed with aqueous sodium bicarbonate and then with water, and dried. The recrystallization of the residue from ethanol gave IX as colorless needles; m. p. 145—147°C; yield 330 mg. UV: λ_{max}^{EtOH} mμ (log ε); 260 (4.41), 324 (3.82).

Found: C, 68.99; H, 3.95. Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08%.

5-Methoxy-6, 7; 3′, 4′-bismethylenedioxyisoflavone (X).—From the ketone VII (3.9 g.), freshly-distilled ethyl formate (320 ml.) and sodium powder (7.0 g), synthesis was carried out by a method similar to that used for IX. The product was recrystallized from chloroform-methanol to give X as yellow needles; m. p. 223—224°C; yield 1.5 g. UV: λ_{max}^{EtOH} mμ (log ε); 267 (4.41), 290[*2] (4.18), 320[*2] (3.84).

Found: C, 63.36; H, 3.67. Calcd. for $C_{18}H_{12}O_7$: C, 63.53; H, 3.55%.

3′, 4′, 5-Trimethoxy-6, 7-methylenedioxyisoflavone (XI). — From the ketone VIII (450 mg.), freshly-distilled ethyl formate (60 ml.) and sodium powder (1.0 g.), synthesis was carried out by a method similar to that used for IX. The product was recrystallized from ethanol to give XI as colorless needles; m. p. 178—178.5°C; yield 110 mg. UV: λ_{max}^{EtOH} mμ (log ε); 266.5 (4.45), 324 (3.82).

Found: C, 63.99; H, 4.61. Calcd. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53%.

5-Hydroxy-6, 7-methylenedioxyisoflavone (XII).—A mixture of IX (1.3 g.) and anhydrous aluminum chloride (13.0 g.) in dry ether (130 ml.) was refluxed for 10 hr. The reaction mixture was then poured into ice water and kept for 14 hr. at room temperature. The resulting yellow precipitate was collected and refluxed with a solution of acetic acid (45 ml.) and concentrated hydrochloric acid (45 ml.) for 30 min. The reaction mixture was then diluted with water. The precipitate was collected, washed with water, and recrystallized from acetone to give XII as yellow prisms, m. p. 198—199°C, which gave a green ferric chloride reaction in ethanol; yield 0.9 g. UV: λ_{max}^{EtOH} mμ (log ε); 244 (4.32), 270.5 (4.38), 332[*2] (3.58).

Found: C, 68.03; H, 3.53. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57%.

The acetate of XII: acetic anhydride-pyridine method; m. p. 178—179°C (colorless needles from ethanol). UV: λ_{max}^{EtOH} mμ (log ε); 251 (4.40), 321 (3.95).

Found: C, 66.42; H, 3.80. Calcd. for $C_{18}H_{12}O_6$: C, 66.67; H, 3.73%.

XII was methylated, by the usual dimethyl sulfate - potassium carbonate method, to IX, which was undepressed on admixture with the above sample.

5-Hydroxy-6, 7; 3′, 4′-bismethylenedioxyisoflavone (XIII). — A mixture of X (1.47 g.), anhydrous aluminum chloride (12.0 g.) and dry ether (100 ml.) was treated by a method similar to that used for XII. The product was recrystallized from acetone to give XIII as yellow needles, m. p. 232.5—233.5°C, which gave a green ferric chloride reaction in ethanol; yield 780 mg. UV: λ_{max}^{EtOH} mμ (log ε); 274 (4.39), 294[*2] (4.29), 336[*2] (3.59).

Found: C, 62.87; H, 2.98. Calcd. for $C_{17}H_{10}O_7$: C, 62.58; H, 3.09%.

The acetate of XIII: acetic anhydride - pyridine method; m. p. 216—217°C (colorless needles from aqueous methanol). UV: λ_{max}^{EtOH} mμ (log ε); 265 (4.29), 293.5 (4.11), 317[*2] (3.94).

Found: C, 61.71; H, 3.24. Calcd. for $C_{19}H_{12}O_8$: C, 61.96; H, 3.29%.

XIII was methylated, by the usual dimethyl sulfate - potassium carbonate method, to X, which was undepressed on admixture with the above sample.

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Department of Chemistry
Faculty of Science
Hiroshima University
Higashi-Sendamachi, Hiroshima