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THE SYNTHESIS OF TLATLANCUAYIN*

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Abstract—Methods of synthesis of the naturally occurring isoflavone, tlatlancuayin, are described.

TLATLANCUAYIN, a colourless substance was isolated from the Mexican plant, *Iresine celosioides* L. by Crabbé *et al.*[1] They also established its constitution as 5,2′-dimethoxy-6,7-methylenedioxy-isoflavone (V) based on analytical, spectroscopic and degradative studies. As an isoflavone it possesses several rare features. It is one of the few with a lone 2′-methoxyl in the side phenyl and a methylenedioxy group in the condensed benzene ring. Further, it has a fully alkylated system and the substitution pattern belongs to the 5,6,7-hydroxy or methoxy type as found in irigenin,[2] tectorigenin,[2] muningin,[2] podospicatin[3] and caviunin.[4]

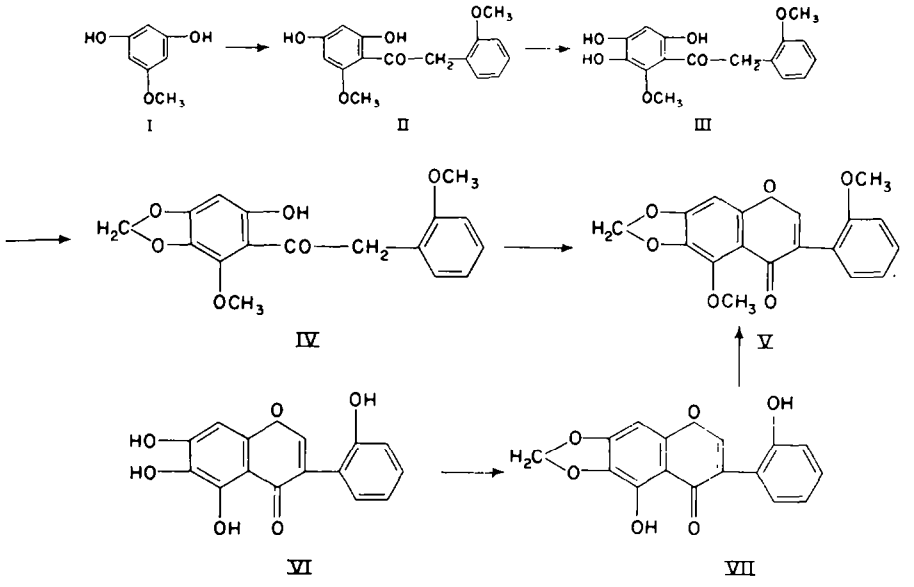
In this laboratory, three methods of synthesizing 5,6,7-trihydroxyisoflavones have been carried out. In one method antiarol is acylated by the Friedel-Crafts procedure to a deoxybenzoin which undergoes smooth condensation with ethyl formate to a fully methylated 5,6,7-trihydroxyisoflavone in good yield.[5] Thus O-trimethyl tectorigenin was synthesized by Krishnamurti and Seshadri.[6] Another method makes use of an observation by Mahesh *et al.*[7,8] that 5-hydroxy-7,8-dimethoxyisoflavone undergoes isomerization in alkali to 5-hydroxy-6,7-dimethoxyisoflavone. As the former group (5,7,8-trisubstituted) of isoflavones is comparatively easily accessible, this indirect method has been applied to the synthesis of muningin[9], irigenin,[10] tectorigenin[11] and caviunin.[12] The third method consists in subjecting 6-hydroxy-7-methoxyisoflavone to the *ortho* hydroxylation process[13] and has been used only in one case.

More recently Baker *et al.*[14] have used iretol in the Hoesch reaction to give a

* For a preliminary communication of a part of this work, see *J. Sci. Industr. Res. India* **18B**, 494 (1959).

[1] P. Crabbé, P. R. Leeming and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 5258 (1958).
[2] T. R. Seshadri, *Tetrahedron* **6**, 169 (1959).
[3] L. H. Briggs and T. P. Cebalo, *Tetrahedron* **6**, 143 (1959).
[4] O. R. Göttlieb and M. T. Magalhaes, *J. Org. Chem.* **26**, 2449 (1961).
[5] M. Krishnamurti and T. R. Seshadri, *J. Sci. Industr. Res. India* **12B**, 120 (1953).
[6] M. Krishnamurti and T. R. Seshadri, *Proc. Indian Acad. Sci.* **39A**, 144 (1954).
[7] V. B. Mahesh, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **39A**, 165 (1954).
[8] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **14B**, 671 (1955).
[9] M. L. Dhar and T. R. Seshadri, *Tetrahedron* **7**, 77 (1959).
[10] L. Farkas and J. Varady, *Tetrahedron Letters*, No. 20, 23 (1960); *Chem. Ber.* **93**, 2685 (1960).
[11] L. Farkas and J. Varady, *Chem. Ber.* **93**, 1269 (1960).
[12] L. Farkas and J. Varaday, *Tetrahedron Letters*, No. 6, 197 (1961); *Chem. Ber.* **94**, 2501 (1961).
[13] K. Aghoramurthy, T. R. Seshadri and G. B. V. Subramaniam, *J. Sci. Industr. Res. India* **15B**, 11 (1956).
[14] W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert, W. D. Ollis and R. C. Russel, *Tetrahedron Letters*, No. 5, 6 (1960).

deoxybenzoin which can be cyclized with ethoxalyl chloride giving a separable mixture of 5,6,7- and 5,7,8-trisubstituted isoflavones, Thus 5,7-dihydroxy-6-methoxy-isoflavones, such as tectorigenin,[14] irigenin[14] and caviunin[15] have been synthesized. Extraordinarily, no ψ-isomer is formed in the last synthesis.



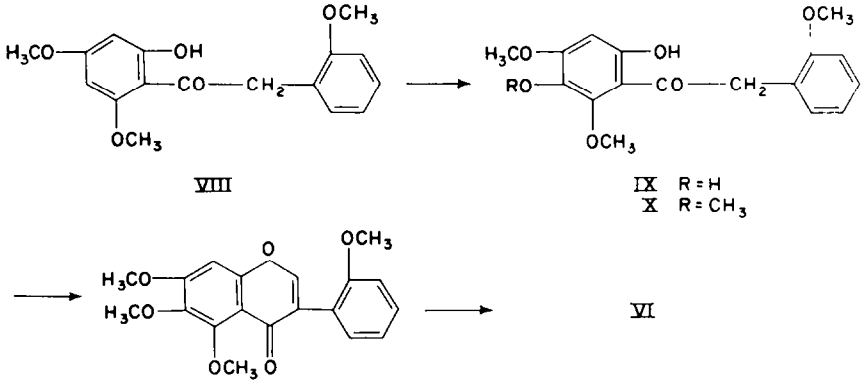
The synthesis of tlatlancuayin has been achieved in two ways. The first method consists in preparing 2-hydroxy-4,5-methylenedioxy-6-methoxyphenyl 2-methoxybenzyl ketone (IV). Phloroglucinol monomethyl ether (I) undergoes Hoesch reaction with *o*-methoxybenzyl cyanide to give 2,4-dihydroxy-6-methoxyphenyl 2-methoxybenzyl ketone (II). In this reaction resinification is avoided by limiting the amount of zinc chloride. The ketone (II) subjected to *para* hydroxylation afforded 2,4,5-trihydroxy-6-methoxyphenyl 2-methoxybenzyl ketone (III) in 20 per cent yield. Subsequent methylenation using the potassium carbonate–acetone method gave the required deoxybenzoin (IV) which agreed in m.p. and spectral characteristics with that obtained from the degradation of tlatlancuayin by Crabbé *et al.*;[1] who also describe the isoflavone ring closure. This synthesis may follow the biogenetic path in plants. It has been suggested that methylation of the hydroxyl in the 5-position should take place prior to the oxygen ring closure.[16] This would make the concerned hydroxyl group sufficiently reactive to undergo methylation. Further, the entry of a hydroxyl in the 6-position could be the result of a biochemical oxidation at the same ketonic stage.[17] These two points are incorporated in the above synthesis. This scheme renders the introduction of the methylene group involving two *o*-hydroxyls in a natural way.

The second method of tlatlancuayin synthesis involves the preparation of 5,6,7,2′-tetrahydroxy-isoflavone (VI) which is first methylenated in the 6,7-positions using the potassium carbonate–acetone method, and then completely methylated with excess

[15] S. F. Dyke, W. D. Ollis and M. Sainsbury, *J. Org. Chem.* **26,** 2453 (1961).
[16] P. S. Sarin and T. R. Seshadri, *Proc. Nat. Inst. Sci. India* **26,** 162 (1960).
[17] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res. India* **20A,** 577 (1961).

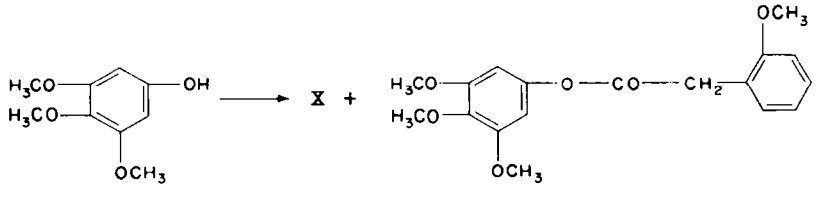
dimethyl sulphate to give a product identical in all respects with the natural sample.

In the preparation of VI, of the three methods examined the best is the third involving alkaline isomeric change. First, *para* hydroxylation at the deoxybenzoin stage was investigated. 2-Hydroxy-4,6-dimethoxyphenyl 2-methoxybenzyl ketone (VIII) prepared according to Seshadri and Varadarajan[18] was oxidized with alkaline persulphate to 2,5-dihydroxy-4,6-dimethoxyphenyl 2-methoxybenzyl ketone (IX) in 10 per cent yield. This deoxybenzoin underwent partial methylation in the 5-position with one molecular equivalent of dimethyl sulphate to give X and subsequent ring closure with ethyl formate to 5,6,7,2′-tetramethoxyisoflavone (XI) identical with that described by Crabbé *et al.*[1] In the last reaction the corresponding 2-hydroxy-isoflavanone is usually formed, but it is easily dehydrated to the isoflavone by heating with acetic anhydride.[19] Final demethylation of XI gave VI identical with the compound described by Crabbé *et al.*[1]



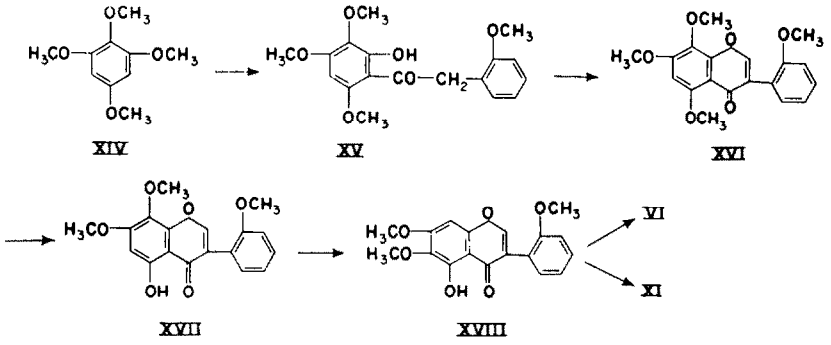
The second method for the synthesis of VI involves the preparation of the ketone (X) from antiarol (XII) and *o*-methoxyphenyl acetyl chloride.[6] This condensation, however, gave only a small amount of X, the major product being the antiaryl ester of *o*-methoxyphenyl acetic acid (XIII). The structure of this product was proved by its negative ferric reaction, insolubility in alkali and an ester band at 5·7 μ in the I.R. spectrum. Attempts to effect the Fries migration of this ester failed.

The third synthesis of VI starts from 1,2,3,5-tetramethoxybenzene (XIV) which undergoes Friedel-Crafts acylation with *o*-methoxyphenyl acetyl chloride. The resulting ketone (XV) condensed with ethyl formate giving good yields of 5,7,8,2′-



[18] T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* **37A**, 514 (1953).
[19] S. K. Arora, A. C. Jain and T. R. Seshadri, *J. Indian Chem. Soc.* **38**, 61 (1961).

tetramethoxyisoflavone (XVI). Partial demethylation to XVII and alkali isomerization of the latter yielded 5-hydroxy-6,7,2'-trimethoxyisoflavone (XVIII) in 50 per cent yield. Identity of this product was established by methylation as well as by demethylation to known products.



XIV XV XVI XVII XVIII

EXPERIMENTAL

U.V. spectra were taken in methanolic solution; the ferric reaction in ethanolic solution and light petroleum had b.p. 40–60° unless otherwise stated. The molecular extinction coefficients given in brackets are all in terms of logarithmic values, the m.p.'s are uncorrected.

2,4-*Dihydroxy-6-methoxyphenyl-2-methoxybenzyl ketone* (II)

A stream of dry hydrogen chloride was passed through an ethereal solution of O-monomethyl phloroglucinol[20] (I; 5 g) and *o*-methoxybenzyl cyanide[21] (5·3 g) containing in suspension fused zinc chloride (0·4 g) at 0°. The mixture was left overnight at 0°, and the ketimine hydrochloride separated as an oil. The ether layer was decanted off, the oily liquid washed twice with dry ether, extracted with ice-cold water (75 ml) and the clear aqueous solution separated from the viscous mass (A) and refluxed for 2 hr. The solution was cooled and the product crystallized from ether–light petroleum giving colourless elongated rectangular prisms (2·0 g), m.p. 176–177°; wine-red ferric reaction, λ_{max} 240, 285 and 350 mμ (3·72, 3·90 and 3·45 respectively), λ_{min} 233, 258 and 330 mμ (3·67, 3·34 and 3·30 respectively) (Found: C, 66·3; H, 5·9. $C_{16}H_{16}O_5$ requires: C, 66·7; H, 5·6%).

More of this ketone (0·7 g) could be obtained from the viscous mass (A) by dissolving it in ethanol and heating the solution with an equal volume of water for 2 hr. Ethanol was distilled off and the residue extracted with ether. The ether concentrate yielded crystals on the addition of light petroleum.

2,4,5-*Trihydroxy-6-methoxyphenyl 2-methoxybenzyl ketone* (III)

To a cooled stirred solution of II (3 g) in aqueous sodium hydroxide (4%, 50 ml) an aqueous solution of sodium persulphate (3 g in 30 ml) was added dropwise during 4 hr. The mixture was left overnight at room temp, acidified to congo-red and extracted with ether to remove unchanged compound. The aqueous solution was then heated with concentrated hydrochloric acid (20 ml) and sodium sulphite (1 g) on a water bath for 30 min, cooled, extracted with ether and the ethereal solution dried and concentrated to a small bulk. The product crystallized on the addition of light petroleum and was recrystallized from ether–light petroleum affording colourless plates (0·6 g), m.p. 126–127°; light green ferric reaction, λ_{max}^{EtOH} 290 mμ (4·48), λ_{min}^{EtOH} 248 mμ (3·27). (Found: C, 62·9; H, 6·0. $C_{16}H_{16}O_6$ requires: C, 63·2; H, 5·3%).

2-*Hydroxy-4,5-methylenedioxy-6-methoxyphenyl 2-methoxy-benzyl ketone* (IV)

Ketone (III; 0·5 g) was refluxed with dry acetone (50 ml), methylene iodide (1·5 g) and freshly ignited potassium carbonate (5 g) for 40 hr. Acetone was distilled off and water added to the residue and the methylenated product filtered, washed with water and dried. The desired deoxybenzoin crystallized from ether–light petroleum as yellow needles (0·1 g), m.p. 115–116°; green ferric reaction

[20] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* **38A**, 80 (1953).

[21] F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.* 263 (1944).

and a greenish blue-colour with gallic acid in sulphuric acid. Crabbé *et al.*[1] recorded the same properties for the sample obtained by the fission of tlatlancuayin.

2,5-*Dihydroxy*-4,6-*dimethoxyphenyl* 2-*methoxybenzyl ketone* (IX)

An aqueous solution of sodium persulphate (1·3 g in 15 ml) was added dropwise to a well-stirred solution of the ketone[18] (VIII; 1·5 g) in aqueous sodium hydroxide (5%, 16 ml) and pyridine (5 ml) at 10° for 4 hr. The sulphate ester after hydrolysis with hydrochloric acid (15 ml) was cooled, extracted with ether and the ethereal solution dried. The residue crystallized from benzene–light petroleum as colourless needles (0·15 g), m.p. 192°; light green ferric reaction, λ_{max} 291 mμ (4·39), λ_{min} 250 mμ (3·33) (Found: C, 63·7; H, 5·5. $C_{17}H_{18}O_6$ requires: C, 64·1; H, 5·7%).

2-*Hydroxy*-4,5,6-*trimethoxyphenyl* 2-*methoxybenzyl ketone* (X)

(i) *From ketone* (IX). The ketone (IX; 0·45 g) in acetone (40 ml), potassium carbonate (1 g) and dimethyl sulphate (0·16 ml) were refluxed for 4 hr; the product crystallized from ether–light petroleum as colourless plates (0·4 g), m.p. 63–65°; green ferric reaction. Crabbé *et al.*[1] reported the same properties.

(ii) *From antiarol* (XII). This phenol was prepared from pyrogallol[22] and *o*-methoxyphenyl acetic acid prepared from *o*-methoxyacetophenone by the following modification of the method of Schwenk *et al.*[23] The ketone (22·5 g) was refluxed with morpholine (26 ml) and sulphur (9 g) at 145–155° (bath temp.) for 8 hr. The mixture was poured on ice, extracted with chloroform, the chloroform solution washed with hydrochloric acid, evaporated and the residue boiled with aqueous sodium hydroxide (80 g in 600 ml) for 12 hr. The mixture was cooled, extracted with ether and the aqueous solution acidified. The solid product crystallized from ether–light petroleum as feather-like crystals (10 g), m.p. 121–122°; Hey and Nagdy[24], m.p. 120–123°. It was converted into its acid chloride as described by Pfeiffer *et al.*[25]

Anhydrous aluminium chloride (3·2 g) was dissolved in dry ether (75 ml). To this solution (ice-cold) was added, while shaking, a solution of antiarol (1·9 g) in dry ether (100 ml) followed by *o*-methoxyphenyl acetyl chloride (1·9 g in 25 ml dry ether) in small lots. The resulting mixture was stirred well for 2 hr. After leaving it overnight at room temp., ether was distilled off and the residual aluminium chloride complex decomposed with ice (15 g) and hydrochloric acid (15 ml) by keeping it at room temp. for 12 hr and then warming at 60° for 30 min. The mixture was extracted with ether and the ethereal solution was washed with aqueous sodium bicarbonate (5%) and then with water, dried and concentrated to 10 ml. On cooling below 0°, a white crystalline solid of antiaryl *o*-methoxyphenyl acetate (XIII) separated. It crystallized from ethanol as colourless thin plates (1·0 g), m.p. 90°; insoluble in aqueous sodium hydroxide, no ferric reaction and λ_{max}^{KBr} 5·70 μ (ester) (Found: C, 64·5; H, 6·5. $C_{18}H_{20}O_6$ requires: C, 65·1; H, 6·0%). The ethereal mother-liquor on dilution with light petroleum yielded the desired deoxybenzoin (0·25 g), m.p. 63–65° alone or when mixed with the above preparation.

5,6,7,2′-*Tetramethoxyisoflavone* (XI)

A solution of ketone (X; 2·5 g) in freshly distilled ethyl formate (95 ml) was added in small amounts to pulverized sodium (2 g), cooled in an ice-salt mixture bath during 30 min with shaking. After leaving the mixture in the refrigerator for 48 hr, ice was added to decompose excess of sodium and the mixture extracted with ether. The ether residue was dehydrated by refluxing with acetic anhydride (20 ml) for 1 hr and the product crystallized from ethanol giving colourless plates (0·75 g), m.p. 148–149°; Crabbé *et al.*[1] also reported the same m.p.

2-*Hydroxy*-3,4,6-*trimethoxyphenyl* 2-*methoxybenzyl ketone* (XV)

An ethereal solution of *o*-methoxyphenyl acetyl chloride (13·7 g in 50 ml) was added gradually to

[22] W. Baker, *J. Chem. Soc.* 665 (1941).
[23] E. Schwenk and E. Bloch, *J. Amer. Chem. Soc.* **64**, 3051 (1942).
[24] D. H. Hey and K. A. Nagdy, *J. Chem. Soc.* 1897 (1953).
[25] P. Pfeiffer and E. Enders, *Chem. Ber.* **84**, 247 (1951).

an ice-cold solution of 1,2,3,5-tetramethoxybenzene[22] (XIV; 14·8 g) and aluminium chloride (35 g) in ether (400 ml). After stirring for 2 hr at 0°, leaving overnight at room temp. and decomposing the complex, the product was isolated. It crystallized from ethanol as colourless rectangular prisms (20·0 g), m.p. 126°; brown-red ferric reaction, λ_{max} 285 mμ (4·31), λ_{min} 250 mμ (3·44) (Found: C, 65·6; H, 6·6. $C_{18}H_{20}O_6$ requires: C, 65·1; H, 6·0%).

5,7,8,2′-*Tetramethoxyisoflavone* (XVI)

The ketone (XV; 6 g) in ethyl formate (250 ml) was added to sodium (5 g) at 0°, left at room temp. (about 20°C), for 48 hr and the product worked up. The ether residue gave 5,7,8,2′-tetramethoxy-2-hydroxyisoflavanone which crystallized from ethanol as colourless needles (4·2 g), m.p. 162–163° (decomp); λ_{max} 285, 316 and 330 mμ (4·28, 3·72 and 3·75 respectively), λ_{min} 250, 311 and 320 mμ (3·64, 3·68 and 3·71 respectively) (Found: C, 63·3; H, 6·3. $C_{19}H_{20}O_7$ requires: C, 63·3; H, 5·6%). This 2-hydroxyisoflavanone (4·2 g) was dehydrated by refluxing with acetic anhydride (125 ml) as usual and the product crystallized from ethanol when 5,7,8,2′-tetramethoxyisoflavone formed colourless rectangular prisms (3·2 g), m.p. 140°; λ_{max} 258 and 325 mμ (4·49 and 3·81 respectively), λ_{min} 232 and 305 mμ (4·33 and 3·73 respectively) (Found: C, 66·4; H, 5·6. $C_{19}H_{18}O_6$ requires : C, 66·7; H, 5·3%).

5-*Hydroxy*-7,8,2′-*trimethoxyisoflavone* (XVII)

A solution of (XVI; 2·8 g) in ether (500 ml) was added to a well shaken ice-cold solution of aluminium chloride (2·4 g) in ether (75 ml) and the resulting mixture kept at room temp. for 42 hr and then refluxed for 6 hr. Ether was distilled off and the resulting complex decomposed with ice and hydrochloric acid (15 ml). The solid crystallized from ethanol in pale yellow prismatic needles (2·2 g), m.p. 134–135°; bluish-green ferric reaction, λ_{max} 264 and 340 mμ (4·49 and 3·61 respectively), λ_{min} 234 and 315 mμ (4·17 and 3·44 respectively) (Found: C, 65·6; H, 5·3. $C_{18}H_{16}O_6$ requires: C, 65·9; H, 4·9%).

5-*Hydroxy*-6,7,2′-*trimethoxyisoflavone* (XVIII)

The *iso*flavone (XVII; 3 g) was refluxed with absolute ethanolic potash (2%, 300 ml) for 15 min, cooled, acidified and the product crystallized from ethanol giving colourless rectangular rods (1·5 g), m.p. 170–171°; violet ferric reaction changing to brown on adding excess of the reagent, λ_{max} 263 and 319 mμ (4·34 and 3·61 respectively), λ_{min} 240 and 316 mμ (4·21 and 3·58 respectively) (Found: C, 66·1; H, 5·2. $C_{18}H_{16}O_6$ requires: C, 65·9; H, 4·9%).

5,6,7,2′-*Tetrahydroxyisoflavone* (VI)

To a solution of either (XVIII; 1·2 g) or (XI; 1·2 g) in dry benzene (50 ml) was added a solution of aluminium chloride in benzene (4·5 g in 450 ml). The resulting mixture was refluxed on a boiling water bath for 10 hr. Benzene was distilled off and the complex decomposed with ice and hydrochloric acid (20 ml). The product crystallized from ethyl acetate–light petroleum (60–80°) as yellow plates (0·4 g), m.p. 204–206°; it gives olive green ferric reaction. Crabbé *et al.*[1] reported the same properties.

5,2′-*Dihydroxy*-6,7-*methylenedioxyisoflavone* (VII)

An acetone solution of (VI; 0·6 g in 60 ml) was refluxed with freshly ignited potassium carbonate (1·5 g) and methylene iodide (0·3 ml) for 24 hr. Inorganic salts were filtered off and washed with warm acetone. The solvent was removed under red. press. and the residue extracted with ether. The ethereal extract was washed twice with aqueous sodium carbonate and then with water. It was dried over anhydrous sodium sulphate, ether distilled off and petroleum ether (60–80°, 20 ml) added to remove excess of methylene iodide. The residue was crystallized from ethyl acetate–light petroleum (60–80°) affording very pale yellow rectangular plates (0·12 g), m.p. 212–213°; green ferric reaction and emerald green gallic acid test (Found: C, 64·5; H, 4·0. $C_{16}H_{10}O_6$ requires: C, 64·4; H, 3·4%).

Tlatlancuayin (V)

First method. 5,2′ Dihydroxy-6,7-methylenedioxy-*iso*flavone (VII; 0·1 g) was refluxed with dimethyl sulphate (0·2 ml), potassium carbonate (1 g) and acetone (20 ml) until ferric reaction was negative (42 hr). The crystalline product crystallized from benzene–petroleum ether (60–80°) as colourless rectangular prisms (0·1 g), m.p. 147–148°; negative ferric reaction, greenish blue gallic acid reaction, λ_{max} 246, 285 and 310 mμ (4·40, 4·13 and 3·88 respectively), λ_{min} 236, 276 and 307 mμ (4·36, 4·11 and 3·83 respectively); λ_{max}^{Nujol} 6·04 μ (–C=O); 8·94, 9·28, 9·52 μ (methylenedioxy). In all these properties it agrees with the description given for natural tlatlancuayin by Crabbé *et al.*[1]

Second method. 2-Hydroxy-4,5-methylenedioxy-6-methoxyphenyl 2-methoxybenzyl ketone (IV; 0·1 g) was condensed with ethyl formate (10 ml) and sodium (0·2 g) as described by Crabbé *et al.*[1] The product (30 mg) agreed in all its properties with that obtained by the first method.