Synthesis of Isoflavones. Part V.[1] Irigenin and Tectorigenin

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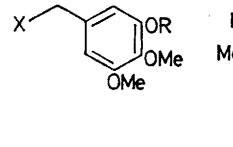
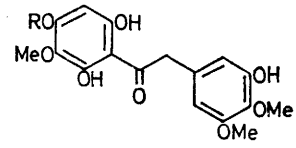
The general ethoxalylation procedure for the synthesis of isoflavones has been applied to the synthesis of irigenin (VII) and tectorigenin (XVI). This synthetic route also yields the isomers, ψ-irigenin (XI) and ψ-tectorigenin (XX). Information concerning the product ratio in certain ethoxalylation reactions and the relative thermodynamic stabilities of 5,6,7- and 5,7,8-trisubstituted isoflavones is discussed.

When this study was carried out,[2] twenty-one natural isoflavones were known,[3] of which three, tectorigenin, irigenin, and caviunin were derivatives of 5,7-dihydroxy-6-methoxyisoflavone. In recent years, the number of known natural isoflavones which have been identified has substantially increased[4] and the isoflavones are now recognised as belonging to the isoflavanoids,[5] a large family of constitutionally related natural products. Interest in the natural occurrence of isoflavones has been matched by a corresponding interest in their synthesis.[4,6] One of the general methods for the synthesis of isoflavones involves the reaction of deoxybenzoins with ethoxalyl chloride [7,8] and the application of this method to the synthesis [2] of irigenin and tectorigenin is now reported in detail. When this work was carried out (1954—1960), the synthesis of tectorigenin had already been described.[9] However, although irigenin was the first natural isoflavone to be isolated (1893)[10] and its constitution had been established (1928),[11] its synthesis had not at that time (1960) been described. More recent studies on the synthesis of 5,7-dihydroxy-6-methoxyisoflavones are discussed later.

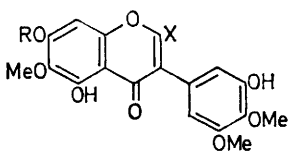
The projected synthesis of irigenin (VII) by the ethoxalylation method [7,8] required the preparation of the intermediate deoxybenzoin (V). Lithium aluminium hydride reduction of the *O*-benzyl ether obtained by benzylation of methyl 3-hydroxy-4,5-dimethoxybenzoate gave the benzyl alcohol (I). This alcohol (I) and thionyl chloride gave the benzyl chloride (II), which was transformed into the cyanide (III) by treatment with potassium cyanide under carefully controlled conditions. Hydrogenolysis of the benzyloxy-cyanide (III) gave 3-hydroxy-4,5-dimethoxybenzyl cyanide (IV) and this, by a Hoesch reaction with iretol (2,4,6-trihydroxyanisole), gave the required deoxybenzoin (V). It is not possible to effect the alkaline hydrolysis of 5,7-dihydroxyisoflavones directly to the corresponding deoxybenzoins, so this precluded any possibility of preparing the deoxybenzoin (V) by alkaline hydrolysis of irigenin (VII). However, this transformation could be effected indirectly by partial benzylation of irigenin (VII), yielding the 7-*O*-benzylirigenin (VIII) which, by



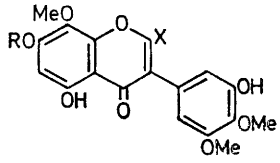
	R	X
(I)	CH_2Ph	OH
(II)	CH_2Ph	Cl
(III)	CH_2Ph	CN
(IV)	H	CN



(V) R = H
(VI) R = CH_2Ph



	R	X
(VII)	H	H, Irigenin
(VIII)	CH_2Ph	H
(IX)	H	CO_2Et
(X)	H	CO_2H



	R	X
(XI)	H	H, ψ-Irigenin
(XII)	H	CO_2Et
(XIII)	H	CO_2H

mild alkaline hydrolysis, gave the deoxybenzoin (VI) leading, by catalytic hydrogenolysis, to the deoxybenzoin (V).

The reaction of the deoxybenzoin (V) with ethoxalyl chloride in the presence of pyridine could, on the basis of our earlier experience,[8,12] be expected to yield either one or a mixture of both possible products with the 5,6,7-orientation (IX) or the 5,7,8-orientation (XII) of substituents. Chromatographic examination of the ethoxalylation product indicated that it was a mixture, but it was not possible to separate this mixture easily into its constituents. In these circumstances, the

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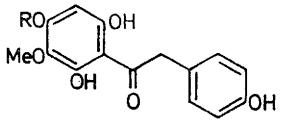
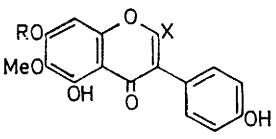
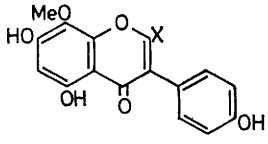
reaction product was assumed to be a mixture of the esters (IX) and (XII), so it was hydrolysed directly to the corresponding carboxylic acids (X) and (XIII), and the mixture was then thermally decarboxylated. The product from the decarboxylation reaction was separated chromatographically yielding two isomeric isoflavones. One of these was identical with irigenin (VII) and the other product was recognised as the isomer (XI) and was named ψ-irigenin.[2]

This successful synthesis of irigenin (VII) encouraged us to re-examine the reaction which was investigated earlier [12a] as a possible route to tectorigenin (XVI).



(XIV) R = H
(XV) R = CH_2Ph



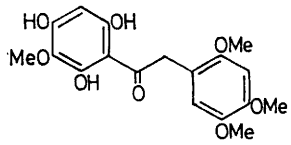


	R	X
(XVI)	H	H, Tectorigenin
(XVII)	CH_2Ph	H
(XVIII)	H	CO_2Et
(XIX)	H	CO_2H

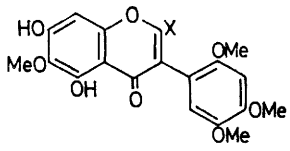
(XX) X = H, ψ-Tectorigenin
(XXI) X = CO_2Et
(XXII) X = CO_2H

It was then found [12a] that reaction of the deoxybenzoin (XIV) with ethoxalyl chloride gave one easily isolable product which was identified as the ester (XXI) because its alkaline hydrolysis gave the carboxylic acid (XXII) which, on thermal decarboxylation, gave an isomer of tectorigenin named ψ-tectorigenin (XX).[2] Reinvestigation of the ethoxalylation of the deoxybenzoin (XIV) shows that the product is in fact a mixture of two esters (XVIII) and (XXI), from which the ester (XXI) is easily isolated by direct crystallisation. After the separation of the ester (XXI), the residue, enriched with respect to the other ester (XVIII), was hydrolysed, thermally decarboxylated, and chromatographically fractionated to give tectorigenin (XVI).

In the ethoxalylation reaction, the formation of two products in the irigenin synthesis [(V) ⟶ (IX) + (XII)] and in the tectorigenin synthesis [(XIV) ⟶ (XVIII) + (XXI)] may be compared with the observation of, apparently, only one product [(XXIII) ⟶ (XXIV)] in the caviunin synthesis.[12b] The ethoxalylation of deoxybenzoins is an irreversible process so that when two isomeric products can be formed, then the product ratio is determined by two alternative kinetically controlled processes. This opinion, as well as the results obtained by others,[13] is not compatible with the rationalisations recently offered [14] of the product ratios which have been observed in ethoxalylation and anhydroacylation reactions of certain deoxybenzoins.

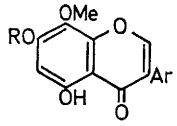


(XXIII)

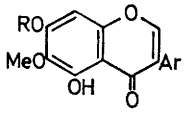


(XXIV) X = CO_2Et
(XXV) X = H, Caviunin

Since this work was completed, there has been considerable interest in the possibility of synthesising natural 5,7-dihydroxy-6-methoxyisoflavones by a base-catalysed rearrangement of the type (XXVI) ⟶ (XXVII). This approach was initiated by the observations of Seshadri and his colleagues [15] on the base-catalysed Wessely–Moser rearrangement of isoflavones and was successfully used for the synthesis of muningin, involving the isomerisation of 4′,8-dibenzyloxy-5-hydroxy-7-methoxyisoflavone.[16]



(XXVI)



(XXVII)

The general features of the base-catalysed isomerisation (XXVI) ⟶ (XXVII) have been explored in detail [17] and with one exception [(XXVI) ⟶ (XXVII) (R = H, Ar = Ph)] it appeared that the isomerisation was restricted to those cases in which R was alkyl, usually methyl or benzyl. By use of appropriate 7-alkoxyisoflavones (XXVI; R = Me or $PhCH_2$) and potassium ethoxide as the basic reagent, tectorigenin [18] (XVI),

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irigenin [19] (VII), and caviunin [20] (XXV) were synthesised. This synthetic route did not lead directly to the natural isoflavones, but subsequently it was found [21] that 5,7-dihydroxy-8-methoxyisoflavones (XXVI; R = H) could be isomerised directly to 5,7-dihydroxy-6-methoxyisoflavones (XXVII; R = H) by use of potassium carbonate as the basic reagent in high boiling point alcohols

The base-catalysed isomerisations [(XXVI) ⟶ (XXVII) (R = H, Me or $PhCH_2$)] take place under equilibration conditions and from these results it may be concluded that 5,6,7-trisubstituted isoflavones (XXVII) are usually the thermodynamically more stable partners in the equilibrium (XXVI) ⇌ (XXVII). The relationship between this opinion and the fact that the reaction of appropriately substituted deoxybenzoins with ethoxalyl chloride can lead to mixtures of 5,6,7- and 5,7,8-isoflavone-2-carboxylic esters supports the view that the product ratio in the ethoxalylation reaction is kinetically controlled.[4] The product ratio will therefore be determined by many factors and it is unlikely that discussions [14] limited to stereochemical and hydrogen-bonding effects are acceptable.

EXPERIMENTAL

Separations by column chromatography were carried out with Hopkins and Williams MFC grade silica. Whatman no. 1 paper was used for identification by paper chromatography and the eluting solvent was the upper layer of a mixture of benzene, acetic acid, formic acid, and water (8 : 2 : 1 : 1 v/v). Preparative chromatographic fractionation was carried out with Whatman no. 3MM thick paper which had been previously water-washed with the same eluting solvent. Paper chromatograms were examined under u.v. illumination and by spraying with ethanolic iron(III) chloride solution (1%).

All evaporations were carried out under diminished pressure. Substances stated to be identical were correlated by m.p. comparison, mixed m.p. determination, and direct comparison by paper chromatography.

3-Hydroxy-4,5-dimethoxybenzoic Acid.—Dimethyl sulphate (144 ml.) was added to a cooled (< 30°), vigorously stirred solution of gallic acid (400 g.) and sodium hydroxide (70 g.) in water (3 l.). During the reaction, a brisk current of nitrogen was passed through the mixture. Further quantities of dimethyl sulphate (4 × 144 ml.) and sodium hydroxide (4 × 70 g.) in water (4 × 240 ml.) were added at 25 min. intervals and after 1 hr. the mixture was acidified and the precipitate collected. The filtrate was saturated with sodium chloride and the additional precipitate was collected. The combined precipitates were dissolved in ethylene dichloride (300 ml.) and dried ($MgSO_4$); then methanol (140 ml.) and concentrated sulphuric acid (16 ml.) were added and the mixture was heated (24 hr.) under reflux. Water was removed azeotropically and concentrated sulphuric acid (2 × 3 ml.) was added at 8 hr. intervals. The cooled mixture was neutralised with solid magnesium carbonate, filtered, and evaporated. The residue was dissolved in ether and shaken, first with saturated aqueous sodium carbonate (1 l.) and then with aqueous sodium hydroxide (2%; 200 ml.). The ethereal solution was extracted with aqueous sodium hydroxide (8%; 500 ml.) and the alkaline extract was heated (50°; 30 min.), acidified, and cooled. Crystallisation of the precipitate from water gave 3-hydroxy-4,5-dimethoxybenzoic acid (82 g.; 18%) as needles, m.p. 190° (lit.,[22] 193—194°).

Methyl 3-Hydroxy-4,5-dimethoxybenzoate.—3-Hydroxy-4,5-dimethoxybenzoic acid (114 g.), methanol (50 ml.), ethylene dichloride (100 ml.), and concentrated sulphuric acid (5 ml.) were heated (24 hr.) under reflux yielding methyl 3-hydroxy-4,5-dimethoxybenzoate (104 g., 85%) as prisms, m.p. 79—81° (lit.,[22] 81—83°) [from benzene–light petroleum (b.p. 60—80°)].

Methyl 3-Benzyloxy-4,5-dimethoxybenzoate.—The preceding ester (139 g.), benzyl bromide (78 ml.), and potassium carbonate (200 g.) in dry acetone (2 l.) were heated (24 hr.) under reflux. Filtration and evaporation gave a residue which was crystallised from light petroleum (b.p. 60—80°) giving methyl 3-benzyloxy-4,5-dimethoxybenzoate (163 g., 82%), m.p. 73° (lit.,[23] 73°) (Found: C, 67·4; H, 6·0. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·0%).

3-Benzyloxy-4,5-dimethoxybenzyl Alcohol (I).—Methyl 3-benzyloxy-4,5-dimethoxybenzoate (100 g.) in warm ether (600 ml.) was added during 20 min. to a stirred solution of lithium aluminium hydride (12·7 g.) in ether (600 ml.) under nitrogen. After 12 hr. at room temperature, water (225 ml.) and then aqueous sulphuric acid (10%; 280 ml.) were cautiously added. The ethereal layer was separated, washed, dried, and evaporated, yielding 3-benzyloxy-4,5-dimethoxybenzyl alcohol (87·2 g., 97%) as a colourless oil. It was characterised as its *3,5-dinitrobenzoate*, m.p. 130° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 59·2; H, 4·5; N, 6·0. $C_{23}H_{20}N_3O_9$ requires C, 59·0; H, 4·3; N, 6·0%).

3-Benzyloxy-4,5-dimethoxybenzyl Chloride (II).—A solution of purified thionyl chloride (22·4 ml.) in chloroform (80 ml.) was added during 20 min. to a solution of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (86·2 g.) in chloroform (250 ml.) and pyridine (25·1 ml.). The mixture was kept at −4 ± 1° for 1 hr., then poured into iced water (600 ml.). The chloroform layer was shaken with aqueous sodium hydrogen carbonate (5%; 500 ml.) and evaporated; the residue was crystallised from light petroleum (b.p. 60—80°; 1200 ml.) giving 3-benzyloxy-4,5-dimethoxybenzyl chloride as prisms, m.p. 69° (lit.,[24] 69—70°) (Found: C, 65·9; H, 6·0; Cl, 12·8. Calc. for $C_{16}H_{17}ClO_3$: C, 65·6; H, 5·9; Cl, 12·1%).

3-Benzyloxy-4,5-dimethoxybenzyl Cyanide (III).—A solution of potassium cyanide (33·5 g.) in water (37 ml.) was added to a solution of the chloride (II) (33·5 g.) in acetone (37 ml.) and the mixture was stirred vigorously for 5 days at 50—55°. After cooling, extraction with ether, and distillation (b.p. 90—100°/10^{-5} mm.), crystallisation from

[19] L. Farkas and J. Várady, *Tetrahedron Letters*, 1960, **20**, 23; *Chem. Ber.*, 1960, **93**, 2685; *Acta Chim. Acad. Sci. Hung.*, 1962, **32**, 103.

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[21] J. Várady, *Tetrahedron Letters*, 1965, 4273, 4277.

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[23] V. Inubushi and K. Fujitani, *J. Pharm. Soc. Japan*, 1958, **78**, 486.

[24] M. Satomi and M. Hasegawa, *Pharm. Bull. Nippon Univ.*, 1965, **7**, 12 (*Chem. Abs.*, 1966, **65**, 13,581).

light petroleum (b.p. 60—80°) gave 3-benzyloxy-4,5-dimethoxybenzyl cyanide (24·1 g., 75%) as rhombs, m.p. 57° (lit.,[24] 55—57°) (Found: C, 71·6; H, 5·8; N, 4·7. Calc. for $C_{17}H_{17}NO_3$: C, 72·1; H, 6·1; N, 4·9%).

3-Hydroxy-4,5-dimethoxybenzyl Cyanide (IV).—Hydrogenation (1 atmos.; 1 hr.) of a solution of 3-benzyloxy-4,5-dimethoxybenzyl cyanide (1 g.) in ethanol (300 ml.) at room temperature over palladium–charcoal (10%; 750 mg.) gave 3-hydroxy-4,5-dimethoxybenzyl cyanide as a colourless oil (560 mg., 82%). It was characterised by reaction with benzoyl chloride and aqueous N-sodium hydroxide yielding a *benzoate* as prisms, m.p. 103° (from ethanol) [Found: C, 68·3; H, 4·7; N, 4·7; OMe, 21·0. $C_{15}H_9NO_2$-$(OMe)_2$ requires C, 68·7; H, 5·1; N, 4·7; OMe, 20·9%].

Iretol (2,4,6-*Trihydroxyanisole*).—In our hands, the yields by the published method [25] were erratic, but the following method gave reproducible results.

Hydrogenation (initial pressure 50—55 lb./cm.^{2}) of 2,4,6-trinitroanisole (10 g.) was carried out in ethanol-free anhydrous ethyl acetate (140 ml.) over freshly prepared Raney nickel (10 g.). Satisfactory results were obtained only if the hydrogenation was rapid (25—30 min.) and was associated with a rise in temperature to about 50°. The catalyst was then removed and the solution was concentrated rapidly (*ca.* 15 ml.) with exclusion of air. After 1 hr. at 0° under nitrogen, the precipitated 2,4,6-triaminoanisole (4·7 g., 74%), m.p. 116° (lit.,[25] 116°), was collected and directly hydrolysed.

2,4,6-Triaminoanisole (14 g.) was heated (4½ days) under reflux with air-free water (200 ml.) and concentrated hydrochloric acid (35 ml.) under nitrogen. The cooled solution was continuously extracted (14 hr.) with ether (500 ml.). The dried ($MgSO_4$) extract was concentrated (*ca.* 10 ml.) and the crystalline iretol (7·2 g., 50%), m.p. 188° (lit.,[25] 187°), was collected.

7-O-Benzylirigenin (VIII).—Irigenin (5·5 g.), benzyl bromide (2 ml.), anhydrous potassium carbonate (20 g.), and acetone (250 ml.) were heated (1 hr.) under reflux, and then the hot solution was filtered. Evaporation of the filtrate and crystallisation of the residue from benzene gave 7-O-*benzylirigenin* (4·0 g., 62%) as pale yellow needles, m.p. 175° (Found: C, 67·0; H, 5·2. $C_{25}H_{22}O_8$ requires C, 66·7; H, 4·9%). It was characterised (acetic anhydride–pyridine) as a *diacetate*, needles, m.p. 182° (Found: C, 65·6; H, 4·8. $C_{29}H_{24}O_{10}$ requires C, 65·2; H, 4·9%).

4,5-Dimethoxy-3-hydroxybenzyl 4-Benzyloxy-2,6-dihydroxy-3-methoxyphenyl Ketone (VI).—A solution of sodium hydroxide (24 g.) in water (150 ml.) was added to 7-*O*-benzylirigenin (3 g.) in ethanol (300 ml.). The mixture was heated (30 min.) under reflux and poured into water (1 l.), and the ethanol was evaporated off. Carbon dioxide was passed through the solution at 0° and the precipitate was collected. Crystallisation from aqueous methanol gave the deoxybenzoin (VI) as a *monohydrate* (1·9 g.; 67%), pale yellow needles, m.p. 134° (Found: C, 62·2; H, 5·6. $C_{24}H_{24}O_8,H_2O$ requires C, 62·8; H, 5·7%).

4,5-Dimethyl-3-hydroxybenzyl 2,4,6-Trihydroxy-3-methoxyphenyl Ketone (V).—(*a*) A mixture of iretol (800 mg.), 3-hydroxy-4,5-dimethoxybenzyl cyanide (1 g.), and anhydrous zinc chloride (1 g.) in ether (80 ml.) was saturated with dry hydrogen chloride during 2 hr. at 0° and the mixture was then kept at 0° for 5 days, after which a heavy red oil had separated. The ethereal layer was removed by decantation and the remaining oil was shaken with anhydrous ether (3 × 75 ml.), dissolved in water (100 ml.), and heated (1 hr.) with nitrogen passing through the solution. The precipitate which separated on cooling was collected; careful crystallisation from ether–methanol (99 : 1) gave 4,5-*dimethoxy-3-hydroxybenzyl* 2,4,6-*trihydroxy-3-methoxyphenyl ketone* (1·2 g., 66%) as colourless needles, m.p. 191° (Found: C, 58·3; H, 4·8. $C_{17}H_{18}O_8$ requires C, 58·3; H, 5·1%).

(*b*) Hydrogenation (1 hr. for the uptake of 1 equiv.) of 4,5-dimethoxy-3-hydroxybenzyl 4-benzyloxy-2,6-dihydroxy-3-methoxyphenyl ketone (100 mg.) in acetic acid (20 ml.) over palladium black (50 mg.) at room temperature and atmospheric pressure gave the deoxybenzoin (V) (55 mg., 64%), m.p. and mixed m.p. 191°, [from ether–methanol (99 : 1)].

Irigenin (VII) *and ψ-Irigenin* (XI).—Ethoxalyl chloride (2·1 ml.) was added with shaking to a cooled (0°) solution of 4,5-dimethoxy-3-hydroxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (1·3 g.) in pyridine (40 ml.). After 2 days at room temperature, the mixture was poured into water and extracted with chloroform. This extract was shaken with dilute hydrochloric acid and with water, dried ($MgSO_4$), and evaporated, yielding a mixture (R_F 0·54 and 0·85 by chromatography on Whatman no. 1 paper) of isomeric 2-ethoxycarbonylisoflavones, (IX), and (XII), as an oil (1·12 g.). This oil was dissolved in acetone (240 ml.) and added to a mixture of 2N-aqueous sodium hydroxide (9 ml.) and water (240 ml.). It was then set aside at room temperature and after 12 hr. the acetone was evaporated off. Acidification followed by extraction with chloroform yielded a mixture of the two isoflavone-2-carboxylic acids, (X) and (XIII), as a gum (890 mg.).

This gum was divided into small portions (*ca.* 20 mg.) and placed in ignition tubes which were heated (295°; 1 min.) until decarboxylation was complete. The residues were extracted with warm ethanol yielding a brown oil (650 mg.) which was chromatographed (silica–chloroform). The main eluate (540 mg.) was then fractionated by chromatography on Whatman no. 3MM thick paper giving two main bands.

One main band (R_F 0·40—0·60) was cut out; elution with ethanol followed by chromatography (silica–chloroform) gave irigenin (106 mg.), m.p. 191°. Recrystallisation from aqueous ethanol gave white needles, m.p. 185—186°, whereas recrystallisation from chloroform gave yellow needles, m.p. 191°. Irigenin obtained by acid hydrolysis of iridin gave two forms, m.p. 185—186° (lit.,[10,11] 185°) (from aqueous ethanol), and m.p. 191° (from chloroform); no depression of m.p. was observed for mixed m.p. of corresponding forms of natural and synthetic irigenin. Natural and synthetic irigenin were both characterised as *irigenin triacetate*, colourless needles, m.p. and mixed m.p. 118° (lit.,[11] 127—128°) (from aqueous ethanol).

The other major band (R_F 0·20—0·35) similarly yielded *ψ-irigenin* (180 mg.) as pale yellow needles, m.p. 159° (from chloroform) [Found: C, 60·3; H, 4·6; OMe, 25·8. $C_{15}H_7O_5(OMe)_3$ requires C, 60·0; H, 4·5; OMe, 25·3%]. It was characterised as *ψ-irigenin triacetate*, colourless needles, m.p. 147° (from aqueous ethanol) [Found: C, 59·1; H, 4·8. $C_{24}H_{22}O_{11}$ requires C, 59·3; H, 4·5%].

7-O-Benzyltectorigenin (XVII).—Tectorigenin (10 g.), benzyl bromide (4 ml.), anhydrous potassium carbonate (60 g.), and acetone (500 ml.) were heated (1 hr.) under reflux with stirring. Filtration and evaporation of the

[25] R. E. Damschroeder and R. Shriner, *J. Amer. Chem. Soc.*, 1937, **59**, 931.

acetone gave a residue yielding 7-O-*benzyltectorigenin* (4·2 g., 32%) as needles, m.p. 199° (from benzene) (lit.,[26] 195—196°) (Found: C, 70·5; H, 4·5. $C_{23}H_{18}O_6$ requires C, 70·7; H, 4·6%). Acidification of the insoluble material and crystallisation of the precipitate gave tectorigenin (4·6 g.).

4-Hydroxybenzyl 4-Benzyloxy-2,6-dihydroxy-3-methoxyphenyl Ketone (XV).—A solution of sodium hydroxide (32 g.) in water (85 ml.) was added to 7-*O*-benzyltectorigenin (5 g.) in ethanol and the mixture was heated (30 min.) under reflux. Water (1 l.) was added, the ethanol was evaporated off, and the solution was then saturated with carbon dioxide. Recrystallisation of the precipitate from aqueous ethanol gave the deoxybenzoin monohydrate (3·3 g.), m.p. 132—135°, which after heating (3 hr.; 110°/0·2 mm.) gave *4-hydroxybenzyl 4-benzyloxy-2,6-dihydroxy-3-methoxyphenyl ketone* (3·15 g., 65%), m.p. 163° (Found: C, 70·0; H, 5·3. $C_{22}H_{20}O_6$ requires C, 69·5; H, 5·2%).

4-Hydroxybenzyl 2,4,6-Trihydroxy-3-methoxyphenyl Ketone (XIV).—(*a*) (with I. Dunstan). A mixture of iretol (1·7 g.), 4-hydroxybenzyl cyanide (1·36 g.), and fused zinc chloride (2 g.) in ether (160 ml.) was cooled (0°) and saturated with hydrogen chloride during 4 hr. After 10 days at room temperature, ether (600 ml.) was added and a solid precipitated. This solid was separated by decantation and washed with ether; water (150 ml.) was added, and the mixture was heated (2 hr.; 100°). The hot solution was filtered and the cooled filtrate yielded *4-hydroxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone* (2·56 g., 81%) as yellow plates, m.p. 228° (from benzene–ethanol) [Found: C, 61·9; H, 5·1; OMe, 10·2. $C_{14}H_{11}O_5$(OMe) requires C, 62·0; H, 4·8; OMe, 10·7%].

(*b*) Hydrogenation (3 hr.; 3 atmos.) of 4-hydroxybenzyl 4-benzyloxy-2,6-dihydroxy-3-methoxyphenyl ketone (3·5 g.) in acetic acid (200 ml.) over palladium–charcoal (1·75 g., 10%) gave, after filtration, removal of the acetic acid, and crystallisation from benzene, 4-hydroxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (2·12 g., 81%), m.p. and mixed m.p. 228°.

Tectorigenin (XVI).—Ethoxalyl chloride (3·8 ml.) was added with shaking to a cooled solution (0°) of 4-hydroxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (880 mg.) in pyridine (15 ml.). After 16 hr. at room temperature the mixture was poured into iced water (100 ml.) and extracted with chloroform. This extract yielded an oil (750 mg.) which by trituration with ether yielded a crystalline precipitate which was collected (fraction A; 325 mg.). Removal of the ether gave fraction B which by paper chromatography was shown to be a mixture (R_F 0·25 and 0·34). The transformation of fraction A into ψ-tectorigenin (XX) is described later.

Fraction B was dissolved in acetone (35 ml.), added to a mixture of aqueous 2N-sodium hydroxide (1·6 ml.) and water (45 ml.), and set aside (12 hr.) at room temperature. The acetone was then evaporated off and the aqueous solution was acidified and extracted with ethyl acetate giving a mixture (200 mg.) of isoflavone-2-carboxylic acids. This mixture was divided among twenty ignition tubes which were heated (280°; 3·5 min.) until decarboxylation was complete. The product (115 mg.) was collected by extraction with ethanol and fractionated by chromatography on Whatman no. 3MM paper. Elution of the major band with ethanol followed by crystallisation from benzene–ethanol gave tectorigenin (65 mg.) as colourless needles, m.p. 228—230° (from benzene–ethanol), identical with material m.p. 228—230° (lit.,[27] 230°), obtained by acid hydrolysis of tectoridin. The synthetic tectorigenin was characterised as tectorigenin triacetate, m.p. and mixed m.p. 194° (lit.,[27] 190°).

2-Ethoxycarbonyl-4′,5,7-trihydroxy-8-methoxyisoflavone (XXI) (with I. Dunstan).—Crystallisation of fraction A from ethanol gave *2-ethoxycarbonyl-4′,5,7-trihydroxy-8-methoxyisoflavone* as yellow needles, m.p. 222° (from ethanol) (Found: C, 61·3; H, 4·6. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%). It was characterised as *4′,5,7-triacetoxy-2-ethoxycarbonyl-8-methoxyisoflavone*, needles, m.p. 172° (from ethanol) (Found: C, 60·3; H, 4·3. $C_{25}H_{22}O_{11}$ requires C, 60·2; H, 4·4%).

ψ-Tectorigenin (XX) (with I. Dunstan).—Aqueous 2N-sodium hydroxide (2·07 ml.) and water (50 ml.) were added to a solution of 2-ethoxycarbonyl-4′,5,7-trihydroxy-8-methoxyisoflavone (370 mg.) in acetone (40 ml.), and the mixture was set aside (12 hr.) at room temperature. Evaporation of the acetone and acidification precipitated 4′,5,7-trihydroxy-8-methoxyisoflavone-2-carboxylic acid (250 mg.; 73%) as yellow microcrystals, m.p. 290—292° (decomp.).

This carboxylic acid (120 mg.) was decarboxylated by heating 30 mg. portions at 285° until decarboxylation was complete (3·5 min.). Crystallisation of the residue from aqueous ethanol gave *ψ-tectorigenin* (99 mg.; 94%) as pale yellow needles, m.p. 240° (lit.,[28] 241—242°) (Found: C, 63·2; H, 4·4. Calc. for $C_{16}H_{12}O_6$: C, 63·9; H, 4·0%). It was characterised as *4′,5,7-triacetoxy-8-methoxyisoflavone*, needles, m.p. 153° (lit.,[28] 167°) (from aqueous ethanol) [Found: C, 61·5; H, 3·9; OMe, 7·0. Calc. for $C_{21}H_{15}O_8$(OMe): C, 62·0; H, 4·3; OMe, 7·3%].

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