A New General Synthesis of Hydroxy- and Methoxy-isoflavanones

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A new general synthesis of hydroxy- (**5e—h**) and methoxy- (**5a—d**) isoflavanones has been accomplished in overall yields of 47—73% from the corresponding 2-hydroxydeoxybenzoins (**1a—h**). The first step involves reaction with appropriate amounts of ethoxymethyl chloride in the presence of dry K_2CO_3 and acetone, which gives the corresponding α-hydroxymethyldeoxybenzoins (**4a—d**) and (**4i—l**). The explanation for the formation of unexpected alcohols has been provided on the basis of an elimination–addition mechanism. Subsequent refluxing with 4% aqueous ethanolic Na_2CO_3 afforded protected isoflavanones (**5a—d**) and (**5i—l**) respectively. Final removal of the ethoxymethyl groups of (**5i—l**) with 10% MeOH–HCl afforded the corresponding hydroxyisoflavanones (**5e—h**).

Nearly 40 isoflavanones are known to occur in nature;[1a] these may contain hydroxy, methoxy, methylenedioxy, *C*-methyl, and *C*-prenyl† groups, and condensed 2,2-dimethylpyrano- or furano-units. Some of them have already been synthesized but in very poor yields.[1b] Isoflavanones are also needed for the synthesis of more complex natural compounds such as pterocarpenoids and rotenoids.[1a] For the synthesis of isoflavanones having protected hydroxy groups (*e.g.* methoxy), the following methods have been reported: (*i*) reduction of the readily available alkoxyisoflavones using a noble metal catalyst or complex metal hydrides;[2–5] (*ii*) hydroboration of 3-phenylcoumarin or 4-hydroxy-3-phenylcoumarin followed by oxidation with chromic acid;[6] (*iii*) Heck arylation of 4-acyloxy-2*H*-chromenes with aryl mercury(II) compounds using palladium acetate as a catalyst;[7] (*iv*) reaction of 2-hydroxy alkoxydeoxybenzoins with methylene iodide;[8a] and (*v*) Mannich reaction of 2-hydroxyalkoxydeoxybenzoins with paraformaldehyde in boiling methanol in the presence of secondary amines such as piperidine or dimethylamine.[9] Some of these methods particularly (*i*) and (*v*), are promising and the former has often been used in the literature. For the preparation of hydroxyisoflavanones, some of the above methods such as (*i*) and (*iv*) are used after protecting the hydroxy groups by easily removable protecting groups such as methoxymethyl,[8b] or tetrahydropyran.[10] However, the overall yield from the starting deoxybenzoin is highly discouraging. This lack of a good synthetic method led Dewick [1b] to write that synthetic routes to isoflavanones are in general not efficient, and new approaches are thus welcome.

A new general method of synthesizing methoxy-[11] as well as hydroxy-[12] isoflavanones has now been developed which makes isoflavanones available in extremely good yields from the corresponding *o*-hydroxydeoxybenzoins. In the projected synthesis of methoxyisoflavanones, it was proposed that an *o*-hydroxydeoxybenzoin should be allowed to react with ethoxymethyl chloride‡ in the presence of dry potassium carbonate and dry acetone so that the ethoxymethyl group would be introduced at the bridge methylene group. This alkyl chloride was preferred over methoxymethyl chloride because of its greater stability and lower volatility. However, the product after aqueous work-up was not the expected α-ethoxymethyl derivative but the α-hydroxymethyl derivative. Thus, benzyl 2-hydroxy-4,6-dimethoxyphenyl ketone (**1a**) on ethoxymethylation gave 2-hydroxy-4,6-dimethoxyphenyl α-hydroxymethylbenzyl ketone (**4a**) in *ca.* 90% yield. Its structure was first indicated by its positive ferric reaction, analysis, and finally by the ^{1}H n.m.r. spectrum which showed three double doublets of an AMX system at δ 3.79, 4.20, and 5.04 (J_{AM} 11.2 J_{MX} 8.0, and J_{AX} 4.8 Hz) and a hydroxy proton exchangeable with D_2O. Further, the ^{13}C n.m.r. spectrum showed the presence of a triplet at δ 65.61 and a doublet at δ 59.80 for the β-CH_2OH and α-CH groups respectively. Chemical evidence for this structure was obtained by the treatment of (**4a**) with acetic acid, which afforded α-acetoxymethylbenzyl 2-hydroxy-4,6-dimethoxyphenyl ketone (**6a**) as the major product. This was identified by its positive ferric reaction, elemental analysis, and its ^{1}H n.m.r. spectrum (see the Experimental section).

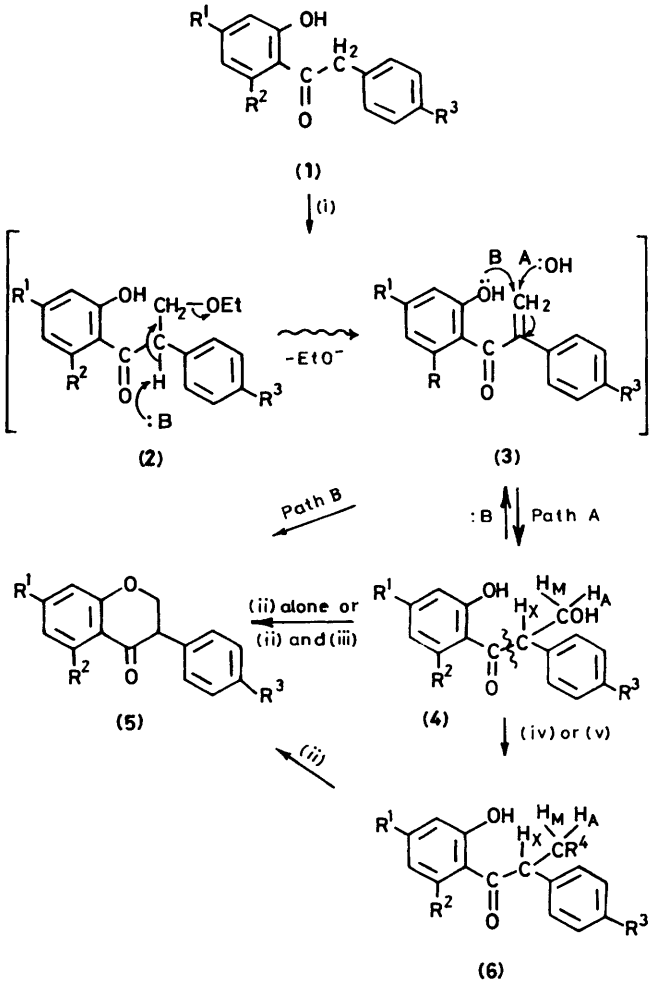
A parallel series of experiments with 2-hydroxy-4-methoxy- (**1b**), 2-hydroxy-4,4′-dimethoxy-(**1c**), and 2-hydroxy-4,4′,6-trimethoxy- (**1d**) deoxybenzoins yielded similar α-hydroxymethyl derivatives [(**4b—d**) respectively]. In all these cases, similar ^{1}H n.m.r. spectra were obtained to that of (**1a**). Further, (**1b**) could also be converted into the corresponding α-acetoxymethyl derivative (**6b**) by solvolysis with acetic acid, and into the α-chloromethyl derivative (**6c**) by treatment with 60% ethanolic HCl. Hence, ethoxymethylation of 2-hydroxydeoxybenzoins may be considered to yield consistently α-hydroxymethyl derivatives.

The formation of α-hydroxymethyl derivatives (**4a—d**) in yields of 85—92% may possibly be explained as follows. In the first step, the α-ethoxymethylated product (**2**) may be formed. But, this being a β-ethoxy ketonic compound, undergoes facile elimination of ethoxide ion in the presence of a base to give an α,β-unsaturated ketone or an α-methylene derivative (**3**). This is followed by nucleophilic addition of hydroxide ion to give the product (**4**) (see path A in the Scheme).

The above α-hydroxymethyl deoxybenzoins (**4a—d**) have been converted into the corresponding methoxyisoflavanones (**5a—d**) by refluxing with 4% aqueous ethanolic sodium carbonate in 78—80% yields. The products (**5a—d**) were characterized by their ^{1}H n.m.r. spectra and by m.p.s which were similar to those reported earlier. This cyclization also possibly follows a similar elimination–addition mechanism as outlined above, but involves an intramolecular addition *via* path B. The overall yields of isoflavanones obtained from *o*-hydroxydeoxybenzoins were found to be 68—73%. It was also found that the above synthesis of isoflavanones could be achieved from 2-hydroxydeoxybenzoins in a one-pot reaction without isolating the intermediates (**4**) but with lower yields, emphasizing that the purification of the intermediate is very necessary. The variety of isoflavanones synthesized shows the synthesis to be efficient for differently substituted compounds. Further, it was observed that treatment of either α-acetoxymethyl (**6a**) and (**6b**) or α-chloromethyl- (**6c**) derivatives with aqueous base also gave the corresponding isoflavanones.

† prenyl = $Me_2CH{=}CHCH_2-$

§ **CAUTION** Homologous to methoxymethyl chloride, the reagent may be carcinogenic.



(1)—(5)

	R¹	R²	R³		R¹	R²	R³
a;	OMe	OMe	H	**g**;	OH	OH	H
b;	OMe	H	H	**h**;	OH	OH	OMe
c;	OMe	H	OMe	**i**;	OCH_2OEt	H	H
d;	OMe	OMe	OMe	**j**;	OCH_2OEt	H	OMe
e;	OH	H	H	**k**;	OCH_2OEt	OCH_2OEt	H
f;	OH	H	OMe	**l**;	OCH_2OEt	OCH_2OEt	OMe

(6)

	R¹	R²	R³	R⁴
a;	OMe	OMe	H	OAc
b;	OMe	H	H	OAc
c;	OMe	H	H	Cl

Scheme. *Reagents:* (i), $ClCH_2OEt$–dry Me_2CO–dry K_2CO_3; (ii), 4% Aqueous ethanolic Na_2CO_3; (iii) 10% methanolic HCl; (iv) glacial acetic acid; (v), 60% ethanolic HCl

For the synthesis of polyhydroxyisoflavanones, it was thought that all the hydroxy groups except the one hydrogen bonded in the starting polyhydroxydeoxybenzoin should be protected by ethoxymethylation prior to performing the two reactions discussed above. In the first experiment, 2,4-dihydroxydeoxybenzoin (**1e**) was treated with one mol equiv. of ethoxymethyl chloride in the presence of dry potassium carbonate and dry acetone at room temperature for 20 min. The resulting product considered to be benzyl 4-ethoxymethoxy-2-hydroxyphenyl ketone (**1i**) was not isolated but treated with a

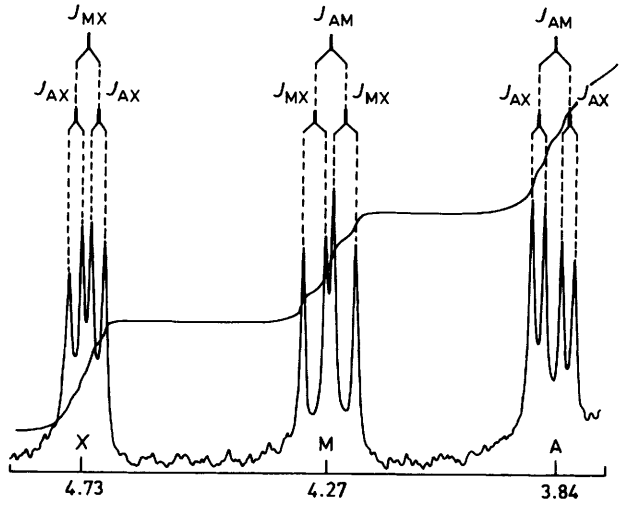


Figure 1. ^1H N.m.r. spectrum (200 MHz; $CDCl_3$) of the alcohol (**4i**)

further equivalent of ethoxymethyl chloride. From this procedure the corresponding α-hydroxymethylbenzyl 4-ethoxymethoxy-2-hydroxyphenyl ketone (**4i**) was obtained in nearly 85% yield. The product showed a positive ferric reaction and the following characteristic ^1H n.m.r. spectrum: an AMX pattern of three double doublets in the range δ 3.84—4.73 (J_{AM} 11.2, J_{MX} 8 and J_{AX} 4.8 Hz) and ethoxymethoxy signals, (the Me group as a triplet at δ 1.18, the methylene as a quartet at δ 3.67 and the methylenedioxy group as a singlet at δ 5.19). Similarly, the ^{13}C n.m.r. spectrum showed a doublet and a triplet resonating at δ 55.79 and 64.82 due to α-CH and β-CH_2OH groups respectively. Finally, the mass spectrum showed a molecular ion at *m/z* 316, ($M^+ - H_2O$) ion at *m/z* 298 and a base peak at *m/z* 195 due to fragmentation as shown in formula (**4**).

A parallel series of reactions with three other polyhydroxydeoxybenzoins *viz.* 2,4-dihydroxyphenyl 4-methoxybenzyl ketone (**1f**), 2,4,6-trihydroxyphenyl benzyl ketone (**1g**) and 2,4,6-trihydroxyphenyl 4-methoxybenzyl ketone (**1h**) were carried out. In the first case (**1f**), initially the ketone was stirred with 1 mol equiv. of ethoxymethoxy chloride as in (**1e**) but the other ketones (**1g**) and (**1h**) were stirred with 2.2. mol equiv. of ethoxymethyl chloride at room temperature for nearly 45 min. However, in the next step the same 1.1 mol equiv. of ethoxymethyl chloride was added in all the cases and the mixture was heated at 60—70 °C. The product in each case was characterised as the ethoxymethylated α-hydroxymethyl derivatives (**4j**—l) in 88—91% yield.

Cyclization of these carbinols (**4i**—**l**) separately with 4% aqueous ethanolic sodium carbonate afforded the corresponding ethoxymethoxyisoflavanones (**5i**—**l**) respectively in 60—72% yields. Each of these isoflavanones was characterized by its spectral data particularly the ^1H n.m.r. spectrum which showed signals due to the ethoxymethoxy group and an ABX pattern as a 2H doublet at δ 4.50—4.60 (*J* 6 Hz) and a distorted 1H triplet at δ 3.80—3.87. The yields in these steps are only slightly lower than in the cases of the methoxyisoflavanones. Final removal of the ethoxymethyl group was accomplished with 10% methanolic HCl (7—10 min) which afforded the corresponding hydroxyisoflavanones (**5e**—**h**) in 92—93% yields. Thus, 7-hydroxy- (**5e**), 7-hydroxy-4′-methoxy- (**5f**), 5,7-dihydroxy- (**5g**), and 5,7-dihydroxy-4′-methoxy- (**5h**) isoflavanones were synthesized in overall yields of 47, 56, 57, and 59% respectively, starting from the corresponding deoxybenzoin (**1e**—**h**) (error limit ±0.5%). The products were found to be identical with those described in literature. Again, the one-pot reaction

showed that the four steps when combined together resulted in lower overall yields. On the other hand, if purification is achieved at the carbinol stage, the other two steps of cyclisation and deprotection can be combined without adversely affecting the yield.

Experimental

All m.p.s reported are uncorrected. Light petroleum used had a boiling range of 60—80 °C; ether refers to diethyl ether and ethoxymethyl chloride was always freshly distilled before the reaction; silica gel was used for column chromatography; all products were routinely checked for homogeneity by t.l.c. on silica gel G plates. Spots were detected by spraying with dilute H_2SO_4 and heating at 110 °C for 5—10 min; solvent systems for t.l.c. were (*i*) benzene–ethyl acetate (10:1) and (*ii*) benzene–ethyl acetate (4:1); i.r. spectra were recorded using KBr discs either on a Perkin-Elmer IR 599-B or on Shimadzu 435 spectrophotometer; u.v. data were recorded on Perkin-Elmer model 554 or Shimadzu 260 spectrophotometer in methanol solution. All ^1H n.m.r. spectra were recorded in $CDCl_3$ with $SiMe_4$ as an internal standard either on an R-32 (90 MHz) Perkin-Elmer spectrometer or a JNM FX 200 (200 MHz) Jeol fourier transform; proton decoupling experiments were performed with a computer-controlled homonuclear decoupling accessory to determine the *J* values in the ketones (**6**) and alcohols (**4**); all ^{13}C n.m.r. spectra were also recorded on the latter machine; all chemical shifts are expressed in δ (p.p.m.) and *J* values in Hz.

α-Hydroxymethylbenzyl 2-Hydroxy-4,6-dimethoxyphenyl Ketone (**4a**).—A solution of benzyl 2-hydroxy-4,6-dimethoxyphenyl ketone[13,14] (**1a**) (2.72 g, 10 mmol) in dry acetone (200 ml) and anhydrous potassium carbonate (6.9 g, 50 mmol) was treated with a solution of ethoxymethyl chloride[15] (1.45 ml, 11 mmol) in dry acetone (15 ml). The resulting mixture was refluxed at 60—70 °C for 2.5 after which period t.l.c. showed full conversion into a new ferric positive product. The reaction mixture was filtered whilst hot and the filtrate concentrated at room temperature. The residue when treated with crushed ice gave a solid which crystallised from benzene–light petroleum to give the alcohol (**4a**) as a white crystalline solid (2.7 g, 90%), m.p. 119—120 °C; R_F [solvent (*ii*)] 0.44; green Fe^{III} reaction (Found: C, 67.9; H, 6.1. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%); $\nu_{max.}$(KBr) 3 100—3 700 and 1 640 cm^{-1}; $\lambda_{max.}$ 283 (log ε 4.34), 226sh (4.32), and 207 nm (4.49); δ_H (90 MHz) 2.35—2.60 (1 H, s, exchangeable with D_2O, OH), 3.62, 3.79 (7 H, 2s, 2 × OMe merged with dd, H_A), 4.20 (1 H, dd, J_{AM} 11.20, J_{MX} 8.0, H_M), 5.04 (1 H, dd, J_{AX} 4.8 and J_{MX} 8.0, H_X), 5.77 (1 H, d, *J* 2.0, 3-H), 6.04 (1 H, d, *J* 2.0, 5-H), 7.23 (5 H, s, Ph), and 13.80 (1 H, s, chelated OH); δ_C 55.29, 55.39 (2 q, 2 × OMe), 59.80 (d, α-C), 65.61 (t, β-C), 91.07 (d, C-3), 93.88 (d, C-5), 94.01 (s, C-1), 127.4 (d, C-4′), 128.59 (d, C-2′, C-3′, C-5′, C-6′), 137.31 (s, C-1′), 162.60 (s, C-2), 166.80 (s, C-6), 168.70 (s, C-4), and 205.1 (s, CO).

α-Acetoxymethylbenzyl 2-Hydroxy-4,6-dimethoxyphenyl Ketone (**6a**).—Compound (**4a**) (1 g) was refluxed with acetic acid (10 ml) for 8 h, after which it was cooled and poured onto crushed ice. The solid was collected and purified by column chromatography using light petroleum–benzene (5:1) as the eluant. A solid was obtained which crystallized from methanol to give the *ketone* (**6a**) as a white crystalline solid (0.78 g, 68%), m.p. 94—95 °C; R_F [solvent (*i*)] 0.69; green Fe^{III} reaction (Found: C, 66.5; H, 6.0. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.9%); $\nu_{max.}$ 3 100—3 600 and 1 730 cm^{-1}; $\lambda_{max.}$ 316 (log ε 4.31), 276 (4.90), and 220 nm (4.43); δ_H (90 MHz), 2.04 (3 H, s, OAc), 3.79 (6 H, 2s, 2 × OMe), 4.32 (1 H, dd, J_{AX} 4.8 and J_{AM} 11.2, H_A), 4.78 (1 H, distorted dd, J_{MX} 8.8 and J_{AM} 11.2, H_M), 5.23 (1 H, dd, J_{AX} 4.8 and J_{MX} 8.8, H_X), 5.82 (1 H, d, *J* 2, 5-H), 6.07 (1 H, d, *J* 2, 3-H), 7.29 (5 H, s, Ph), and 13.90 (1 H, s, chelated OH).

5,7-*Dimethoxyisoflavanone* (**5a**).—*Method* 1. The ketone (**4a**) (2.7 g) in ethanol (25 ml) was refluxed with 4% aqueous Na_2CO_3 (25 ml) for 40 min. The reaction mixture was concentrated under reduced pressure and poured onto crushed ice. Neutralization with cold dilute HCl, gave a solid which crystallized first from methanol and then from a light petroleum–benzene mixture to afford (**5a**) as colourless crystals (2.0 g, 78%), m.p. 150—151 °C (lit.,[3] 151 °C); R_F [solvent (*ii*)] 0.46; $\nu_{max.}$ 1 665 cm^{-1}; $\lambda_{max.}$ 281 (log ε 4.29), 230 (4.30) and 208 nm (4.47); δ_H (90 MHz) 3.85—3.91 (7 H, distorted t, 3-H, and 1s, 2 × OMe), 4.65 (2 H, *J* 6, 2-H), 6.11 (2 H, d, *J* 2 Hz, 6-H and 8-H), and 7.30 (5 H, s, Ph).

Method 2. The ketone (**6a**) also cyclized with 4% ethanolic Na_2CO_3 in 20 min to give 5,7-dimethoxyisoflavanone in 80% yield.

2-*Hydroxy-4-methoxyphenyl α-Hydroxymethylbenzyl Ketone* (**4b**).—A solution of benzyl 2-hydroxy-4-methoxyphenyl ketone[16] (**1b**) (2.42 g, 10 mmol) in dry acetone (200 ml) was heated with anhydrous K_2CO_3 (6.9 g, 50 mmol) and a solution of ethoxymethyl chloride (1.45 ml, 11 mmol) in dry acetone (15 ml) for 2.5 h at 60—70 °C. The oily product was extracted with ether and the residue after evaporation at room temperature was subjected to column chromatography. The column was first eluted with light petroleum to remove impurities and then with benzene to give a viscous oil which crystallised from benzene–light petroleum to afford the *alcohol* (**4b**) as a white solid (2.3 g, 84%), m.p. 64—66 °C; R_F [solvent (*i*)] 0.32; green Fe^{III} reaction (Found: C, 70.5; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%); $\nu_{max.}$ 3 000—3 600 and 1 620 cm^{-1}; $\lambda_{max.}$ 312 (log ε 4.60), 272 (4.18), 224sh (4.10), and 216 nm (4.25); δ_H (90 MHz) 2.82 (1 H, s, exchangeable with D_2O, OH), 3.62 (3 H, s, OMe), 3.74 (1 H, dd, J_{AX} 4.8, J_{AM} 11.20, H_A), 4.20 (1 H, dd, J_{AM} 11.20, J_{MX} 8.0, H_M), 4.62 (1 H, dd, J_{AX} 4.8, J_{MX} 8, H_X), 6.17 (1 H, dd, *J* 9.5 and 2, 5-H), 6.22 (1 H, d, *J* 2, 3-H), 7.14 (5 H, s, Ph), 7.50 (1 H, d, *J* 9.5, 6-H), and 12.70 (1 H, s, chelated OH).

α-Acetoxymethylbenzyl 2-Hydroxy-4-methoxyphenyl Ketone (**6b**).—The ketone (**4b**) (1.5 g) was refluxed with acetic acid (15 ml) for 18 h, and the product purified by column chromatography. Crystallization from methanol gave the *ketone* (**6b**) as shining white needles (1.1 g, 64%), m.p. 109—110 °C; R_F [solvent (*i*)] 0.64; green Fe^{III} reaction (Found: C, 68.6; H, 6.0. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.8%); $\nu_{max.}$ 3 000—3 600, 1 715, and 1 615; $\lambda_{max.}$ 316 (log ε 4.06), 282 (4.30), 230sh (4.24) and 219 nm (4.35); δ_H (200 MHz) 2.01 (3 H, s, OAc), 3.75 (3 H, s, OMe), 4.35 (1 H, dd, J_{AX} 4.8, J_{AM} 11.20, H_A), 4.75 (1 H, distorted dd, J_{MX} 8.8, J_{AM} 11.20, H_M), 4.93 (1 H, dd, J_{AX} 4.8, J_{MX} 8.8, H_X), 6.32 (1 H, dd, *J* 2 and 9.5, 5-H), 6.37 (1 H, d, *J* 2, 3-H), 7.30 (5 H, s, Ph), 7.62 (1 H, d, *J* 9.5, 6-H), and 12.35 (1 H, s, chelated OH).

α-Chloromethylbenzyl 2-Hydroxy-4-methoxyphenyl Ketone (**6c**).—The ketone (**4b**) (1 g) was dissolved in 60% ethanolic hydrochloric acid (12.5 ml) and the solution was refluxed for 8 h. The product was crystallized twice from methanol to give the *ketone* (**6c**) as a white solid (0.75 g, 70%), m.p. 93—94 °C; R_F [solvent (*ii*)] 0.66; green Fe^{III} reaction (Found: C, 65.9; H, 5.3; Cl, 12.1. $C_{16}H_{15}ClO_3$ requires C, 66.1; H, 5.2; Cl, 12.2%); $\nu_{max.}$ 3 200—3 600 and 1 610 cm^{-1}; $\lambda_{max.}$ 317 (log ε 4.02), 273 (4.28), 227sh (4.18), and 217 nm (4.39); δ_H (90 MHz) 3.60—3.80 (4 H, dd, H_A merged with s, OMe), 4.38 (1 H, distorted dd, J_{AM} 11.20, J_{MX} 8.8, H_M), 4.84 (1 H, dd, J_{AX} 4.8, J_{MX} 8.8, H_X), 6.38 (1 H, dd, *J* 9.5 and 2-H and 5-H), 6.42 (1 H, d, *J* 2, 3-H), 7.28 (5 H, s, Ph), 7.64 (1 H, d, *J* 9.5, 6-H), and 12.75 (1 H, s, chelated OH).

7-Methoxyisoflavanone (**5b**).—*Method* 1. A solution of the ketone (**4b**) (2.3 g) in ethanol (25 ml) was refluxed with 4% aqueous Na_2CO_3 (25 ml) for 3.5 h. The product was crystallized twice from methanol to give (**5b**) (1.7 g, 79%) as a colourless solid, m.p. 91—92 °C (lit.,[3] 90—91 °C); R_F [solvent (*ii*)] 0.67 (Found: C, 75.3; H, 5.2. Calc. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6%); $\nu_{max.}$(KBr) 1 680, 1 610, and 1 575 cm^{-1}; $\lambda_{max.}$ 320 (log ε 4.05), 282 (4.29), 240 (4.21) and 232sh nm (4.17); δ_H (90 MHz) 3.77—3.85 (4 H, s, OMe merged with a t, 3-H), 4.57 (2 H, d, *J* 6, 2-H), 6.32 (1 H, d, *J* 2.5, 8-H), 3.52 (1 H, dd, *J* 2.5 and 9.5, 6-H), 7.17 (5 H, s, Ph), and 7.79 (1 H, d, *J* 9.5, 5-H).

Method 2. The ketones (**6b**) and (**6c**) separately also cyclized to (**5b**) with 4% aqueous Na_2CO_3 and ethanol in 1 h and 45 min respectively, and in 72 and 75% yield respectively.

2-Hydroxy-4-methoxyphenyl α-Hydroxymethyl-4-methoxybenzyl Ketone (**4c**).—A solution of the ketone[17] (**1c**) (2.75 g, 10 mmol) in dry acetone (200 ml) and anhydrous potassium carbonate (6.9 g, 50 mmol) was refluxed with a solution of ethoxymethyl chloride (1.45 ml, 11 mmol) in dry acetone (15 ml) for 50 min. The oily product was purified by column chromatography when to give the alcohol (**4c**) as a colourless viscous oil (2.8 g, 92%), R_F [solvent (*ii*)] 0.37; $\nu_{max.}$ 3 020—3 600, 1 630 cm^{-1}; $\lambda_{max.}$ 312, 272, 228sh, and 220 nm; δ_H (90 MHz) 1.92—2.20 (1 H, s, exchangeable with D_2O, OH), 3.70—3.87 (7 H, two s, 2 × OMe merged with dd, H_A), 4.20 (1 H, dd, J_{AM} 11.20 and J_{MX} 8, H_M), 4.64 (1 H, dd, J_{MX} 8 and J_{AX} 4.8, H_X), 6.27 (1 H, dd, *J* 9.5 and 2, 5-H), 6.34 (1 H, d, *J* 2 Hz, 3-H), 6.82 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.16 (2 H, d, *J* 9.5, 2′-H and 6′-H), 7.59 (1 H, d, *J* 9.5, 6-H), and 12.75 (1 H, s, chelated OH).

4′,7-Dimethoxyisoflavanone (**5c**).—The ketone (**4c**) (2.8 g) was refluxed with 4% aqueous Na_2CO_3 (25 ml) and ethanol (25 ml) for 2.25 h to give a product which crystallized from benzene–light petroleum to afford (**5c**) as colourless crystals (1.95 g, 74%), m.p. 134—135 °C (lit.,[2,9] m.p. 128—129 °C, 134—135 °C); R_F [solvent (*ii*)] 0.48 (Found: C, 71.6; H, 5.8. Calc. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7%); $\nu_{max.}$(KBr) 1 675 cm^{-1}; $\lambda_{max.}$ 310 (log ε 4.16), 226 (4.46) and 222 nm (4.57); δ_H (90 MHz) 3.77—3.94 (7 H, distorted t, 3-H and s, 2 × OMe), 4.61 (2 H, d, *J* 6, 2-H), 6.49 (1 H, dd, *J* 2, 9.5, 6-H), 6.59 (1 H, d, *J* 2, 8-H) 6.95 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.20 (2 H, d, *J* 9.5, 2′-H and 6′-H), and 7.89 (1 H, d, *J* 9.5, 5-H).

2-Hydroxy-4,6-dimethoxyphenyl α-Hydroxymethyl-4-methoxybenzyl Ketone (**4d**).—A solution of the ketone[13] (**1d**) (3.02 g, 10 mmol) in dry acetone (200 ml) was refluxed with anhydrous potassium carbonate (6.9 g, 50 mmol) and ethoxymethyl chloride (1.45 ml, 11 mmol) dissolved in acetone (15 ml). The product was purified by passage through a small column of silica gel and was crystallized from benzene–light petroleum to give the alcohol (**4d**) as white crystals (3 g, 90%), m.p. 124—125 °C R_F [solvent (*ii*)] 0.41; green Fe^{III} reaction (Found: C, 65.4; H, 6.4. $C_{18}H_{20}O_6$ requires C, 65.1; H, 6.1%); $\nu_{max.}$ 3 200—3 700 and 1 630 cm^{-1}; $\lambda_{max.}$ 292 (log ε 4.29), 228 (4.39), and 220 nm (4.320); δ_H (200 MHz) 2.43 (1 H, s, exchangeable with D_2O, OH), 3.62—3.90 (10 H, dd, H_A merged with 3 s, 3 × OMe), 4.18 (1 H, dd, J_{MX} 8.0 and J_{AM} 11.20, H_M), 4.96 (1 H, dd, J_{MX} 8 and J_{AX} 4.8, H_X), 5.68 (1 H, d, *J* 2, 6-H), 6.02 (1 H, d, *J* 2, 8-H), 6.82 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.16 (2 H, d, *J* 9.5, 2′-H and 6′-H), and 13.98 (1H, s, chelated OH.)

4′,5,7-Trimethoxyisoflavanone (**5d**).—A solution of the ketone (**4d**) (2.6 g) in 4% aqueous Na_2CO_3 (25 ml) and ethanol (25 ml) was refluxed for 20 min and the product was crystallized from benzene–light petroleum to give (**5d**) as shining white crystals (2.2 g, 75%), m.p. 156—157 °C (lit.,[2] m.p. 156—157 °C) (Found: C, 69.2; H, 6.0. Calc. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8%); $\nu_{max.}$ 1 673 cm^{-1}; $\lambda_{max.}$ 271 (log ε 4.49) and 223 nm (4.60); δ_H (90 MHz) 3.64 (3 H, s, OMe), 3.72 (7 H, t, 3-H merged with two s, 2 × OMe), 4.47 (2 H, d, *J* 6, 2-H), 5.96 (2 H, 2d, 6-H and 8-H), 6.72 (2 H, d, *J* 9.5, 3′-H and 5′-H), and 7.99 (2 H, d, *J* 9.5, 2′-H and 6′-H).

2-Hydroxy-4-ethoxymethoxyphenyl α-Hydroxymethylbenzyl Ketone (**4i**).—To a solution of the ketone[16] (**1e**) (2.28 g, 10 mmol) in dry acetone (200 ml) and anhydrous potassium carbonate (6.9 g, 50 mmol) was added a solution of ethoxymethyl chloride (1.32 ml, 10 mmol) in dry acetone (15 ml). The resulting mixture was stirred for 20 min after which time t.l.c. showed complete conversion into a product assumed to be benzyl 2-hydroxy-4-ethoxymethoxyphenyl ketone (**1i**). Further ethoxymethyl chloride (1.45 ml, 11 mmol) was added to the above reaction mixture and the solution was warmed to 40—50 °C for 10—15 min and then to 60—70 °C for 1.5 h when t.l.c. showed complete conversion into another product. This was worked up as described for (**4a**). The product was crystallized from benzene–light petroleum to give the alcohol (**4i**) as a white crystalline solid (2.70 g, 85%), m.p. 90—91 °C; R_F [solvent (*ii*)] 0.41; green Fe^{III} reaction (Found: C, 68.0; H, 6.6. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4%); $\nu_{max.}$ 3 000—3 400 and 1 615 cm^{-1}; $\lambda_{max.}$ 308 (log ε 4.05), 264 (4.34), 221 (4.28), and 212 nm (4.33); δ_H (200 MHz) 1.18 (3 H, t, OCH_2Me), 2.27 (1 H, br s, exchangeable with D_2O, OH), 3.67 (2 H, q, OCH_2Me), 3.84 (1 H, dd, J_{AM} 11.2, J_{AX} 4.8, H_A), 4.27 (1 H, dd, J_{MX} 8.0 and J_{AM} 11.2, H_M), 4.73 (1 H, dd, J_{AX} 4.8 and J_{MX} 8.0, H_X), 5.19 (2 H, s, OCH_2O), 6.39 (1 H, d, *J* 9.5 and 2, 5-H), 6.56 (1 H, d, *J* 2, 3-H), 7.29 (5 H, s, Ph), 7.61 (1 H, d, *J* 9.5, 6-H) and 12.60 (1 H, s, chelated OH); δ_C (50 MHz) 14.99 (q, Me), 55.79 (d, α-C), 64.82 (t, β-C and OCH_2Me), 92.76 (t, OCH_2O), 103.89 (d, C-3), 108.54 (d, C-5), 114.02 (s, C-1), 127.73 (d, C-4′), 128.22 (d, C-3′, C-5′), 129.25 (d, C-2′, C-6′), 132.38 (d, C-6), 136.55 (C-1′), 163.94 (C-2), 165.65 (s, C-4), and 203.50 (s, CO); *m/z* 316 (10.5, M^+), 298 (15.9, $M^+ - H_2O$) and 195 (100, $M^+ - PhCHCH_2OH$).

7-Ethoxymethoxyisoflavanone (**5i**).—The above ketone (**4i**) (2.7 g) was refluxed with ethanol (20 ml) and 4% aqueous Na_2CO_3 (20 ml) for 2.5 h. The viscous oily product was purified by column chromatography to give a solid which crystallized from benzene–light petroleum to afford the isoflavanone (**5i**) (1.5 g, 59%), m.p. 83—84 °C, R_F [solvent (*ii*)] 0.53 (Found: C, 72.2; H, 6.3. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.1%); $\nu_{max.}$ 1 660 cm^{-1}; $\lambda_{max.}$ 308 (log ε 4.16), 268 (4.51), and 204 nm (4.40); δ_H (90 MHz), 1.20 (3 H, t, OCH_2Me), 3.69 (2 H, q, OCH_2Me), 3.87 (1 H, t, 3-H), 4.60 (2 H, d, *J* 6, 2-H), 5.21 (2 H, s, OCH_2O), 6.66 (1 H, dd, *J* 9.5 and 2, 6-H), 6.71 (1 H, d, *J* 2, 8-H), 7.25 (5 H, s, Ph), and 7.86 (1 H, d, *J* 9.5, 5-H).

7-Hydroxyisoflavanone (**5e**).—A solution of the above isoflavanone (**5i**) (1.5 g) in methanol (20 ml) was warmed slowly with 10% methanolic HCl (20 ml) for 7 min. The solution was concentrated to half the volume, cooled, treated with an equal amount of cold water, and left overnight in a refrigerator. The solid that separated was collected and crystallized to give (**5e**) as shining white crystals (1.12 g, 93%), m.p. 174—175 °C (lit.,[18] 173 °C); R_F [solvent (*ii*)] 0.44 (Found: C, 78.3; H, 5.4. Calc. for $C_{15}H_{12}O_3$: C, 78.3; H, 5.2%); $\nu_{max.}$(KBr) 1 650 cm^{-1}; $\lambda_{max.}$ 312 (log ε 4.23), 273 (4.45), 228sh (4.32) and 218 nm (4.43); δ_H (90 MHz) 4.00 (1 H, t, 3-H), 4.58 (2 H, d, *J* 6 Hz, 2-H), 6.48 (1 H, dd, *J* 9.5 and 2, 6-H), 6.53 (1 H, d, *J* 2, 8-H), 7.26 (5 H, s, Ph), and 7.78 (1 H, d, *J* 9.5, 5-H).

2-Hydroxy-4-ethoxymethoxyphenyl α-Hydroxymethyl-4-methoxybenzyl Ketone (**4j**).—To a solution of the ketone[17] (**1f**) (2.58 g, 10 mmol) in dry acetone (200 ml) was added anhydrous potassium carbonate (6.9 g, 50 mmol) and a solution of ethoxymethyl chloride (1.32 ml, 10 mmol) in dry acetone (15 ml)

and the whole solution was stirred for 20 min. Further ethoxymethyl chloride (1.45 ml, 10 mmol) was added to this reaction mixture, which was warmed gently at 40—50 °C and then at 60—70 °C for 1 h, to give the *alcohol* (**4j**) as a viscous oil (3.14 g, 91%); R_F [solvent (*ii*)] 0.42; $\nu_{max.}$(KBr) 3 100—3 700 and 1 620 cm^{-1}; $\lambda_{max.}$ 326s (log ε 4.07), 290 (4.58), 224 (4.53), and 214 nm (4.53); δ_H (90 MHz) 1.26 (3 H, t, OCH_2Me), 2.50 (1 H, br s, exchangeable with D_2O, OH), 3.71 (3 H, s, OMe merged with q, OCH_2Me), 3.87 (1 H, dd, J_{AX} 4.8 and J_{AM} 11.20, H_A), 4.21 (1 H, dd, J_{MX} 8 and J_{AM} 11.20, H_M), 4.67 (1 H, dd, J_{MX} 8 and J_{AX} 4.8, H_X), 5.16 (2 H, s, OCH_2O), 6.40 (1 H, dd, *J* 9.5 and 2, 5-H), 6.55 (1 H, d, *J* 2, 3-H), 6.81 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.20 (2 H, d, *J* 9.5, 2′-H and 6′-H), 7.65 (1 H, d, *J* 9.5, 6-H), and 12.70 (1 H, s, chelated OH).

7-Ethoxymethoxy-4′-methoxyisoflavanone (**5j**).—The above ketone (**4j**) (3.14 g) was refluxed in ethanol (25 ml) and 4% aqueous Na_2CO_3 (25 ml) for 3 h when the *isoflavanone* (**5j**) was obtained as an oil (1.95 g, 65%); R_F [solvent (*ii*)] 0.60; $\nu_{max.}$ 1 675 cm^{-1}; $\lambda_{max.}$ 313, 270, and 228 nm; δ_H (90 MHz) 1.20 (3 H, t, CH_2Me), 3.56 (2 H, q, OCH_2Me), 3.75 (3 H, s, OMe), 3.85 (1 H, t, 3-H), 4.57 (2 H, d, *J* 6, 2-H), 5.21 (2 H, s, OCH_2O), 6.70 (1 H, dd, *J* 9.5 and 2, 6-H), 6.75 (1 H, d, *J* 2, 8-H), 6.85 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.20 (2 H, d, *J* 9.5, 2′-H and 6′-H and 7.90 (1 H, d, *J* 9.5, 5-H).

7-Hydroxy-4′-methoxyisoflavanone (**5f**).—The above isoflavanone (**5j**) (1.95 g) was warmed slowly in methanol (20 ml) with 10% methanolic HCl (20 ml) for 10 min. The product crystallized from benzene–light petroleum to give (**5f**) as white crystals (1.5 g, 93%), m.p. 184—186 °C (lit.,[19] 185—188 °C); R_F [solvent (*ii*)] 0.48 (Found: C, 70.8; H, 5.5. Calc. for $C_{16}H_{14}O_4$: C, 71.1; 5.2%); $\nu_{max.}$(Nujol) 1 652 cm^{-1}; $\lambda_{max.}$ 312 (log ε 4.33), 273 (4.49) and 219 nm (4.65); δ_H (90 MHz) 3.9 (3 H, s, OMe), 4.05 (1 H, t, 3-H), 4.62 (2 H, d, *J* 6, 2-H), 6.56 (1 H, dd, *J* 9.5, 2, 6-H), 6.63 (1 H, d, *J* 2, 8-H), 6.96 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.24 (2 H, d, *J* 9.5, 2′-H and 6′-H), and 7.89 (1 H, d, *J* 9.5, 5-H).

α-Hydroxymethylbenzyl 2-Hydroxy-4,6-bisethoxymethoxyphenyl Ketone (**4k**).—A solution of the ketone[13] (**1g**) (2.44 g, 10 mmol) in acetone (200 ml) was stirred with dry K_2CO_3 (6.9 g, 50 mmol) and a solution of ethoxymethyl chloride (2.9 ml, 22 mmol) in acetone (20 ml) for 45 min. Further ethoxymethyl chloride (1.45 ml, 11 mmol) was added, and the mixture was warmed for 1 h. Column chromatography eluting with benzene–light petroleum yielded (**4k**) as a viscous oil (3.5 g, 90%); R_F [solvent (*ii*)] 0.50; $\nu_{max.}$ 3 200—3 500 and 1 620; $\lambda_{max.}$ 308sh, 282, and 248; δ_H (90 MHz) 1.18 (6 H, t, 2 × OCH_2Me), 2.40 (1 H, br s, exchangeable with D_2O, OH), 3.30—3.80 (5 H, q, 2 × OCH_2Me merged with dd, H_A), 4.14 (1 H, dd, J_{MX} 8 and J_{AM} 11.20, H_M), 5.14 (5 H, s, 2 × OCH_2O merged with a dd, H_X, J_{AX} 4.8 and J_{MX} 8), 6.37 (2 H, s, 3-H and 5-H), 7.34 (5 H, s, Ph), and 13.77 (1 H, s, chelated OH).

5,7-Bisethoxymethoxyisoflavanone (**5k**).—The above ketone (**4k**) (3.5 g) was refluxed in ethanol (15 ml) and 4% aqueous Na_2CO_3 (15 ml) for 45 min and the product after purification by chromatography was identified as the isoflavanone (**5k**), a viscous oil (2.3 g, 68%); R_F [solvent (*ii*)] 0.57; $\nu_{max.}$ 1 650 cm^{-1}; $\lambda_{max.}$ 308, 268, and 204 nm; δ_H (90 MHz) 1.31 (6 H, 2t, 2 × OCH_2Me), 3.61—3.82 (5 H, 2 q, 2 × OCH_2Me merged with t, 3-H), 4.58 (2 H, d, *J* 6, 2-H), 5.23 (4 H, 2s, 2 × OCH_2O), 6.33 (1 H, d, *J* 2, 8-H), 6.45 (1 H, d, *J* 2, 6-H), and 7.36 (5 H, s, Ph).

5,7-Dihydroxyisoflavanone (**5g**).—A solution of the above isoflavanone (**5k**) (2.3 g) in methanol (20 ml) was warmed with 10% HCl–methanol (20 ml) for 12 min. Crystallization from benzene–light petroleum afforded (**5g**) as a white crystalline solid (1.4 g, 92%), m.p. 162—163 °C (lit.,[20] 163.5 °C); R_F [solvent (*ii*)] 0.48 (Found: C, 70.2; H, 5.0. Calc. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7%); $\nu_{max.}$(Nujol) 3 100—3 600, 1 633 cm^{-1}; $\lambda_{max.}$ 322 (4.31), 290 (4.39), and 212 nm (4.40); δ_H (90 MHz) 4.02 (1 H, t, 3-H), 4.52 (2 H, d, *J* 6, 2-H), 6.56 (2 H, d, *J* 2.0, 6-H and 8-H) and 7.22 (5 H, s, Ph).

2-Hydroxy-4,6-bisethoxymethoxyphenyl α-Hydroxymethyl-4-methoxybenzyl Ketone (**4l**).—A solution of the ketone[21] (**1h**) (2.7 g, 10 mmol) in acetone (200 ml) was stirred with dry K_2CO_3 (6.9 g, 50 mmol) and a solution of ethoxymethyl chloride (2.9 ml, 22 mmol) in dry acetone (20 ml) for 45 min. Further ethoxymethyl chloride (1.45 ml, 10 mmol) was added and the mixture was warmed for 1.25 h. Purification afforded the *carbinol* (**4l**) as a colourless viscous oil (3.7 g, 88%), R_F [solvent (*ii*)] 0.56; $\nu_{max.}$(Nujol) 3 100–3 800 and 1 620 cm^{-1}; $\lambda_{max.}$ 289, 222, and 211 nm; δ_H (90 MHz) 1.17 (6 H, t, 2 × OCH_2Me), 2.47—2.87 (1 H, br s, exchangeable with D_2O, OH), 3.37—3.77 (8 H, 2 s merged with dd and q, H_A, OMe, and 2 × OCH_2Me), 4.08 (1 H, dd, J_{MX} 8.0 and J_{AM} 11.20, H_M), 4.84 (1 H, dd, J_{AX} 4.8 and J_{MX} 8.0, H_X), 5.20 (4 H, s, 2 × OCH_2O), 6.14 (2 H, d, *J* 2, 3-H and 5-H), 6.65 (2 H, d, *J* 9.5, 3′-H and 5′-H), 7.02 (2 H, d, *J* 9.5, 2′-H and 6′-H), and 13.88 (1 H, s, chelated OH).

5,7-Bisethoxymethoxy-4′-methoxyisoflavanone (**5l**).—The above ketone (**4l**) (3.7 g) was refluxed in ethanol (25 ml) and 4% aqueous Na_2CO_3 (25 ml) for 45 min. Purification by column chromatography gave the *isoflavanone* (**5l**) as a viscous oil (2.5 g, 70%); R_F [solvent (*ii*)] 0.49; $\nu_{max.}$ (liquid film) 1 670 cm^{-1}; $\lambda_{max.}$ 281, 226 and 211 nm; δ_H (90 MHz) 1.19 (6 H, 2 t, 2 × OCH_2Me), 3.68—3.78 (7 H, q, 2 × OCH_2 merged with s, OMe), 3.85 (1 H, distorted t, 3-H), 4.50 (2 H, d, *J* 6, 2-H), 5.19 (2 H, s, OCH_2O), 6.27 (1 H, d, *J* 2, 6-H), 6.37 (1 H, d, *J* 2, 8-H), 6.80 (2 H, d, *J* 9.5, 3′-H and 5′-H) and 7.17 (2 H, d, *J* 9.5, 2′-H and 6′-H).

5,7-Dihydroxy-4′-methoxyisoflavanone (**5h**).—A solution of the above isoflavanone (**5l**) (2.5 g) in methanol (10 ml) was warmed with 10% HCl–MeOH (10 ml) for 10 min. The product crystallized from benzene–light petroleum to yield (**5h**) as a colourless solid (1.7 g, 93%), m.p. 168—169 °C (lit.,[22] 167—169 °C); R_F [solvent (*ii*)] 0.42; green Fe^{III} reaction; $\nu_{max.}$(KBr) 1 625 cm^{-1}; δ_H (200 MHz) 3.79 (3 H, s, OMe), 3.90 (1 H, t, 3-H), 4.55 (2 H, dd, 2-H), 5.95 (2 H, d, *J* 2, 6, 8-H), 6.89 (2 H, d, *J* 9.5, 3′-H and 5′-H), and 7.19 (2 H, d, *J* 9.5, 2′-H and 6′-H).

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