

SYNTHESIS OF 12-METHOXYFURANO[3',2':6,7] COUMESTAN

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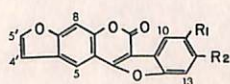
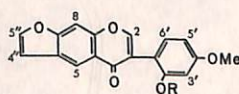
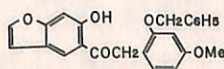
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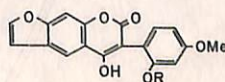
The reaction of 2'-hydroxy-4'-methoxyfurano[3'',2'':6,7]isoflavone with benzyl chloride in the presence of anhydrous potassium carbonate and potassium iodide in acetone gave a corresponding benzyl ether (IV). The ring cleavage of IV with alcoholic alkali gave 6-hydroxy-5- ω -(2-benzyloxy-4-methoxyphenyl)acetyl-coumarone (V). By the treatment of V with diethyl carbonate and sodium, 4-hydroxy-3-(2-benzyloxy-4-methoxyphenyl)furano[3',2':6,7]coumarin (VI) was obtained. The debenzoylation of VI with acid gave a dihydroxycoumarin derivative, and subsequently the intramolecular dehydration in methanol with hydrogen chloride yielded the title compound.

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Naturally occurring coumestans are of interest because of their estrogenic properties¹⁾. Erosnin (I)²⁾, characteristically containing furan ring, was isolated from seeds of *Pachyrrhizus erosus* and its chemical structure was confirmed 11,12-methylenedioxyfurano [3',2':6,7] coumestan. This paper will describe the synthesis of 12-methoxyfurano [3',2':6,7]coumestan (II), containing furan ring as I, from 2'-hydroxy-4'-methoxyfurano [3'',2'':6,7] isoflavone (III)³⁾ according to the same way reported earlier^{4,5)}. II has not yet been found in any natural source, but it is considered useful to synthesize this substance, which may be expected to occur in nature.

I $R_1-R_2 = O-CH_2-O$ II $R_1 = H \quad R_2 = OMe$ III $R = H$ IV $R = CH_2C_6H_5$ 

V

VI $R = CH_2C_6H_5$ VII $R = H$

The reaction of III with benzyl chloride in the presence of anhydrous potassium carbonate and potassium iodide in acetone gave a corresponding 2'-benzyloxyisoflavone derivative (IV) in a good yield. By the ring cleavage of IV with alcoholic potassium hydroxide, 6-hydroxy-5- ω -(2-benzyloxy-4-methoxyphenyl)-acetylcoumarone (V) was obtained, which showed positive with alcoholic ferric chloride reaction. The treatment of V in diethyl carbonate with metallic sodium gave 4-hydroxy-3-(2-benzyloxy-4-methoxyphenyl) furano [3', 2' : 6, 7] coumarin (VI) which was easily converted into a monoacetate by an ordinary method. The infrared spectrum of VI exhibits the carbonyl absorption at 1675 cm^{-1} , while the hydroxyl absorption is scarcely shown at the range of 3000 to 3600 cm^{-1} . In the infrared spectrum of its acetate, however, the strong absorption due to the carbonyl groups of acetyl and δ -lactone were observed at 1770 and 1725 cm^{-1} , respectively. These facts indicate the structure of VI. The debenzilation of VI in glacial acetic acid with concentrated hydrochloric acid yielded a dihydroxy compound (VII). The intramolecular dehydration of VII with methanol-hydrogen chloride readily led to a coumestan, 12-methoxyfurano [3', 2' : 6, 7] coumestan (II), which showed a strong fluorescence in ethanol and acetone. The ultraviolet spectrum of II is shown in Fig. 1. The compound contains two absorption maxima at ca. 240 nm and ca. 350 nm. The former strong absorption is characteristic of benzofuran grouping and

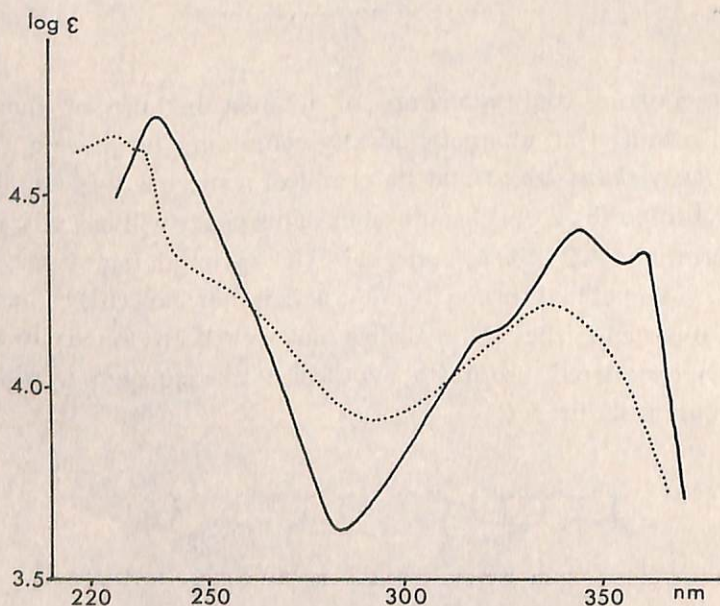


Fig. 1 UV Spectra of 12-Methoxyfurano[3', 2' : 6, 7]-coumestan (II) (—) and 4-Hydroxy-3-(2-Hydroxy-4-methoxyphenyl)furano[3', 2' : 6, 7]coumarin (VIII) (.....)

the latter of coumestan nucleus⁵⁻⁸⁾. In the NMR spectrum of II (Fig. 2), the

signals at δ 7.95 (1H, doublet, $J=9.0$ Hz), 7.15 (1H, doublet, $J=2.0$ Hz) and 7.00 (double doublet, $J=9.0$ and 2.0 Hz) can be assigned to the aromatic protons at C-10, C-13 and C-11 respectively in view of their coupling constants due to an ABX system. Furthermore, a set of one-proton signals at δ 8.12 (1H, singlet) and 7.59 (1H, doublet, $J\sim 1$ Hz) can be attributed to the aromatic protons at C-5 and C-8, indicating that the two protons are oriented in *para* position to one another. The remaining two protons at C-5' and C-4' on the furan ring resonate at δ 7.72 (doublet, $J=2.5$ Hz) and 6.87 (double doublet $J=2.5$ and 1.0 Hz), respectively, being observed a long range coupling between the aromatic proton at C-8 and the β -furano-proton at C-4' in the compound, II. These facts show that the structure of II belong to the linear ring system. Similar observations have been reported in several earlier reports⁸⁻¹¹). In addition, in the mass spectrum of II (Fig. 3), the molecular ion appears at m/e 306 and the ions resulting from fragmentation are observable at m/e 291, 263, 235 and 219, respectively.

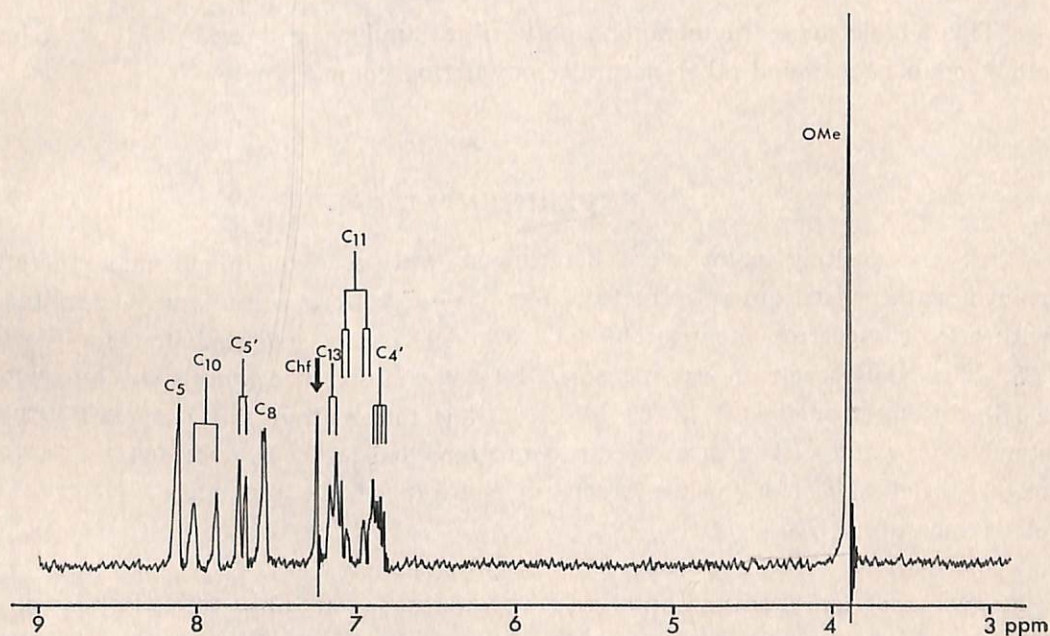


Fig. 2 NMR Spectrum of 12-Methoxyfurano[3',2':6,7]-coumestan (II) in $CDCl_3$.

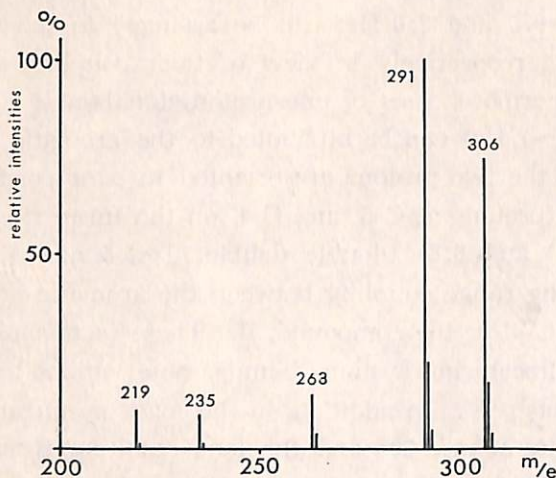


Fig. 3 MS Spectrum of 12-Methoxyfurano[3',2':6,7]-coumestan (II).

This simple mass fragmentation pattern is similar to those of 7,11,12-trimethoxycoumestan⁵⁾ and other naturally occurring coumestans¹²⁾.

EXPERIMENTAL

All the melting point were determined with a Yanagimoto micromelting point apparatus and are uncorrected. The UV and IR spectra were determined with a Carry spectrophotometer Model 118 and a Hitachi spectrophotometer Model 285. The NMR spectrum was measured for the solution in deuteriochloroform with a Hitachi spectrometer R-20 (60 MHz), using tetramethylsilane as an internal standard (δ -value). The mass spectra were recorded on a Hitachi mass spectrometer Model RMU-6MG, using direct insertion probe; electron impact energy, 70 eV; temperature, 230°C.

2'-Benzyloxy-4'-methoxyfurano [3'', 2'': 6, 7] *isoflavone* (IV). A mixture of 2'-hydroxy-4'-methoxyfurano [3'', 2'': 6, 7] *isoflavone* (III, mp 210-211°C) (1.0g), benzyl chloride (0.5g), anhydrous potassium carbonate (3.0g), potassium iodide (1.5g) and acetone (30ml) was refluxed on a water bath for 3 hr. After inorganic salts were filtered off, the filtrate was condensed to about 10ml and diluted with water. The separated solid was collected, washed with water and crystallized from ethanol to give IV as colorless needles, mp 195-197°C; yield, 1.1g. IR cm^{-1} : 1640 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 243 (4.37), 284 (4.07), 308 (4.09). MS (M^+ , m/e): 398.

Found: C, 70.98; H, 4.95%. Calcd for $\text{C}_{25}\text{H}_{18}\text{O}_5 \cdot 2\text{H}_2\text{O}$: C, 70.75; H, 5.18%.

6-Hydroxy-5- ω -(2-benzyloxy-4-methoxyphenyl)acetyl coumarone (V). A mixture of

IV (1.0 g), 10% potassium hydroxide solution (15 ml) and ethanol (15 ml) was refluxed on an oil bath for 2 hr. The solvent was condensed under reduced pressure to about 15 ml and the residual solution was acidified with 2N hydrochloric acid. The separated solid was collected, washed with water and crystallized from ethanol to give V as yellow prisms, mp 126–127°C; yield, 0.8 g. This substance showed brown with alcoholic ferric chloride. IR cm^{-1} : 1640 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 259 (4.07), 274 (4.00), 342 (3.72). MS (M^+ , m/e): 388. Found: C, 73.55; H, 5.19%. Calcd for $\text{C}_{24}\text{H}_{20}\text{O}_5 \cdot 1/4 \text{H}_2\text{O}$: C, 73.36; H, 5.24%.

4-Hydroxy-3-(2-benzyloxy-4-methoxyphenyl)furano[3', 2' : 6, 7]coumarin (VI). Small pieces of metallic sodium (1.0 g) were added to a solution of V (0.8 g) in diethyl carbonate (20 ml) and then the mixture was warmed on a boiling water for 1 hr. After cooling, methanol was added to the solution to destroy the excess of metallic sodium. The resulting mixture was diluted with water (ca. 50 ml), washed with ether and acidified with hydrochloric acid. The separated solid was collected, washed with water and crystallized from methanol to give VI as light yellow prisms, mp 162–163°C; yield, 0.6 g. IR cm^{-1} : 1675 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 322 (4.19). MS (M^+ , m/e): 414.

Found: C, 71.63; H, 4.45%. Calcd for $\text{C}_{25}\text{H}_{18}\text{O}_6 \cdot 1/4 \text{H}_2\text{O}$: C, 71.68; H, 4.45%.

Acetate of VI. Acetic anhydride was added to a solution of VI in pyridine and the mixture was allowed to stand overnight at the temperature in the room. The reaction mixture was poured into ice-water, the separated solid was collected, washed with water and crystallized from ethanol to give a corresponding acetate as colorless needles, mp 253–254°C. IR cm^{-1} : 1770, 1725 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 239 (4.47), 284 (4.01), 335 (4.10). MS (M^+ , m/e): 456.

Found: C, 70.39; H, 4.36%. Calcd for $\text{C}_{27}\text{H}_{20}\text{O}_7 \cdot 1/4 \text{H}_2\text{O}$: C, 70.35; H, 4.48%.

4-Hydroxy-3-(2-hydroxy-4-methoxyphenyl)furano[3', 2' : 6, 7]coumarin (VII). Concentrated hydrochloric acid (3 ml) was added to a solution of VI (0.5 g) in acetic acid (10 ml) and the mixture was refluxed on an oil bath for 1 hr. After cooling, the mixture was diluted with water, the separated solid was collected, washed with water and crystallized from methanol to give VII as colorless powder, mp 235–238°C; yield, 0.35 g. IR cm^{-1} : 3200 (OH), 1680 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 227 (4.65), 232i* (4.62), 336 (4.21). MS (M^+ , m/e): 324.

Found: C, 66.04; H, 3.94%. Calcd for $\text{C}_{18}\text{H}_{12}\text{O}_6 \cdot 1/4 \text{H}_2\text{O}$: C, 65.75; H, 3.83%.

Diacetate of VII. Acetylation was carried out by the method described above, mp 208–210°C (colorless needles, from ethanol). IR cm^{-1} : 1775, 1760, 1720 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 239 (4.46), 245 (4.45), 330 (4.10). MS (M^+ , m/e): 408.

12-Methoxyfurano (3', 2' : 6, 7) coumestan (II). VII (150mg) was dissolved in methanol (50ml) saturated with hydrogen chloride and the mixture was refluxed on a water bath for 10 hr. The reaction mixture was diluted with water (50ml), the separated solid was collected, washed with a small amount of 50% methanol and crystallized from ethanol to give II as colorless needles, mp 267-268°C; yield, 90mg. This substance showed a strong fluorescence in ethanol and acetone. IR cm^{-1} : 1740 (CO) (Nujol). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 237 (4.70), 343 (4.39), 359 (4.33). NMR (ppm): 3.90 (singlet, 3H, $-\text{CH}_3$).

Found: C, 69.98; H, 3.22%. Calcd for $\text{C}_{18}\text{H}_{10}\text{O}_5 \cdot 1/4 \text{H}_2\text{O}$: C, 69.75; H, 3.41%.

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* i=inflection.