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THE SYNTHESIS OF 7, 11, 12-TRIMETHOXYCOUMESTAN

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Abstract

The reaction of 2′-hydroxy-7, 4′, 5′-trimethoxyisoflavone with benzyl chloride in the presence of anhydrous potassium carbonate in acetone gave a corresponding 2′-benzyloxyisoflavone. The ring cleavage of the compound with alcoholic alkali gave 2-hydroxy-4-methoxyphenyl 2-benzyloxy-4, 5-dimethoxybenzyl ketone. By the treatment of the ketone with diethyl carbonate and sodium, 4-hydroxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin was obtained. The debenzylation of the coumarin with acid gave a dihydroxycoumarin, and subsequently the intramolecular dehydration in methanol with hydrogen chloride yielded the title compound.

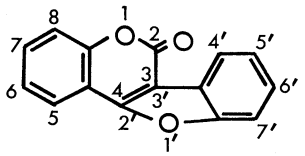
INTRODUCTION

Coumestans have a skeleton of benzofurano [3′, 2′: 3, 4] coumarin* and an oxygen pattern similar to those of pterocarpans and 2′-oxygenated isoflavones in the aromatic rings. The coumestan derivative replaced the oxygen at C_{11}- and C_{12}-positions had been synthesized from 4-hydroxycoumarin and catechol with a method of dehydrogenatic condensation[1,2,3]. The author and others have been reported a conventional conversion of a 2′-hydroxyisoflavone into the corresponding coumestan derivative[4]. This paper will describe the synthesis of 7, 11, 12-trimethoxycoumestan (I) from 2′-hydroxy-7, 4′, 5′-trimethoxyisoflavone (II)[5] according to the modification of a procedure reported earlier[4].

MATERIALS AND METHODS

1) Preparation of 2′-hydroxy-7, 4′, 5′-trimethoxyisoflavone (II) as starting materials.

*1 Benzofuranocoumarin is numbered on the nucleus as follow:



2′-hydroxy-7, 4′, 5′-trimethoxyisoflavone (II) as starting materials was prepared from the synthetic 7, 2′, 4′ 5′-tetramethoxyisoflavone[6] (mp 190-191°C) by the method of selective demethylation at the 2′-position of 2′-methoxyisoflavone derivatives[5]. The detailed preparations of this compound were as follow: Small pieces of anhydrous alluminum chloride (4.0 g) were added to a solution of 7, 2′, 4′, 5′-tetramethoxyisoflavone (1.2 g) in anhydrous acetonitrile (30 ml). The mixture was refluxed on an oil bath for 12 hr. After the solvent had been removed, the residue was treated with 10% hydrochloric acid. The resulting solid was collected, washed with a large amount of water. Recrystallization of this solid from ethanol gave crystals as light yellow needles with mp 200-201°C (lit.[5] mp 200-201°C); yield, 1.0 g. This substance showed negative reaction with alcoholic ferric chloride. In the infrared spectrum of this compound, the absorption band due to the hydroxyl group was not observed at the range of 3000-3600 cm^{-1} but that of the carbonyl group on the γ-pyrone ring at 1614 cm^{-1} which was shifted to lower frequencies. In addition, the ultraviolet spectrum of this compound in ethanol was identified with the data reported earlier[5].

2) Preparation of 2′-benzyl ether of II (Preparation of 2′-benzyloxy-7, 4′, 5′-trimethoxyisoflavone (III)).

A mixture of II (1.0 g), benzyl chloride (1.0 g) and anhydrous potassium carbonate (3.0 g) in acetone (30 ml) was refluxed on a water bath for 3 hr. After inorganic salts were filtered off, the solvent was removed as much as possible. The residual solution was diluted with water. The resulting solid was collected, washed with water and then recrystallized from ethanol to give crystals as colorless needles with mp 126-127°C; yield, 1.0 g.

3) Ring cleavage of III (Preparation of 2-hydroxy-4-methoxyphenyl 2-benzyloxy-4, 5-dimethoxybenzyl ketone (IV)).

A mixture of III (1.0 g), 10% potassium hydroxide solution (20 ml) and ethanol (20 ml) was refluxed on an oil bath for 2 hr. The reaction mixture was condensed to about 20 ml and acidified with 10% hydrochloric acid. The resulting solid was collected, washed with water and then recrystallized from ethanol to give crystals as colorless prisms with mp 145-146°C; yield, 0.8 g. This substance showed brown color with alcoholic ferric chloride.

4) Preparation of 4-hydroxycoumarin (Preparation of 4-hydroxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin (V)).

Small pieces of metallic sodium (1.0 g) were added to a solution of IV

(1.0 g) in diethyl carbonate (15 ml), and then the mixture was gradually heated to 100°C. The mixture had been kept at the temperature for 1 hr. After cooling, methanol was added to a reaction mixture to destory the excessive sodium. The resulting mixture was diluted with water (100 ml), washed with ether (50 ml×2) and then acidified with 10% hydrochloric acid. The resulting solid was collected, washed with water and recrystallized from methanol to give crystals as colorless needles with mp 186-187°C; yield, 0.8 g. This substance showed negative with alcoholic ferric chloride.

Acetate of V (4-Acetoxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin (VI)).

Acetic anhydride (5 ml) was added to a solution of V (100 mg) in pyridine (10 ml) and then 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 then recrystallized from ethanol to give crystals as light yellow prisms with mp 196-197°C; yield, 90 mg.

5) Debenzylation of V (Preparation of 4-hydroxy-7-methoxy-3-(2-hydroxy-4, 5-dimethoxyphenyl) coumarin (VII)).

A mixture of VI (200 mg), glacial acetic acid (20 ml) and concentrated hydrochloric acid (10 ml) was refluxed for 30 min. The reaction mixture was condensed under reduced pressure to about 5 ml and diluted with water. The separated solid was collected, washed with water and then recrystallized from dilute ethanol to give crystals as colorless microneedles with mp 288-291°C; yield, 150 mg.

6) Preparation of furan ring (Preparation of 7, 11, 12-trimethoxycoumestan (I)).

Several attempts of the preparation of a furan ring with the methods of the intramolecular dehydration were carried out, but the dehydration with hydrogen chloride was effective for the synthesis of the coumestan nucleus.

A solution of VII (100 mg) in methanol (100 ml) saturated with hydrogen chloride was refluxed on a water bath for 7 hr. The solvent was distilled off and the residue was diluted with water. The separated solid was collected, washed with water and then recrystallized from acetone to give crystals as colorless needles with mp 254-256°C; yield, 70 mg. This substance showed a strong fluorescence in ethanol and acetone.

7) All the melting points of these compounds described above were

measured with a Yanagimoto micro-melting point apparatus and not adjusted.

8) Measurements of spectra.
   a) The infrared spectra were measured in Nujol with a Hitachi infrared spectrophotometer Model 285.
   b) The ultraviolet spectra were measured in ethanol with a Cary spectrophotometer Model 118.
   c) The mass spectra were measured with a Hitachi mass spectrometer Model RMU-6MG using a direct insertion probe; electron impact energy, 70 eV; temperature, 220°C.

RESULTS

The chemical structures of the starting material and the synthetic compounds described above are shown in Fig. 1 and the data of the infrared and the ultraviolet spectra and the microanalyses of them in the table.

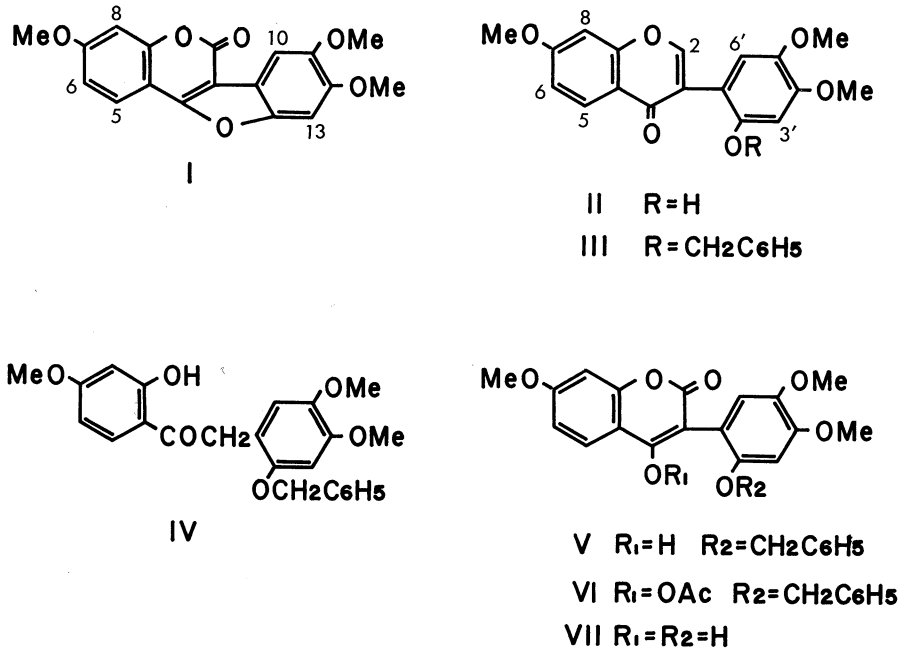


Fig. 1. The chemical structures of the compounds (I~VII).

Furthermore, the correlation of the ultraviolet spectra of I, III, IV and VII is shown in Fig. 2.

TABLE

Compounds (Formulae)	IR : cm^{-1}	UV : λ_{max} nm (log ε)	Analysis			
			Found		Calcd.	
			C%	H%	C%	H%
III ($C_{25}H_{26}O_5$)	1630(CO)	246i*(4.373) 295(4.263)	71.78	5.32	71.76	5.30
IV ($C_{24}H_{24}O_6$)	1635(CO)	229(4.274) 277(4.204) 311i(3.953)	70.68	5.91	70.57	5.92
V ($C_{25}H_{22}O_7$)	1675(CO)	312(4.279)	69.38	5.12	69.11	5.10
VI ($C_{27}H_{24}O_8$)	1770(CO) 1730(CO)	292(4.076) 324(4.230)	68.30	5.15	68.06	5.08
VII ($C_{18}H_{16}O_7$)	3220(OH) 1690(CO)	253(4.188) 328(4.258)	63.09	4.75	62.79	4.68
I ($C_{18}H_{14}O_6$)	1740(CO)	247(4.355), 276i(3.925) 281(3.933), 292(3.915) 306(4.017), 347(4.449)	66.55	4.40	66.25	4.32

* i=inflection.

The mass spectra of these compounds without VI are shown in Fig. 3 and also contained the mass numbers (m/e) of the characteristic fragment ions. In these spectra, in the lower field the fragment ions of II, IV and V at m/e 91 are characteristic and the fragmentation of coumestan (I) in the condition scarecely occurs.

DISCUSSION

The condensation of II with benzyl chloride in the presence of anhydrous potassium carbonate in acetone gave a corresponding benzyl ether (III) with mp 126°127°C. The infrared spectrum of III showed an absorption band due to the carbonyl group at 1630 cm^{-1}. This band is shifted toward higher frequencies than that of the starting material (II). This fact is that the benzyl group is placed at 2′-position. In addition, the ultraviolet and the mass spectra (Fig. 2 and Fig. 3A) show the skeleton of isoflavone and the presence of benzyl ether linkage from the appearance of the fragment ion of benzyl group at m/e 91. The treatment of III with alcoholic alkali yields product (IV) with mp 145-146°C, which showed brown color with alcoholic ferric chloride. This color reaction means that the structure of IV is the aromatic carbonyl compound con-

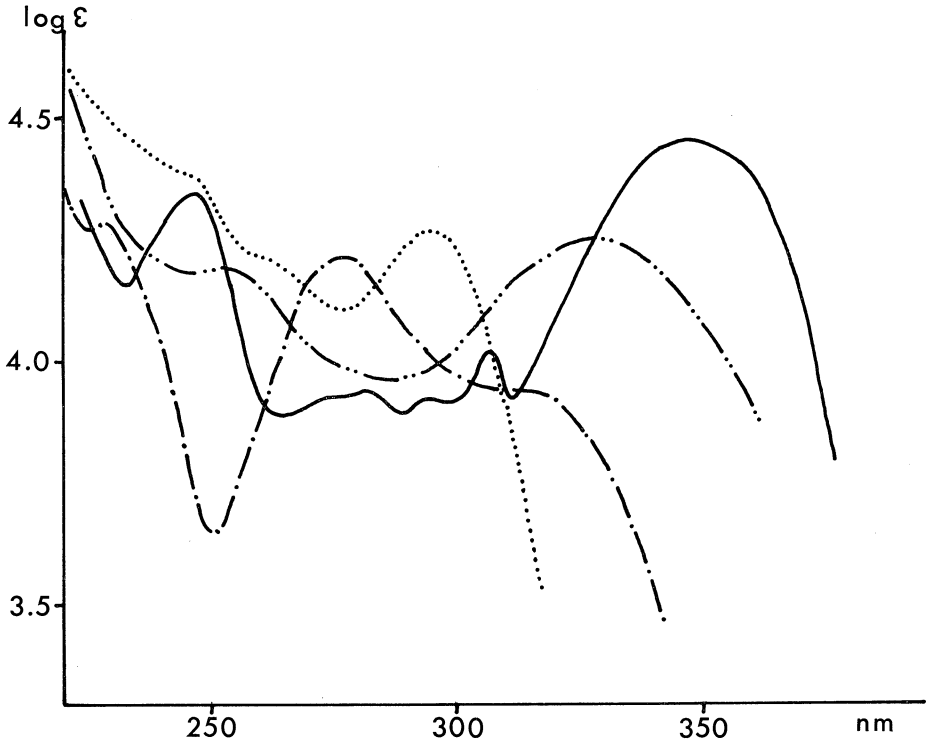


Fig. 2. The ultraviolet spectra of 7, 11, 12-trimethoxycoumestan (I) (————), 2′-benzyloxy-7, 4′, 5′-trimethoxyisoflavone (III) (••••••••), 2-hydroxy-4-methoxyphenyl 2-benzyloxy-4, 5-dimethoxybenzyl ketone (IV) (——•——•) and 4-hydroxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin (VII) (——••——••) in ethanol.

taining the hydroxyl group at the orthoposition. In the mass spectrum of IV (Fig. 3B), the base ion at m/e 151 is the ion of 2-hydroxy-4-methoxyphenylcarbonyl group arising from IV, and the residual ions are observed at m/e 257 and m/e 167, further fragment ion, respectively. This compound (IV) is, therefore, 2-hydroxy-4-methoxyphenyl 2-benzyloxy-4, 5-dimethoxybenzyl ketone. The synthesis of coumarin nucleus was carried out by the treatment of IV in diethyl carbonate with metallic sodium. The compound (V) with mp 186-187°C, which was converted into a monoacetate (VI) with mp 196-197°C by an ordinary method, was obtained. In the infrared spectra of V and VI, the absorption due to the carbonyl group of lactone ring and the acetoxyl group were observed at 1675, 1730 and 1770 cm^{-1}, respectively, while those of the hydroxyl group

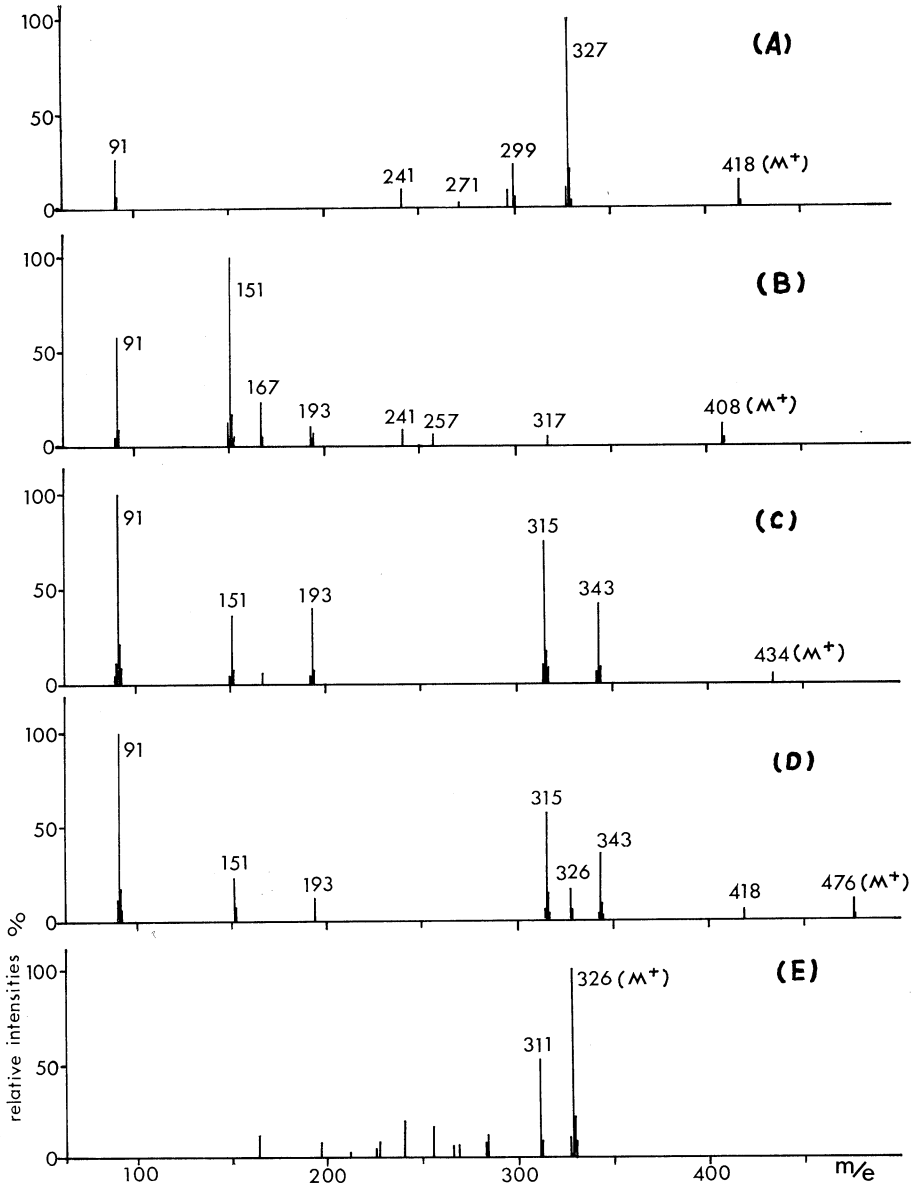


Fig. 3. The mass spectra of 2′-benzyloxy-7, 4′, 5′-trimethoxyisoflavone (III): (A), 2-hydroxy-4-methoxyphenyl 2-benzyloxy-4, 5-dimethoxybenzyl ketone (IV):(B), 4-hydroxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin (V):(C), 4-acetoxy-7-methoxy-3-(2-benzyloxy-4, 5-dimethoxyphenyl) coumarin (VI):(D) and 7, 11, 12-trimethoxycoumestan (I):(E).

in them are scarcely shown at the range of 3000 to 3600^{-1}. The carbonyl absorption of V is well below those of VI and the well-known types of δ-lactone. Therefore, the compound (V) contains the grouping HO-(C=C)-CO-, 4-hydroxycoumarin type. This evidence is also confirmed by results of the ultraviolet spectra of V and VI. A study of the mass spectra of 4-hydroxy-3-phenylcoumarins was made and the mode of fragmentation of these compounds[7] had been confirmed (Fig. 4).

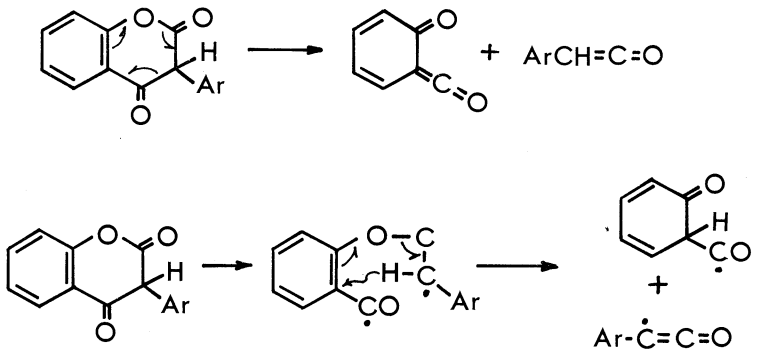


Fig. 4. The mode of fragmentation of 4-hydroxy-3-phenylcoumarin.

The mass spectra of V and VI are referable to the mode of fragmentation figured above. The debenzylation of V in glacial acetic acid with concentrated hydrochloric acid, which the infrared spectrum showed the absorption of the hydroxyl and the carbonyl groups at 3220 cm^{-1} and 1690 cm^{-1}, respectively, yield the compound (VII) with mp 280-291°C. The microanalytical data of the product were in accord with a dihydroxycoumarin, VII. The derivation from VII to coumestan (I) was readily led by the intramolecular dehydration of VII with hydrogen chloride-methanol to give a product with mp 254-256°C, which showed a strong fluorescence in ethanol and acetone. The ultraviolet spectrum, exhibiting the characteristic absorption curve, and the infrared spectrum of I are identical with the data of I and its derivatives reported earlier[1,2,3]. Furthermore, the mass spectrum of I (Fig. 3E) is a simple fragmentation pattern and observed the molecular ion at m/e 354 as the base ion[8]. These facts suggest that the synthesized compound is a 7, 11, 12-trimethoxycoumestan, I. The demethyl derivative of I, 7-hydroxy-11, 12-dimethoxycoumestan, has been isolated from alfalfa (Medicago) by Bickoff et al[9].

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