Synthetic Studies on the Benzofuran Derivatives. Part V. Synthesis of Furano(2′, 3′ : 7, 8)-isoflavone

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In a previous paper[1], furano (2′, 3′ : 7, 8)-2-methylisoflavone (I) was obtained by Tanaka's method[2] for benzofuran synthesis. It is of interest to prepare some furano-isoflavone derivatives and compare their behavior with that of the 2-methyl compounds in a number of reactions.

The present paper describes the synthesis of furano(2′, 3′ : 7, 8)-isoflavone (III). For this purpose two possible methods have been explored. The first method was to complete the isoflavone structure using a suitable coumarone derivative, benzyl 4-hydroxy-5-benzofuranyl ketone (II), as the starting material. The second one consisted in the introduction of a furan nucleus into an isoflavone skeleton (Tanaka's method[2]).

By means of the first method, II[1] (benzyl karanjyl ketone), which was fairly easily obtained as the product of hydrolysis of I, led to III, m.p. 152~152.5°C, on condensation with ethyl orthoformate in pyridine containing a little piperidine (method of Sathe and Venkataraman[3]).

As regards the second method, the application to the present case presented more difficulties than in the case of the synthesis of the 2-methyl derivative (I). The starting material was 7-hydroxyisoflavone (IV) which readily yielded the corresponding 8-aldehyde (V) by the hexamine method. The next step which involved the condensation with bromomalonic ester to 5′-carbethoxy-furano-(2′, 3′ : 7, 8)-isoflavone (VI) also proceeded smoothly.

The reaction of VI with hot aqueous sodium hydroxide brought about a conversion into benzyl 2-carboxy-4-hydroxy-5-benzofuranyl ketone (VIII), which was identical with the sample obtained[1] by hydrolysis of 5′-carbethoxy-furano(2′, 3′ : 7, 8)-2-methylisoflavone (X). By the action of ethanolic sodium hydroxide, 5′-carboxy-furano(2′, 3′ : 7, 8)-isoflavone (VII) could be obtained together with a small quantity of benzyl 2-carbethoxy-4-hydroxy-5-benzofuranyl ketone (IX), which was identical with the sample produced[1] by esterification

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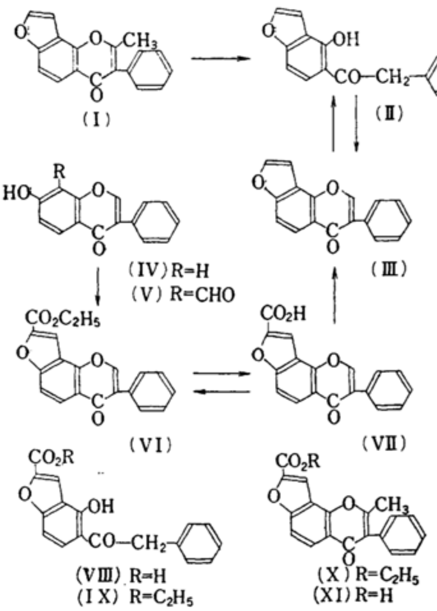
[1] T. Matsumoto, Y. Kawase, M. Nanbu and K. Fukui, This Bulletin, **31**, 688 (1958).

[2] S. Tanaka, *J. Am. Chem. Soc.*, **73**, 872 (1951).

[3] V. R. Sathe and K. Venkataraman, *Current Sci. (India)*, **18**, 378 (1949), *Chem. Abst.*, **44**, 8916 (1950).

of VIII. When VI was refluxed with aqueous sodium carbonate in acetone, VII was also obtained together with a small quantity of VIII. While X gave corresponding acid XI in a satisfactory yield[1], saponification of the ester VI to VII was of lower yield. This difference may be due possibly to the greater reactivity of an isoflavone ring owing to the absence of the 2-methyl group. VII was decarboxylated into III, m.p. 151~151.5°C, which was identical with the isoflavone prepared by the ethyl orthoformate method. The ultraviolet spectrum of III almost agreed with that of I (Fig. 1). Hydrolytic decomposition of III gave II, which was identical with the sample obtained[1] from I.



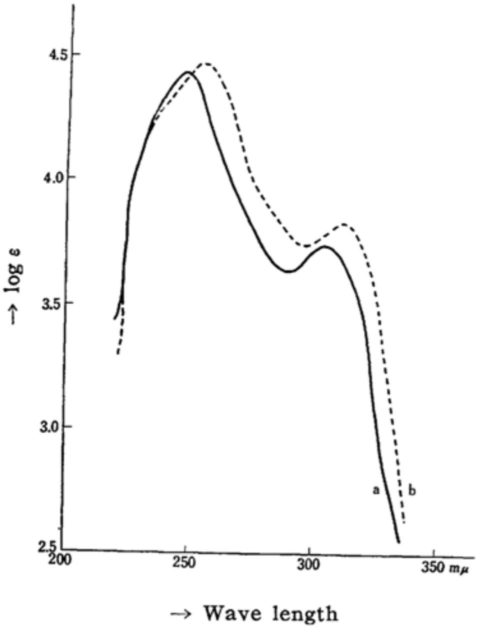


Fig. 1. Ultraviolet absorption of the isoflavone in ethanol.
(a) Furano(2′, 3′:7, 8)-2-methylisoflavone(I)
(b) Furano(2′, 3′:7, 8)-isoflavone(III)

Experimental*

7-Hydroxy-8-formyl-isoflavone(V).—A mixture of 7-hydroxy-isoflavone (IV) (1.5 g.), hexamine (8 g.) and glacial acetic acid (25 cc.) was heated in a steam-bath for 6 hr. The resulting hot reddish brown liquid was treated with hydrochloric acid (1:1, 24 cc.) and again heated in a steam-bath for ca. 5 min. After dilution with water (40 cc.) it was allowed to stand overnight. The yellow precipitates were collected, washed with water and dried. The dry solids were extracted twice with hot benzene (25 cc.) and the residue rejected. The benzene solution was evaporated, leaving V which, on repeated purification from ethanol, formed colorless needles, m.p. 197~198°C, which gave a red ferric reaction (in ethanol); yield 0.6 g.

Anal. Found: C, 72.01; H, 4.01. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%.

5′-Carbethoxy-furano(2′, 3′ : 7,8)-isoflavone (VI).—V (3 g.) was treated with ethyl bromomalonate (3.3 g.) and anhydrous potassium carbonate (13.5g.) in anhydrous acetone (150cc.). After being refluxed for 10.5 hr., the mixture was filtered and evaporated to dryness. The residue was collected, and washed with water. Recrystallization from ethanol gave colorless needles, which had a negative ferric reaction (in ethanol); yield 2.5 g., m.p. 172~173°C.

Anal. Found: C, 71.48; H, 4.31. Calcd. for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22%.

Hydrolysis of 5′-Carbethoxy-furano(2′, 3′ : 7,8)-isoflavone (VI).—*a) Hydrolysis by aqueous sodium hydroxide.*—A mixture of VI (0.6 g.) and 5% aqueous sodium hydroxide (50 cc.) was heated in a steam-bath for 3 hr. After the reaction mixture was acidified with dilute sulfuric acid, the precipitates were collected, washed with water and crystallized from ethanol to yield colorless needles (0.5 g.), m.p. 256~257°C, which gave a dark violet ferric reaction in ethanol and was soluble in 5% aqueous sodium hydrogen carbonate. The mixed melting point test showed the identity of the above compound with benzyl 2-carboxy-4-hydroxy-5-benzofuranyl ketone (VIII), m.p. 256~257°C, obtained[1] from 5′-carbethoxy-furano (2′, 3′:7, 8)-2-methylisoflavone (X).

b) Hydrolysis by aqueous sodium carbonate-acetone.—A mixture of VI (0.5 g.), acetone (20 cc.) and 5% aqueous sodium carbonate (20 cc.) was heated under reflux in a steam-bath for

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* All the melting points were uncorrected.

4 hr.; a great amount of the precipitates was formed during the reaction. Acetone was evaporated in vacuo, the reaction mixture was diluted with water (20 cc.) and filtered. The precipitates, perhaps sodium salt of the acid VII, were heated with dilute hydrochloric acid for a few minutes; the deposits were collected and washed with water. Recrystallization from glacial acetic acid gave 5′-carboxy-furano(2′, 3′:7, 8)-isoflavone (VII) in microcrystals. This had a negative ferric reaction in ethanol and produced carbon dioxide and sparingly soluble sodium salt with 5% aqueous sodium hydrogen carbonate; yield 0.2 g., m.p. 283°C (decomp.). The analytical sample was further dried at 120°C over phosphoruspentoxide for 4 hr. in vacuo.

Anal. Found: C, 66.77; H, 3.63. Calcd. for $C_{18}H_{10}O_5 \cdot H_2O$: C, 66.67; H, 3.70%.

VII afforded VI on esterification with ethanol in the presence of sulfuric acid, m.p. and mixed m.p. 172∼173°C. VII was converted into VIII, m. p. 252∼253°C, by further hydrolysis with aqueous sodium hydroxide.

The mother liquor of the sodium salt of VII was acidified with dilute hydrochloric acid and the precipitates obtained were crystallized from ethanol to yield VIII (0.1 g.), m.p. 251°C. This gave a dark violet ferric reaction (in ethanol).

c) *Hydrolysis by ethanolic sodium hydroxide.* —A hot solution of VI (0.5 g.) in ethanol (50 cc.) was added to a hot solution of sodium hydroxide (0.1 g.) in ethanol (20 cc.) and refluxed for 1 hr. After being cooled, the white precipitates were collected and treated with hot dilute hydrochloric acid. Recrystallization from glacial acetic acid gave microcrystals, which had a negative ferric reaction (in ethanol); yield 0.25 g., m.p. 280°C (decomp.). The mixed melting point test proved the compound to be identical with VII.

The filtrate, which was separated from the above precipitates, was acidified with diluted hydrochloric acid and diluted with water until it became turbid. The deposits were collected and recrystallized from ethanol to give colorless needles, which had a brown ferric reaction in ethanol and were insoluble in 5% aqueous sodium hydrogen carbonate; yield 0.1 g., m.p. 163∼164°C.

Anal. Found: C, 70.35; H, 4.83. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98%.

The mixed melting point test proved the compound to be identical with benzyl 2-carbethoxy-4-hydroxy-5-benzofuranyl ketone (IX), m.p. 166∼166.5°C, which was obtained[1] by esterification of VIII. IX produced the acid VIII, m.p. 250∼252°C, on further hydrolysis with aqueous sodium hydroxide.

Furano (2′, 3′ : 7, 8) - isoflavone (III). — *a*) Benzyl 4-hydroxy-5-benzofuranyl ketone (II) (0.7 g.), which was prepared from furano(2′, 3′:7, 8)-2-methylisoflavone[1], was heated under reflux with freshly distillated ethyl orthoformate (2 g.) in anhydrous pyridine (8 cc.) containing one drop of piperidine for 8 hr. After the solution was cooled and acidified with dilute sulfuric acid, the precipitates were collected, washed with 5% aqueous sodium hydroxide and then with water. Recrystallization from ethanol gave colorless needles, which had a negative ferric reaction (in ethanol); yield 0.3 g., m.p. 152∼152.5°C.

Anal. Found: C, 77.64; H, 4.10. Calcd. for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84%.

b) A mixture of VII (0.8 g.), copper powder (0.5 g.) and quinoline (35 cc.) was heated while stirred in an atmosphere of nitrogen for ca. 40 min. at 180∼190°C (bath temperature) until evolution of carbon dioxide ceased. After being cooled and freed from copper powder, quinoline was removed by steam distillation. Dilute sulfuric acid was poured into the remainder and the precipitates were collected. After being treated with 5% aqueous sodium hydrogen carbonate and washed with water, the solids were recrystallized from ethyl acetate and then ethanol to give the isoflavone (III) (0.5 g.) in colorless needles, m.p. 151∼151.5°C. This had a negative ferric reaction (in ethanol). The melting point was undepressed on admixture with the sample in the case *a*).

Hydrolytic Fission of the Isoflavone (III) to II.—A mixture of III (1 g.), potassium hydroxide (1.8 g.) and ethanol (70 cc.) was heated under reflux for 3 hr. in a steam-bath. After the solvent was evaporated, the residue was mixed with water (50 cc.) and acidified with dilute sulfuric acid. The precipitates were collected and washed with water. Recrystallization from ethanol gave colorless needles which had a dark blue ferric reaction (in ethanol); yield 0.8 g., m.p. 85∼86°. The melting point was undepressed on admixture with II, m.p. 86∼87°C, which was obtained[1] from furano(2′, 3′:7, 8) -2 - methylisoflavone (I).

Summary

1) Furano(2′, 3′ : 7,8)-isoflavone (III) was prepared from benzyl 4-hydroxy-5-benzofuranyl ketone (II) and ethyl orthoformate.

2) 7-Hydroxy - 8 - formyl - isoflavone (V) was obtained from 7-hydroxy-isoflavone (IV) by the hexamine method. 5′-Carbethoxy-furano(2′, 3′ : 7, 8)-isoflavone (VI) was prepared from 7-hydroxy-8-formylisoflavone (V) and ethyl bromomalonate by Tanaka's method for benzofuran synthesis. The ester VI was hydrolyzed to the free acid VII and then decarboxylated in quinoline with copper powder to the isoflavone III.

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