Synthetic Studies on the Benzofuran Derivatives. Part III. Reaction of 7-Hydroxy-8-formyl-2-methylisoflavone with Ethyl Bromomalonate and Synthesis of Furano(2',3':7,8)-2-methylisoflavone

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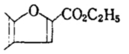
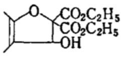
In previous papers of this series[1], it has been found that 2-carbethoxybenzofuran derivatives (I) or 2,2-dicarbethoxy-3-hydroxy-2,3-dihydrobenzofuran derivatives (II) were obtained by interaction of 7-hydroxy-8-formyl-flavone derivatives or *o*-hydroxybenzaldehyde derivatives with ethyl bromomalonate by means of Tanaka's method[2] for benzofuran synthesis. The present investigation was undertaken to examine a reaction of 7-hydroxy-8-formyl-2-methylisoflavone (III) with ethyl bromomalonate and to derive furano-(2',3':7,8)-2-methylisoflavone (VIII) from the condensation product (IV).



(I)



(II)

III and ethyl bromomalonate were refluxed in methyl ethyl ketone or acetone in the presence of potassium carbonate. The resulting condensation product, m.p. 171~172°C, was assigned structure IV (5'-carbethoxy-furano(2',3':7,8)-2-methylisoflavone) on the basis of the following facts. The compound IV was hydrolyzed with methanolic potassium hydroxide to yield the corresponding acid V, m.p. 295~297°C (decomp.). Esterification of V with ethanol gave a compound, m.p. 171~172°C, which was identical with IV. It is of interest that the condensation reaction is analogous to the conversion of *o*-hydroxybenzaldehyde derivatives into I[1]. On hydrolytic fission with aqueous sodium hydroxide, IV gave an acid VI, m.p. 256~257°C, which had a dark violet ferric reaction; it may be benzyl 2-carboxy-4-hydroxy-5-benzofuranyl ketone. VI was esterified with ethanol to give the ester VII, m.p. 166~166.5°C, which was different from IV; it seemed to be benzyl 2-carbethoxy-4-hydroxy-5-benzofuranyl ketone, the ester of VI. The acid V was decarboxylated at 180~190° (bath temperature) into the isoflavone VIII, m.p. 187~188°C, which was thought to be furano(2',3':7,8)-2-methylisoflavone. Ramachandra Row and Seshadri[3] obtained, by an alternate route, 5'-carbethoxy-furano (2',3':7,8)-2-methylisoflavone, 5'-carboxy-furano(2',3':7,8)-2-methylisoflavone and furano(2',3':7,8)-2-methylisoflavone; the melting points of these compounds, however, differed markedly from those of the present products (IV, V and VIII) (see Table I).

TABLE I
THE MELTING POINTS OF SYNTHETIC PRODUCTS

	Our results	Results of Ramachandra Row et al.
5'-carbethoxy-furano(2',3':7,8)-2-methylisoflavone (IV)	171~172°C	225~227°C
5'-carboxy-furano(2',3':7,8)-2-methylisoflavone (V)	295~297°C (decomp.)	253~255°C (decomp.)
furano(2',3':7,8)-2-methylisoflavone (VIII)	187~188°C	95~96°C

To confirm the structure of IV, V and VIII, alkaline hydrolysis of VIII was carried out to give acetic acid and a substance (IX) of colorless needles, m.p. 86~87°C, which gave a dark blue ferric reaction in ethanol. On boiling IX with a mixture of sodium acetate and acetic anhydride, an isoflavone derivative, m.p. 187~188°C, was obtained, which was identical with VIII. On oxidation with hydrogen peroxide IX gave phenylacetic acid (X), m.p. 76°C, and furan-2,3-dicarboxylic acid (XI), m.p. 220~221°C(decomp.); thus

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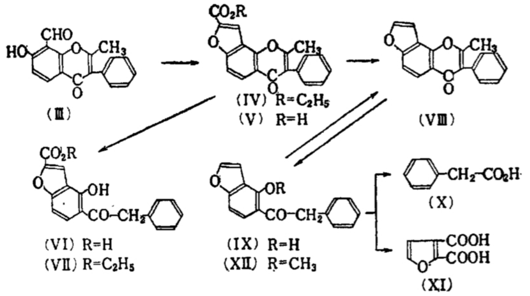
[1] Y. Kawase, T. Matsumoto and K. Fukui, This Bulletin, **28**, 273 (1955); T. Matsumoto and K. Fukui, ibid., **30**, 3 (1957).

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

[3] L. Ramachandra Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **34A**, 187 (1951).

IX was considered to be benzyl 4-hydroxy-5-benzofuranyl ketone. To further confirm the structure of IX, its methyl ether XII, m.p. 61.5~62°C, was derived. This ether was conveniently compared with a ketone prepared from the acid chloride of karanjic acid methyl ether and dibenzylcadmium (m.p. 63~63.5°C). The mixed melting point was undepressed*. VIII, IV and V were thus assigned furano(2′,3′:7,8)-2-methylisoflavone and 5′-carbethoxy-furano(2′,3′:7,8)-2-methylisoflavone and 5′-carboxy-furano(2′,3′:7,8)-2-methylisoflavone, respectively.



Experimental**

7-Hydroxy-8-formyl-2-methylisoflavone (III).—The aldehyde was prepared from 7-hydroxy-2-methylisoflavone by the hexamine method[3].

5′-Carbethoxy-furano(2′,3′:7,8)-2-methylisoflavone (IV).—A mixture of 6.5 g. of the aldehyde III, 6.1 g. of ethyl bromomalonate, 12 g. of anhydrous potassium carbonate and 230 cc. of methyl ethyl ketone was refluxed with stirring for 10 hr. in a steam-bath. After being cooled, the mixture was filtered and evaporated to dryness. Recrystallization from ethanol yielded colorless needles, which gave a negative ferric reaction (in ethanol) and also gave no 2,4-dinitrophenylhydrazone; yield 4.8 g., m.p. 171~172°C.

Anal. Found: C, 72.43; H, 4.38. Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63%.

Acetone was favorably substituted for the methyl ethyl ketone.

5′-Carboxy-furano(2′,3′:7,8)-2-methylisoflavone (V).—A mixture of 2.0 g. of the ester IV, 1.0 g. of potassium hydroxide and 80 cc. of methanol was heated under reflux for 1 hr. in a steam-bath. The reaction mixture was acidified with dilute sulfuric acid. After the solvent was distilled off, the residual solids were collected, washed with water and recrystallized from methanol in colorless needles, m.p. 295~297°C (decomp.), which gave a negative ferric reaction (in ethanol) and was soluble in 5% aqueous sodium hydrogen carbonate; yield 1.7 g.

Anal. Found: C, 71.23; H, 3.90. Calcd. for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78%.

Esterification of V.—A mixture of 0.5 g. of the acid V, 1 cc. of concentrated sulfuric acid and 35 cc. of absolute ethanol was refluxed for 8 hr. The reaction mixture was treated in the usual manner and recrystallized from ethanol to give 0.4 g. of colorless needles, m.p. 171~172°C; the melting point was undepressed on admixture with the above sample IV, m.p. 171~172°C.

Anal. Found: C, 72.28; H, 4.82. Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63%.

Fission of IV.—A mixture of 2.3 g. of the ester IV and 150 cc. of 5% aqueous sodium hydroxide was heated in a steam-bath with occasional shaking for 3 hr. After the reaction mixture was filtered and acidified with sulfuric acid, the precipitates were collected and washed with water. Recrystallization from methanol yielded benzyl 2-carboxy-4-hydroxy-5-benzofuranyl ketone VI, m.p. 256~257°C in colorless needles, which gave a dark violet ferric reaction (in ethanol); yield 1.3 g.

Anal. Found: C, 69.21; H, 4.06. Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08%.

A mixture of 0.5 g. of VI, 1 cc. of concentrated sulfuric acid and 35 cc. of absolute ethanol was refluxed for 8 hr. The reaction mixture was worked up in the usual manner and recrystallized from ethanol to give colorless needles of benzyl 2-carbethoxy-4-hydroxy-5-benzofuranyl ketone (VII), which had a brown ferric reaction (in ethanol); yield 0.4 g., m.p. 166~166.5°C.

Anal. Found: C, 70.23; H, 5.04. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98%.

Furano(2′,3′:7,8)-2-methylisoflavone(VIII).—A mixture of 6.0 g. of V, 3.5 g. of copper powder and 180 cc. of quinoline was heated with stirring in an atmosphere of nitrogen for ca. 30 min. at 180~190° (bath temperature) until evolution of carbon dioxide ceased. After being cooled, the copper powder was filtered off, and the solution was acidified with dilute sulfuric acid. The precipitates thus formed were collected, washed with aqueous sodium hydrogen carbonate and then with water. Recrystallization from ethyl acetate gave colorless needles, which had a negative ferric reaction (in ethanol); yield 3.4 g., m.p. 187~188°C.

Anal. Found: C, 78.44; H, 4.46. Calcd. for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38%.

Fission of VIII.—A mixture of 2.0 g. of VIII, 4.0 g. of potassium hydroxide and 110 cc. of ethanol was heated for 4 hr. in a steam-bath. After the solvent was evaporated, the residue was mixed with water and acidified with dilute sulfuric acid. The resulting precipitates were collected, washed with water and recrystallized from ethanol as colorless needles of benzyl 4-hydroxy-5-benzofuranyl ketone (IX), which had a dark blue ferric reaction (in ethanol); yield 1.6 g., m.p. 86~87°C.

Anal. Found: C, 76.23; H, 5.02. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80%.

The mother liquor, which was freed from the above precipitates, was steam-distilled and the

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* The details of the synthesis of this ketone (XII) will be given in the following paper.

** All the melting points were uncorrected.

distillate was neutralized with 0.1 N sodium hydroxide solution. A part of the neutralized solution (0.0025 mole) was concentrated to ca. 2 cc. in vacuo, and mixed with 0.7 g. of a solution of *p*-bromophenacyl bromide in 100 cc. of ethanol. The mixture was refluxed for 1 hr. in a steam-bath, the solvent, removed, and water was added. The precipitates obtained were collected, washed with water and recrystallized from aqueous ethanol to form colorless plates; yield 0.3 g., m.p., 84~85°C. The melting point was undepressed on admixture with an authentic sample of *p*-bromophenacyl ester of acetic acid, m.p. 84~85°C.

Anal. Found: C, 46.99; H, 3.79. Calcd. for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53%.

Reactions of Benzyl 4-Hydroxy-5-benzofuranyl Ketone (IX).—*a*).—A mixture of 0.35 g. of the ketone IX, 2.0 g. of anhydrous sodium acetate and 10 cc. of acetic anhydride was refluxed for 12 hr. in an oil bath. The excessive acetic anhydride was removed in vacuo, the residue was made alkaline with 5% aqueous sodium hydroxide and then extracted with ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, then with water, dried over anhydrous sodium sulfate and evaporated. The crude residue was recrystallized from ethyl acetate in colorless needles, which had a negative ferric reaction (in ethanol); yield 0.15 g., m.p. 187~188°C (alone or mixed with VIII).

b) *Oxidation.*—On a steam-bath 1.0 g. of IX was heated with 200 cc. of 2.5% aqueous potassium hydroxide until a clear solution was obtained, which was cooled to room temperature, and 50 cc. of hydrogen peroxide solution (8%) was added slowly. Then the reaction mixture was kept for 18 hr. at room temperature and then heated for 6 hr. in a steam-bath to decompose the excessive hydrogen peroxide. The solution was acidified with dilute hydrochloric acid and evaporated in vacuo to dryness and then extracted continuously with ether for 17 hr. The ethereal solution was extracted with 5% aqueous sodium hydrogen carbonate. This solution was made slightly acidic with dilute hydrochloric acid and then made slightly alkaline with dilute aqueous ammonia solution, then a solution of 1.0 g. of calcium chloride was added and the precipitates formed were filtered off. The filtrate was acidified with dilute hydrochloric acid and evaporated to ca. 20 cc. in vacuo. After cooling, the crude phenylacetic acid was removed by filtration. The mother liquor was continuously extracted with ether for 17 hr. The ethereal extracts, upon evaporation, yielded a mixture of phenylacetic acid and furan-2,3-dicarboxylic acid (XI), which were separated by trituration with cold chloroform. The suspended solid was collected. Recrystallization from acetic acid gave XI in colorless needles, m.p. 220~221°C (decomp.) which had a negative ferric reaction (in ethanol); yield 0.1 g. This product did not depress the melting point of authentic furan-2,3-dicarboxylic acid[4] made from karanjic acid.

Anal. Found: C, 46.26; H, 2.90. Calcd. for $C_6H_4O_5$: C, 46.17; H, 2.58%.

Evaporation of the chloroform layer yielded crude phenylacetic acid. The combined crude phenylacetic acid was recrystallized from water in colorless plates; yield 0.15 g., m.p. 76°C. The melting point was undepressed on admixture with an authentic sample of phenylacetic acid, m.p. 76°C.

c) *Methylation.*—A mixture of 1.0 g. of IX, 1.0 g. of anhydrous potassium carbonate and a solution of 1 cc. of dimethyl sulfate in 20 cc. of anhydrous acetone was refluxed for ca. 20 hr. in a steam-bath. The precipitates were filtered off, the acetone was removed and the residue washed with 5% dilute sodium hydroxide and then with water. Recrystallization from ethanol gave colorless plates, m.p. 61.5~62°C, which had a negative ferric reaction (in ethanol); yield 0.7 g. The melting point of this compound was undepressed on admixture with synthetic sample m.p. 63~63.5°C, which was obtained from the acid chloride of karanjic acid methyl ether and dibenzylcadmium.*

Anal. Found: C, 76.98; H, 5.88. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30%.

Summary

5′-Carbethoxy-furano(2′,3′ : 7,8)-2-methylisoflavone (IV) was obtained from 7-hydroxy-8-formyl-2-methylisoflavone (III) and ethyl bromomalonate by Tanaka's method for benzofuran synthesis. The condensation product IV was hydrolyzed to give the free acid V, which was decarboxylated in quinoline with copper powder to yield furano(2′,3′ : 7,8)-2-methylisoflavon (VIII). The structures of the condensation product and its derivatives were discussed.

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[4] B. L. Manjunath, A. Seetharamiath and S. Siddappa, *Ber.*, **72B**, 93 (1939).