Synthetic Studies on the Benzofuran Derivatives. II. Reactions of Aromatic o-Hydroxyaldehyde Derivatives and Ethyl Bromomalonate

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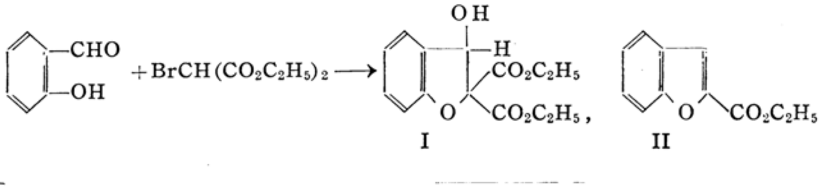
Since the discovery of the new synthetical method of coumarones by Tanaka[1] this process has been widely utilized for obtaining many sorts of benzofuran derivatives, for instance, 6-nitro- and 6-aminocoumarones[2]; 5, 6-dimethoxycoumarone[3]; karanjin[4]; 3-methylcoumarilic acid[5]; coumarones[6].

It was already noticed by Tanaka[7] that his intermediate product I of benzofuran (or its derivatives) synthesis starting from salicylic aldehyde (or its derivatives) and bromomalonic ester, was not obtained in some cases but II was procured instead. The reason for this exceptional appearance of II in the course of benzofuran synthesis was fully interpreted by the oral presentation of S. Akagi[8] who insisted that the essential point lies in the previous dehydration of the solvent (methyl ethyl ketone) applied in this reaction. When the solvent had been completely dried the reaction product was I, while II was obtained in place of I when the solvent there applied had been carelessly dried previously.

In an earlier paper[4], we and Kawase reported that 3-methoxyflavone-7, 8-furan-



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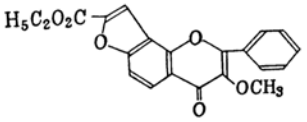
[1] S. Tanaka, *J. Am. Chem. Soc.*, **73**, 872 (1951).
[2] P. Rumpf, Ch. Gansser, *Helv. Chim. Acta.*, **37**, 435 (1954).
[3] F. E. King, J. R. Housley and T. J. King, *J. Chem. Soc.* 1392 (1954).
[4] Y. Kawase, T. Matsumoto and K. Fukui, This Bulletin, **28**, 273 (1955).
[5] T. A. Geissmann and A. Armen, *J. Am. Chem. Soc.*, **77**, 1623 (1955).
[6] Y. Odaira, This Bulletin, **29**, 470 (1956).
[7] S. Tanaka, *J. Chem. Soc. Japan* (*Pure Chem. Sect.*) **73**, 282 (1953)
[8] Presented at the Annual Meeting of Pharmaceutical Society of Japan, April 10, 1955.

α-carboxylic acid ethyl ester (III) was obtained directly as an intermediate product from 7-hydroxy-3-methoxyflavone-8-aldehyde and ethyl bromomalonate by the method of Tanaka⁽¹⁾ for benzofuran synthesis. This compound III corresponds to the intermediate product II.



III

We examined the condensation products between some another aromatic o-hydroxyaldehyde derivatives and ethyl bromomalonate.

2, 6-Dihydroxy-3-carbomethoxybenzaldehyde (IV)[9,10] and ethyl bromomalonate were refluxed in methyl ethyl ketone or acetone in the presence of potassium carbonate, and 2-carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V) was obtained as colorless needles of m. p. 133–4°C.

This condensation product V was hydrolysed to 4-hydroxycoumarone-2, 5-dicarboxylic acid (VI), m. p. 287–9°C (decomp.) or a mixture of VI and 2-carbethoxy-4-hydroxycoumarone-5-carboxylic acid (VII), m. p. 192–3°C by the reaction condition. Then, this dibasic acid VI was decarboxylated at 155–165°C (bath temperature) in quinoline in a stream of nitrogen gas with copper powder into karanjol (VIII), m. p. 55–6°C and karanjic acid (IX), m. p. 219–220°C (decomp.), which was identical with an authentic sample[4,11].

When the same condensation reaction was carried out with 4-benzyloxy-2-hydroxybenzaldehyde (X)[12,13], 2, 2-dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII) was obtained as colorless crystals of m. p. 105–6°C, but ethyl 6-benzyloxycoumarone-2-carboxylate (XIV)[14] was not obtained.

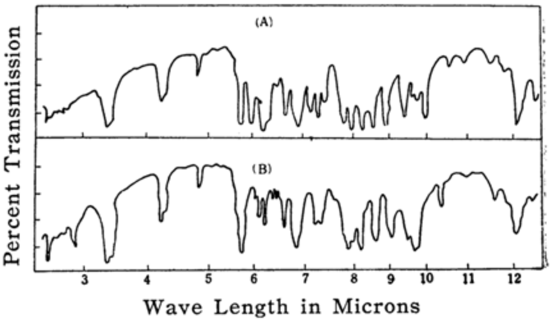
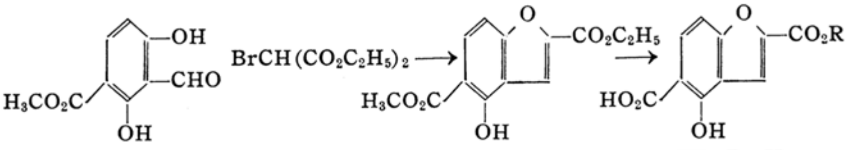


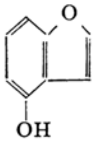
Fig. 1. Infrared Absorption Spectra (in Nujol).

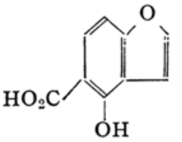
A: Ethyl 5-benzyloxy-2-formylphenoxyacetate (XI)[14].

B: 2, 2-Dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII).

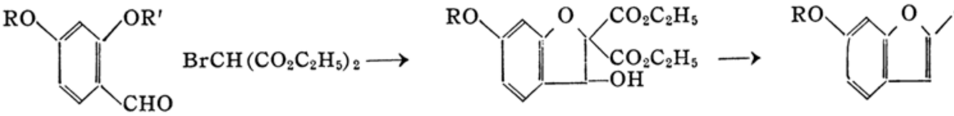


IV V VI R=H
VII R=C_2H_5





VIII IX



X R=$CH_2C_6H_5$ R'=H
XI R=$CH_2C_6H_5$ R'=$CH_2CO_2C_2H_5$
XII R=$CH_2C_6H_5$
XIII R=$CH_2C_6H_5$ R'=H
XIV R=$CH_2C_6H_5$ R'=C_2H_5

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9) K. Nakazawa, *J. Pharm. Soc. Japan*, **59**, 169(1939).

10) R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1828 (1938).

11) R. T. Foster and A. Robertson, ibid., 115 (1948).

12) J. S. H. Davis, P. A. McCrea, W. L. Norris and G R. Ramage, ibid. 3206 (1950).

13) T. Reichstein, R. Oppenauer, A. Grussner, H. Hirt, L. Rhymer and C. Glatthaar, *Helv. Chim. Acta*, **18**, 816 (1935).

14) R. T. Foster, Alexander Robertson and Anis Bushura, *J. Chem. Soc.*, 2254 (1948).

The structure of XII was characterized by microanalytical data and infrared spectra which proved to have a hydroxyl group, as shown in the Fig. 1. This condensation product XII was hydrolysed to 6-benzyloxycoumarone-2-carboxylic acid (XIII), m.p. 199–200°C* (c.f. Reichstein et al.[13], who gave m.p. 208–9°C**) with alkaline solution or a mixture of XIII and XIV, m.p. 94°C with potassium carbonate solution.

As the result of the present investigation, 2-carbethoxy-coumarone (V) or 2,2-dicarbethoxy-3-hydroxycoumaran derivative (XII) was obtained by the condensation reaction of *o*-hydroxybenzaldehyde derivatives and ethyl bromomalonate, and it may be due to the structure of starting *o*-hydroxybenzaldehyde derivatives.

More detailed studies of this reaction are in progress.

Experimental*

2,6-Dihydroxy-3-carbomethoxybenzaldehyde (IV).—This aldehyde was prepared from methyl β-resorcylate by the method of Nakazawa[9].

2-Carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V).—A mixture of 4.7 g. of 2,6-dihydroxy-3-carbomethoxybenzaldehyde (IV), 6.0 g. of ethyl bromomalonate, 12 g. of anhydrous potassium carbonate in 200 cc. of absolute methyl ethyl ketone was refluxed eight hours in a steam bath. The precipitates were filtered off immediately and washed with methyl ethyl ketone. After distilling off the solvent, water and the excess of dilute sulfuric acid were added. The precipitates were collected, washed with water and recrystallised from aqueous acetone in colorless needles of m.p. 133–4°C, which gave a dark violet ferric reaction in alcohol and gave no 2,4-dinitrophenylhydrazone; yield 1.7 g.

Anal. Found: C, 58.88; H, 4.57. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%.

The potassium carbonate salts were dissolved in water and the solution was acidified with dilute sulfuric acid. The precipitates were collected and recrystallised from alcohol. 0.6 g. of unchanged 2,6-dihydroxy-3-carbomethoxybenzaldehyde (IV) was recovered.

The same result was obtained also with acetone.

4-Hydroxycoumarone-2,5-dicarboxylic Acid (VI) and 2-Carbethoxy-4-hydroxycoumarone-5-carboxylic Acid (VII).—**a)** A mixture of 5.1 g. of 2-carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V) and 50 cc. of aqueous potassium hydroxide solution (10%) was heated in a steam bath with occasional shaking for thirty minutes. After cooling, the solution was acidified with dilute sulfuric acid and the precipitates thus formed were collected, washed with water and yielded obtained 4.2 g. of crude 4-hydroxycoumarone-2,5-dicarboxylic acid (VI), m.p. 278–280°C (decomp.). This crude substance was recrystallised from aqueous methanol in colorless crystals of m.p. 287–9°C (decomp.), which gave a blue ferric reaction in alcohol.

Anal. Found: C, 53.98; H, 3.12. Calcd. for $C_{10}H_6O_6$: C, 54.06; H, 2.72%.

b) A mixture of 1.7 g. of 2-carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V) and 1.7 g. of potassium hydroxide in 100 cc. of methanol was refluxed for twenty minutes on a steam bath. After the solvent was acidified with dilute sulfuric acid and distilled off, the precipitates were collected, washed with water and recrystallised from methanol in colorless needles of 2-carbethoxy-4-hydroxycoumarone-5-carboxylic acid (VII), m.p. 192–3°C, having a dark violet ferric reaction in alcohol; yield 0.4 g.

Anal. Found: C, 57.90; H, 4.35. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03%.

From the mother liquor of recrystallisation, 4-hydroxycoumarone-2,5-dicarboxylic acid (VI) was obtained.

Karanjol (VIII) and Karanjic Acid (IX).—A mixture of 3.5 g. of 4-hydroxycoumarone-2,5-dicarboxylic acid (VI), 3.5 g. of copper powder in 110 cc. of quinoline was heated under stirring in an atomosphere of nitrogen gas for about 2.5 hr. at 155–165°C (bath temperature) until evolution of carbon dioxide ceased. After being cooled and filtered from copper powder, the solution was acidified with dilute sulfuric acid and extracted with ether. The ethereal layer was extracted with an aqueous sodium bicarbonate solution and then with an aqueous sodium hydroxide solution (5%). Aqueous sodium bicarbonate extract (acid fraction) was acidified with dilute sulfuric acid and extracted with ether.

The crystals obtained on solvent removal from the dried ethereal extract were recrystallised from aqueous alcohol with the aid of charcoal in colorless needles, m.p. 219–220°C (decomp.), having a blue ferric reaction in alcohol; yield 0.43 g.

Anal. Found; C, 60.84; H, 3.66. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.40%.

These crystals were identical with an authentic karanjic acid prepared by the alkaline decomposition of karanjin[4] or by the method of Robertson et al.[11] Then, aqueous sodium hydroxide extract (phenol fraction) was acidified with dilute sulfuric acid and extracted with ether. The oil obtained on solvent removal from the dried ethereal extract was recrystallised from petroleum ether in colorless needles of karanjol (VIII), m.p. 55–6°C; yield 0.6 g.

Anal. Found: C, 71.70; H, 4.71. Calcd. for $C_8H_6O_2$; C, 71.63; H, 4.51%.

4-Benzyloxy-2-hydroxybenzaldehyde (X).—This aldehyde was prepared from resorcylaldehyde by the method of Davis et al.[12]

Ethyl 5-Benzyloxy-2-formylphenoxyacetate (XI).—This aldehyde was prepared from 4-benzyloxy-2-hydroxybenzaldehyde (X) by the method of Foster et al.[14] for the comparison of infrared spectra.

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* No melting points were corrected.

** The melting point was corrected.

2, 2-Dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII).—A mixture of 11.4 g. of 4-benzyloxy-2-hydroxybenzaldehyde (X), 18 g. of ethyl bromomalonate, 25 g. of anhydrous potassium carbonate in 150 cc. of absolute acetone was refluxed for 7.5 hr. on a steam bath. The reaction mixture was filtered, distilled off the acetone and was mixed with water. The precipitates were collected, washed with water and recrystallised from dilute alcohol in colorless plates, m.p. 105–6°C, which gave a negative ferric reaction in alcohol and gave no 2, 4-dinitrophenylhydrazone. Yield 11.7 g.

Anal. Found: C, 65.36; H, 5.85. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74%.

6-Benzyloxycoumarone-2-carboxylic Acid (XIII) and Ethyl 6-Benzyloxycoumarone-2-carboxylate (XIV).—a) A mixture of 2.0 g. of 2, 2-dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII) and 50 cc. of aqueous sodium hydroxide (1 N) was heated in a steam bath with occasional shaking for twenty minutes. The cooled mixture was filtered and the filtrate was acidified with dilute sulfuric acid. The precipitates were collected, washed with water and then recrystallised from dilute alcohol. 6-Benzyloxycoumarone-2-carboxylic acid (XIII) was obtained in colorless plates, m.p. 199–200°C; yield 1.2 g.

Anal. Found: C, 71.92; H, 4.55. Calcd. for $C_{16}H_{12}O_4$; C, 71.63; H, 4.51%.

b) A mixture of 3.8 g. of 2, 2-dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII), 2.0 g. of potassium carbonate, 50 cc. of alcohol and 15 cc. of water was refluxed for 1.5 hr. on a steam bath. After distilling off the alcohol, the residue was cooled and acidified with dilute sulfuric acid. The precipitates were collected, washed with water and separated by the trituration with dilute sodium bicarbonate solution. Crystallisation of the residual solid from alcohol gave the ethyl 6-benzyloxycoumarone-2-carboxylate (XIV) in colorless plates, m.p. 94°C; yield 0.5 g. The melting point of this substance was not depressed by admixture with the sample prepared by the method of Foster et al.[14] Sodium bicarbonate solution was acidified with dilute sulfuric acid. The precipitates were collected, washed with water and recrystallised from alcohol in colorless plates, m.p. 199–200°C, yield 0.7 g., identical with the above (a).

Summary

2-Carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V) and 2, 2-dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII) were synthesized respectively from 2, 6-dihydroxy-3-carbomethoxybenzaldehyde (IV) or 4-benzyloxy-2-hydroxybenzaldehyde (X) and ethyl bromomalonate by the method of Tanaka for benzofuran synthesis. 2-Carbethoxy-4-hydroxy-5-carbomethoxycoumarone (V) was hydrolysed to 4-hydroxycoumarone-2, 5-dicarboxylic acid (VI).

This dibasic acid VI was decarboxylated in quinoline with copper powder into a mixture of karanjol (VIII) and karanjic acid (IX).

2, 2-Dicarbethoxy-3-hydroxy-6-benzyloxycoumaran (XII) was hydrolysed to 6-benzyloxycoumarone-2-carboxylic acid (XIII).

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