

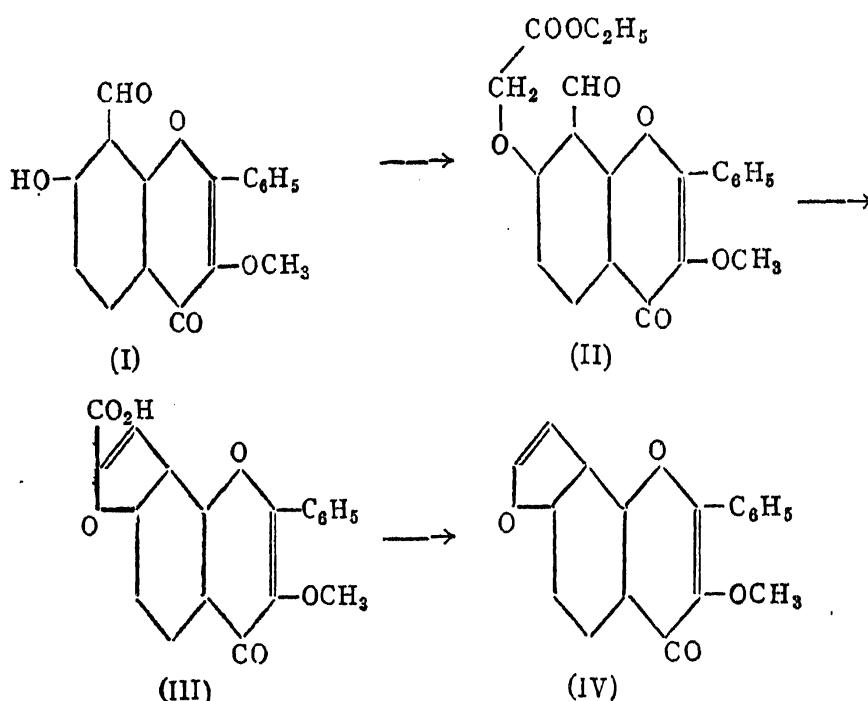
SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XV. Synthesis of Karanjin

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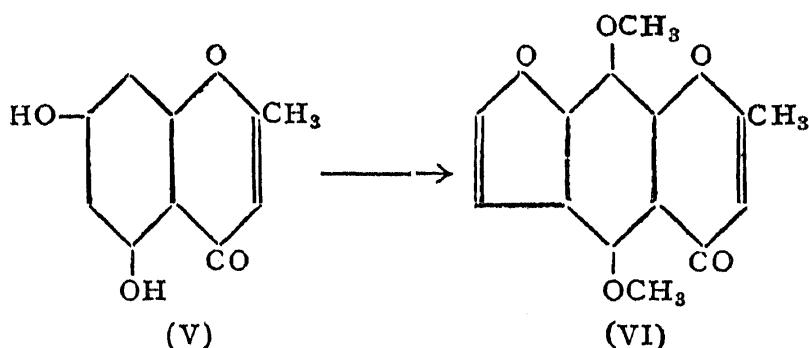
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IN Part I¹ of this series was reported an attempt to synthesise karanjin starting from 3-methoxy-7-hydroxy flavone and passing through the stages indicated by formulæ (I) to (IV). But there was unexpected difficulty and the synthesis was eventually accomplished by another route² which involved the construction of a chromone system on a coumarone unit; this general procedure has subsequently been adopted by others also. The first two stages (I) and (II) proceeded smoothly. Hydrolysis of the aldehydo-ester (II) with aqueous alkali seemed to produce also ring closure which was not noticed in similar but simpler cases.³ That the product was the furan carboxylic acid (III) was suggested not only by analytical evidence, but also by the study of absorption spectra and this is now confirmed by the lack of condensation of the acid with dinitro-phenylhydrazine in acid medium whereas compounds (I) and (II) having free aldehyde groups yield hydrazones. Further evidence is now provided by the use of alcoholic sodium ethoxide. This reagent has been used to convert aldehydo-esters of type (II) into esters of the corresponding furan carboxylic acids of type (III) by simple ring

closure.⁴ In the present case when ester (II) is treated with this reagent furan ring closure takes place yielding a mixture of the furan carboxylic acid (III) and its ester. The ester on hydrolysis produces acid (III). This is found to be identical with the original product obtained by the hydrolysis of (II) with aqueous alkali and there is no doubt therefore about its constitution. The formation of a furan carboxylic acid (type III) besides its ester in the above condensation with alcoholic sodium ethoxide has also been recorded by others⁴ in closely similar cases; but in the present case the yield of the acid is high.

It was originally reported¹ that the decarboxylation of karanjin- α -carboxylic acid (III) was not successful. This decarboxylation has now been carefully reinvestigated. When the acid is heated with acetic anhydride and sodium acetate for a number of hours and the product worked up, the major portion is found to be a complex substance soluble in alkali and a small neutral fraction consists of karanjin which is identical with the natural sample. A better yield of karanjin is obtained by heating the acid (III) with quinoline and copper powder though even here it is only a minor product. Thus the synthesis of karanjin by this route also, *i.e.*, by building up a furan ring on the required flavone system, is now complete. This method was successfully adopted for the first time in the chromono-furan series for the synthesis of kellin⁵ (VI) from 2-methyl-5:7-dihydroxy-chromone (V).



Recently we have had occasion to carry out the synthesis of other furano-compounds similar to karanjin. The conversion of aldehydo-esters of type (II) into furan carboxylic acids of type (III) by aqueous alkali seems to be fairly common and the decarboxylation of these acids gives only poor yields of the final furan derivatives of type (IV).

EXPERIMENTAL

7-Hydroxy-3-methoxy-flavone-8-aldehyde (I)

This has now been obtained by a modification of the method of Ranga-swami and Seshadri,⁶

A solution of the 7-hydroxy-3-methoxy flavone (2 g.) in glacial acetic acid (24 c.c.) was treated with hexamine (6 g.) and heated on a water-bath for six hours. The hot solution became turbid on the addition of hydrochloric acid (24 c.c. of 1:1 acid). After 10 minutes the solution was diluted with water (40 c.c.). Next morning the pale yellow crystalline solid was collected and crystallised from glacial acetic acid. The aldehyde was obtained as pale yellow minute needles melting at 222-23°. Yield 1.6 g. The phenyl-hydrazone crystallised from alcohol as yellow rectangular rods decomposing at 149-50°. The dinitrophenylhydrazone melted at 252-54°.

Carbethoxymethyl ether of 7-hydroxy-3-methoxy-flavone-8-aldehyde (II)

A modification of the original method¹ has now been adopted.

The flavone aldehyde (2 g.) was treated in acetone solution with ethyl bromacetate (4 c.c.) and anhydrous potassium carbonate (12 g.) and the mixture kept refluxing gently for six hours. The potassium salts were filtered off, the solvent was distilled off from the filtrate and the residue treated with water. Ether was then added, the mixture shaken up and the two layers separated. The ethereal layer was dried over anhydrous sodium sulphate. On the distillation of ether a semi-solid mass was obtained which solidified in the course of a few hours. It crystallised from methyl alcohol in the form of prismatic needles melting at 116-17°. Yield 1.5 g. The dinitro-phenylhydrazone melted at 150-52°.

3-Methoxy-flavono-7:8-furan-2'-carboxylic acid (Karanjin-a-carboxylic acid) (III)

Method I.—A modification of the original method¹ has now been adopted.

The carbethoxymethyl ether (II) (0.5 g.) was warmed with 5% aqueous potash (25 c.c.) at 60° for about half an hour. The compound gradually went into solution forming a deep red liquid. It was allowed to cool down to the laboratory temperature and acidified with dilute hydrochloric acid. A brown crystalline solid separated which was filtered and washed. It did not crystallise well from ordinary organic solvents and was originally purified by making use of its sparingly soluble sodium salt.¹ It however came out in the form of rectangular plates from a mixture of acetone and petroleum ether by slow evaporation and melted at 226-7°. Yield 0.3 g.

Method II.—Ring closure with sodium ethoxide.

To a suspension of the carbethoxymethyl ether (II) (1 g.) in absolute alcohol (distilled over calcium metal, 5 c.c.) was added sodium ethoxide

(0.1 g. of sodium and 4 c.c. of absolute ethyl alcohol). The contents were shaken vigorously for about 10 minutes. There was a slight rise in temperature. After 45 minutes excess of ether was added, the mixture stirred well and the solution decanted from the residue. The ether solution was washed with a little water (10 c.c.) and the washing added to the residue in the flask. More water (15 c.c.) was added to dissolve the residue completely. On acidification a pale yellow solid was obtained from the aqueous solution. It crystallised from aqueous alcohol in the form of small rectangular prisms melting at 226-7° (yield 0.7 g.). It did not depress the melting point of the acid sample obtained by the treatment of the carbethoxymethyl ether with aqueous alkali.

The ether extract was dried over calcium chloride and evaporated to dryness, when a colourless crystalline solid (0.1 g.) was obtained. On crystallisation from alcohol, it came out as bunches of needles melting at 158-60°. The yield of this compound (ester) was, however, not uniform (Found: C, 69.4; H, 4.7; $C_{21}H_{16}O_6$ requires C, 69.2 and H, 4.4%). The compound was insoluble in sodium bicarbonate and cold aqueous sodium hydroxide and did not develop any colour with ferric chloride in alcoholic solution. When warmed with aqueous alkali (4%) it went into solution. On acidification a colourless crystalline solid, soluble in sodium bicarbonate with effervescence, was obtained. It melted at 226-7° and did not depress the melting point of the acid obtained above.

Decarboxylation. Synthesis of karanjin (IV)

Method I.—The dry acid (III) (0.8 g.) was dissolved in freshly distilled acetic anhydride (25 c.c.) and refluxed with anhydrous sodium acetate (6 g.). After six hours the solution was cooled and added to alcohol (75 c.c.) to decompose excess of acetic anhydride. Next morning the mixture was distilled and water added to the residue. The pale brown solid product was filtered and added to 2% aqueous alkali and stirred well. Most of it went into solution; the mixture was extracted with ether several times. On distilling off the ether from the extract, a colourless solid was obtained. It crystallised from alcohol in the form of colourless needles melting at 156-7°. When admixed with karanjin, isolated from Pongamia oil, the melting point was not depressed. Yield 45 mg. (Found: C, 73.9; H, 4.0; $C_{18}H_{12}O_4$ requires C, 74.0 and H, 4.1%).

Method II.—The carboxylic acid (III) (0.5 g.), dried at 110° for two hours, was dissolved in absolute quinoline (25 c.c.) and the solution treated with copper bronze (0.5 g.). The mixture was refluxed for 45 minutes. It

was cooled, diluted with ether (100 c.c.) and filtered to separate the copper bronze. The ethereal layer was successively washed with dilute hydrochloric acid (1:1, 5 times), aqueous sodium hydroxide (4%, 3 times) and finally with water. It was then dried over anhydrous magnesium sulphate and the ether distilled off when a brownish crystalline solid was obtained. It crystallised from alcohol (animal charcoal) as prismatic needles melting at 156-7° (yield 75 mg.) and did not depress the melting point of the natural sample of karanjin. Both dissolved in concentrated sulphuric acid to form pale yellow solutions; on warming they turned bright green. When a drop of ferric chloride solution was added to the cold sulphuric acid solution and warmed, a dark green colour with strong dichroic red was developed.

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SUMMARY

The synthesis and identity of karanjin- α -carboxylic acid reported earlier is now confirmed and karanjin obtained from it thus completing the synthesis of this flavono-furan by the process of building up a furan structure on a flavone system.

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