

SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

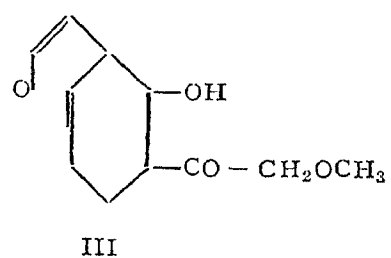
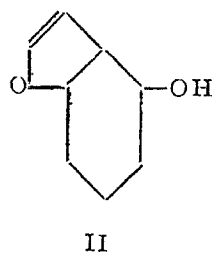
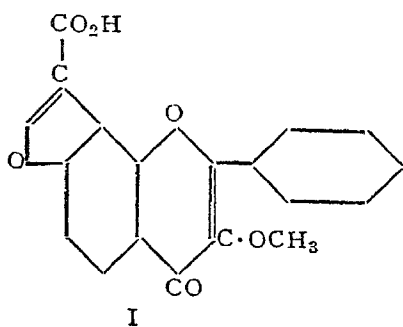
Part IV. Synthesis of Karanjin

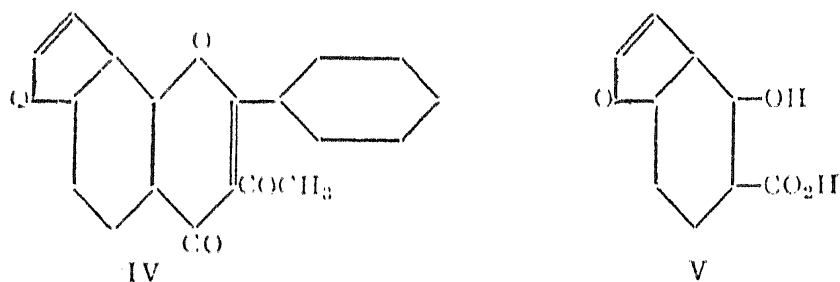
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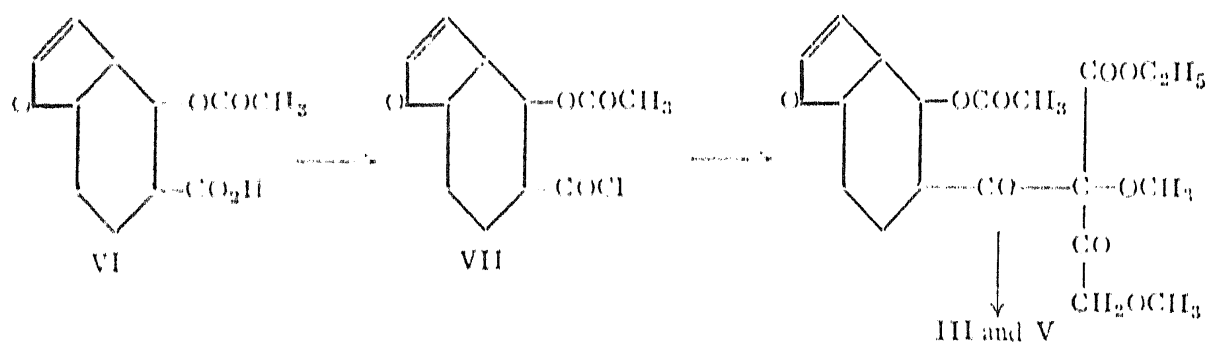
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THE constitution of karanjin as 3-methoxy-flavono-7:8-furan (IV) was proposed by Limaye¹ after a study of its properties and reactions and it has been supported by the work of Manjunath, Seetharamaiah and Siddappa.² Amongst the attempts to synthesise this compound may be mentioned the preparation of karanjin- α -carboxylic acid (I) by Rangaswami and Seshadri³; the final decarboxylation has not so far been successful. In this method 3-methoxy-7-hydroxy-flavone is the starting point and the furan ring is built up. The alternative method proceeds through karanjol or 4-hydroxy coumarone (II), the ω -methoxy ketone (III) and the subsequent synthesis of the flavone ring system to produce karanjin (IV). Karanjol could be prepared by the method of Reichstein⁴ or by that of Limaye.¹ The conversion of the ketone (III) into karanjin has been effected by Manjunath, Seetharamaiah and Siddappa.² Consequently, the stage that has not yet been realised in the complete synthesis of karanjin is the preparation of the ketone (III) from karanjol (II). This could not be accomplished by the action of methoxy-acetonitrile with the hydroxy coumarone (II) since no condensation takes place under the conditions of Hoesh's reaction.² Amongst other possible methods may be mentioned those proceeding through the intermediate stage of karanjic acid (V), the preparation of which from karanjol has been carried out by Limaye.¹ One of the possible routes has now been successfully explored and the results are presented in this paper.



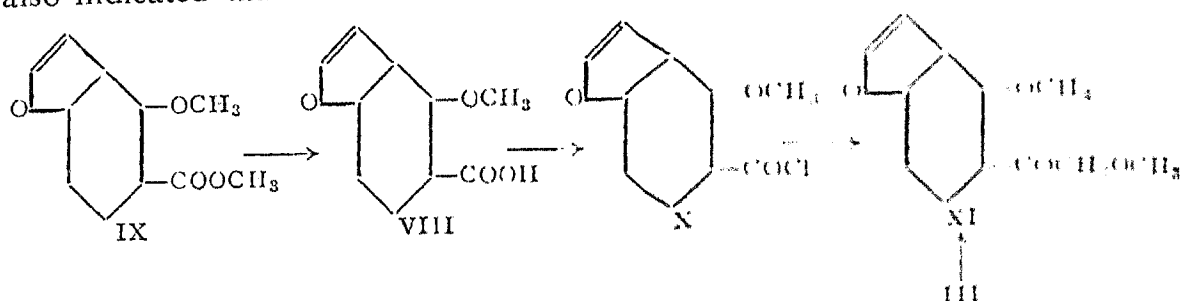


Karanjic acid is acetylated by means of acetyl chloride in the presence of pyridine and the acetyl derivative (VI) is converted into the acid chloride (VII) by the action of phosphorus pentachloride in carbon tetrachloride solution. The acid chloride is subsequently condensed with the mono-sodium salt of α - γ -dimethoxy-ethylacetoacetate. The condensation product is directly hydrolysed with methyl alcoholic potash and as one of the products of hydrolysis 5- ω -methoxyacetyl-4-hydroxy-coumarone (III) is obtained. In the course of the hydrolysis which should be expected to take place in different ways, some karanjic acid is also produced. When aqueous potash is employed for the hydrolysis, mostly the acid is produced, whereas with alcoholic potash, the desired ketone is the main product. It may be pointed out that a similar effect of the reagents is noticed in the decomposition of karanjin. The synthetic ketone has been found to be identical with the sample obtained by the degradation of karanjin.



With a view to explore the feasibility of the several transformations involved in the above synthetic procedure and also to make a preliminary study of the correct conditions, pilot experiments were carried out using the methyl ether of karanjic acid (VIII) which is simpler to deal with. It was obtained from karanjic acid through the intermediate formation of the ether-ester (IX) by the action of methyl iodide and potassium carbonate and by subsequent ester hydrolysis. The ether acid smoothly underwent conversion to the acid chloride (X) which was condensed with the mono-sodium salt of α - γ -dimethoxy-ethylacetoacetate and the product finally hydrolysed. In this case, the conditions of hydrolysis were not so difficult to manipulate and even aqueous potash gave rise to a fairly good yield of the dimethyl ether, 5- ω -methoxyacetyl-4-methoxy coumarone (XI). The synthetic product was

found to be identical with the compound obtained by the methylation of the hydroxy ketone (III) derived from karanjin. This series of transformations not only established the relation between karanjic acid and the ketone, but also indicated that the method is workable.



When the ketone (III) was heated with benzoic anhydride and sodium benzoate,² it yielded karanjin. Thus, as a result of the present work, the synthesis of karanjin in all its stages, as outlined in the scheme, may be said to have been accomplished.

Experimental

Ether-ester of Karanjic Acid—

Method 1(a): Methyl ester of karanjic acid.—Karanjic acid (1 g.) was dissolved in anhydrous methyl alcohol (12 c.c.) and concentrated sulphuric acid (2.2 c.c.) slowly added with cooling under the tap. The mixture was gently boiled on a water-bath for about five hours. Prolonged heating should be avoided, since it produced resinification. As much of alcohol as possible was then distilled off and the residue treated with 100 c.c. of cold water. A crystalline solid separated. However, the whole mixture was shaken with ether and the clear ether solution washed twice with aqueous sodium bicarbonate using 20 c.c. each time. The solvent was then evaporated and the solid residue recrystallised from dilute alcohol. The methyl ester came out in colourless rectangular plates, melting at 105–106°, the yield of the pure substance being 0.9 g. (Found: C, 62.5; H, 4.2; C₁₀H₈O₄ requires C, 62.5; H, 4.2%.)

(b) Methylation of the methyl ester.—The use of dimethyl sulphate and sodium hydroxide for this methylation was not found to be suitable, since the ester was highly sensitive to aqueous alkali. Hence the following method was adopted. The methyl ester (2 g.) was dissolved in acetone (15 c.c.). Excess of methyl iodide (2.5 c.c.) and anhydrous potassium carbonate (2 g.) were added and the solution kept gently boiling under reflux by means of a water-bath for about twenty-eight hours. Small quantities of methyl iodide were added at intervals in order to make up for

the losses due to evaporation. At the end of this time, the reaction was found to be complete from the absence of colour with ferric chloride. The solution was then filtered and the solvent removed by distillation. The ether ester thus obtained was a liquid insoluble in aqueous sodium hydroxide and it did not give any colour with alcoholic ferric chloride. It was directly employed without further purification.

Method 2.—Karanjic acid (1 g.) was dissolved in acetone (10 c.c.) and excess of methyl iodide (2 c.c.) and anhydrous potassium carbonate (1 g.) were added, and the solution kept gently boiling for about forty-five hours. At the end of this period, the product did not give any colour with ferric chloride. The isolation of the ether-ester was effected as before.

O-Methyl-karanjic-acid.—The liquid ether-ester (2 g.) was treated with 25% aqueous sodium hydroxide (20 c.c.) and the mixture gently boiled on a wire-gauze until the solution just became clear. It was cooled, acidified with dilute hydrochloric acid and the precipitate that was obtained was recrystallised from dilute alcohol. The methyl ether of karanjic acid was thus obtained as colourless elongated rectangular plates melting at 148°. The yield of the pure product was 1.6 g. (Found : C, 62.4; H, 4.4; $-\text{OCH}_3$, 16.0; $\text{C}_{10}\text{H}_8\text{O}_4$ requires C, 62.5; H, 4.2; $-\text{OCH}_3$, 16.1%.)

O-Methyl-karanjic-acid chloride.—Well dried and powdered methyl karanjic acid (5 g.) was treated with dry carbon tetrachloride (5 c.c.) and finely powdered phosphorus pentachloride (5 g.). The mixture was shaken well and gently heated on a boiling water-bath till no more fumes of hydrogen chloride were evolved and the solution became clear. The hot solution was then decanted from the unused excess of phosphorus pentachloride. The solid was washed with a little more of hot carbon tetrachloride and the washings added to the original solution. On cooling, the acid chloride separated as a thick mass of pale yellow crystals. It was filtered, washed with plenty of dry petroleum ether and finally recrystallised from carbon tetrachloride. The pure substance appeared as clusters of pale yellow needles melting at 72°. (Found: Cl, 16.5; $\text{C}_{10}\text{H}_7\text{O}_3\text{Cl}$, requires Cl, 16.9%.)

5- ω -Methoxy-acetyl-4-methoxycoumarone.— α - γ -Dimethoxy ethyl acetoacetate was prepared according to the method of Pratt and Robinson.⁵

The ester (1 g.; 1 mol.) was gradually added to finely granulated sodium (0.1 g.; 1 atom) suspended in anhydrous ether (10 c.c.). After about an hour during which the formation of the sodium derivative appeared complete, a solution of the acid chloride (1 g.) in dry ether (15 c.c.) was introduced. A mild reaction started immediately. The mixture was allowed to stand overnight, and was subsequently boiled for about four hours in order to complete

the reaction. After cooling, water was added, the ether layer separated and dried over anhydrous sodium sulphate. On evaporating the solvent, the condensation product was obtained as a liquid which soon solidified. It was mixed with water (8 c.c.) and aqueous potassium hydroxide (9 c.c. of 16% solution) which was added slowly in the course of two hours. The clear solution was then gently boiled for about two hours at the end of which a colourless solid could be seen separating out. The mixture was extracted with ether repeatedly and the ether extract washed with water and evaporated. The solid product thereby obtained readily crystallised from dilute alcohol in the form of colourless rectangular plates melting at 87–88°. It was insoluble in sodium hydroxide and was found to be identical with the sample prepared by methylating 5- ω -methoxyacetyl-4-hydroxy-coumarone described below; the mixed melting point was undepressed.

Methylation of 5- ω -methoxy-acetyl-4-hydroxycoumarone.—The following improved method for the preparation of the ketone was adopted as it was found to give almost quantitative yield. The main difference from the method adopted by Manjunath *et al.*² consists in avoiding water in the preparation of alcoholic potash.

Karanjin (1 g.) was treated with methyl alcoholic potash (2 g. in 30 c.c. anhydrous methyl alcohol) and boiled under reflux in a water-bath for about six hours. As much of the alcohol as possible was then removed, the residue dissolved in water and the solution acidified with excess of dilute sulphuric acid. The product was then ether-extracted and the ether solution washed with plenty of 5% sodium bicarbonate solution till no more could be extracted. The solvent was then distilled off and the solid obtained was recrystallised from dilute alcohol. It appeared as colourless needles and rectangular plates, melting at 96° and it was found to be identical in all properties with a specimen obtained by the degradation of karanjin according to the method of Manjunath *et al.*; yield 95%. The yield of karanjinic acid was very small.

The hydroxycoumarone (0.5 g.) was dissolved in anhydrous acetone (5 c.c.) and excess of methyl iodide (1 c.c.) and potassium carbonate (1 g.) added. The mixture was kept gently boiling for about 30 hours. Small quantities of methyl iodide were added at intervals. The completion of the methylation was proved by the absence of colour with ferric chloride. After distilling off the solvent, water was added to the mixture, the solid product was filtered and recrystallised from dilute alcohol. Colourless rectangular plates were obtained melting at 87–88°. The yield was almost quantitative. (Found: C, 65.4; H, 5.5; $-\text{OCH}_3$, 28.0; $\text{C}_{12}\text{H}_{12}\text{O}_4$ requires C, 65.5; H, 5.5; $-\text{OCH}_3$, 28.2%.)

Acetyl-karanjic acid.—Karanjic acid (1 g.) was dissolved in dry pyridine (3 c.c.) and the solution cooled in freezing mixture for about fifteen minutes. Acetyl chloride (2 c.c.) was slowly added drop by drop in the course of half an hour. The mixture was well stirred and after a few minutes poured on to crushed ice. The solid product was filtered, washed with cold water and after drying, recrystallised from chloroform. It was obtained in the form of long colourless needles melting at 157–58°. It gave no colour with ferric chloride in alcoholic solution. Boiling with water or alcohol should be avoided since it produces decomposition. (Found: C, 60.0; H, 3.8; $C_{11}H_8O_5$ requires C, 60.0; H, 3.6%.)

5- ω -Methoxy-acetyl-4-hydroxy-coumarone.—Well dried acetyl-karanjic acid (2 g.) was mixed with carbon tetrachloride (3 c.c.) and finely powdered phosphorus pentachloride (2 g.). The mixture was heated on a boiling water-bath till the evolution of hydrogen chloride fumes was over and the solution became clear. The hot solution was decanted from the excess of unused phosphorus pentachloride and distilled in order to remove as much of the carbon tetrachloride as possible. A light brown liquid of the acid chloride was thus obtained and it solidified on cooling in ice. It was, however, found to be a liquid at the laboratory temperature and was directly used for further condensation after being washed with petroleum ether, in order to remove carbon tetrachloride and phosphorus oxychloride.

Ethyl- α - γ -dimethoxyacetoacetate (2 g.; 2 mols.) was gradually added to sodium powder (0.22 g.; 2 atoms) suspended in anhydrous ether (30 c.c.) and shaken. After about an hour a solution of the acid chloride (1 g.; 1 mol.) in dry ether (15 c.c.) was introduced causing a mild reaction. The mixture was kept overnight, and gently boiled for about four hours in order to complete the reaction. After distilling off the ether, the product was treated with 10% methyl alcoholic potash (10 c.c.) and the mixture kept gently boiling for about three hours. As much of the alcohol as possible was then distilled off, and the residue treated with excess of dilute sulphuric acid. The solid product was extracted with ether and the ether solution was washed with aqueous sodium bicarbonate in order to remove any karanjic acid that might have been formed. On evaporating the ether solution, the pure ketone was obtained and it was recrystallised from dilute alcohol. It appeared in the form of rectangular plates and needles melting at 96–97°. It gave a bright violet colour with alcoholic ferric chloride and agreed in all respects with an authentic sample of 5- ω -methoxy-acetyl-4-hydroxycoumarone. The mixed melting point was undepressed. (Found: C, 64.0; H, 5.3; $-OCH_3$, 14.7; $C_{11}H_{10}O_4$ requires C, 64; H, 4.9; $-OCH_3$, 15.1%.) When the substance was heated with benzoic anhydride and sodium benzoate at 180° for 6 hours karanjin was obtained in good yield.

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Summary

The methyl ether of karanjic acid has been converted into 5- ω -methoxyacetyl-4-methoxycoumarone which is found to be identical with the methyl ether of the ketone obtained by the hydrolysis of karanjin with alkali. Following a similar procedure 5- ω -methoxyacetyl-4-hydroxycoumarone has been synthesised from karanjic acid and this yields karanjin when condensed with benzoic anhydride and sodium benzoate. Thus all the stages of the complete synthesis of karanjin have been accomplished.

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