

SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part I. Synthesis of Karanjin- α -Carboxylic Acid

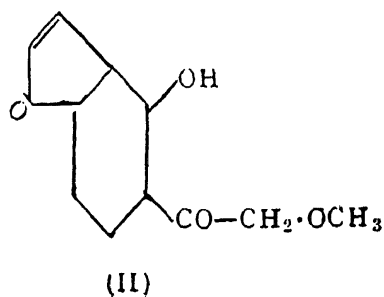
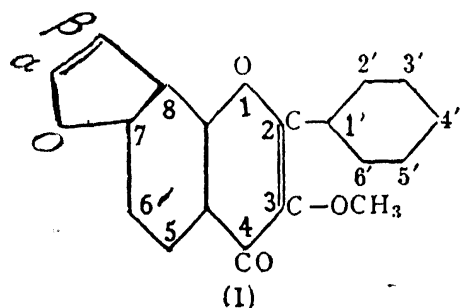
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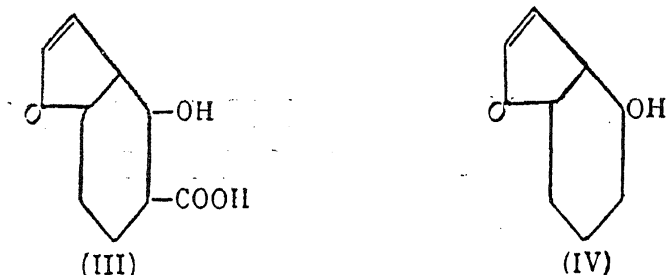
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KARANJIN was first isolated in a crystalline condition from the oil of *Pongamia glabra* by Limaye in 1922. It was subsequently obtained by Beal and Katti¹ from the same source. The constitution of this compound has been under investigation by Limaye for a fairly long period. His results have been reported mostly in the form of abstracts² and details of his experiments are not fully available. Through the kindness of this author we have been able to get a copy of the report of the Ranade Industrial and Economic Institute, Poona, for 1924 wherein some of his early experiments are described. The substance was found to melt at 158° and to have the composition $C_{18}H_{12}O_4$. Demethylation using hydrobromic acid gave rise to a good yield of a hydroxy-compound called karanjonol ($C_{17}H_{10}O_4$) melting at 192–93°. The acetyl derivative of this compound melted at 175–76°, the benzoyl derivative at 180° and the ethyl ether at 125–26°. The reactions of karanjin as well as those of karanjonol indicated that they belong to the flavone group of compounds.

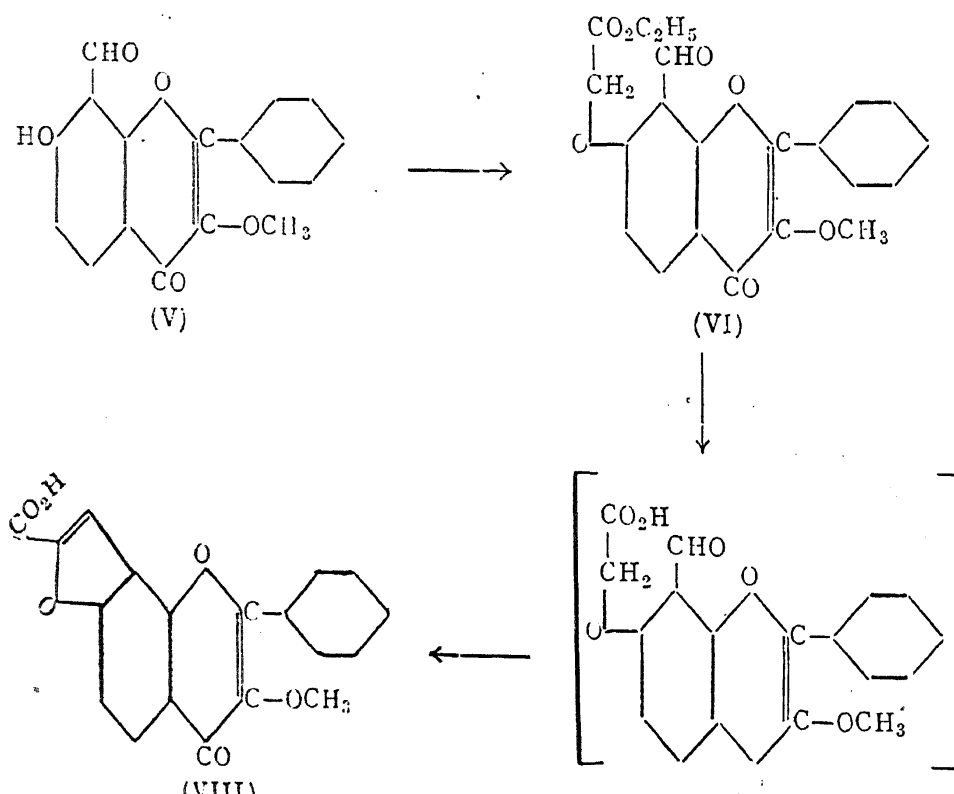
By the decomposition of karanjin with potash Limaye² isolated four products:—(1) a hydroxyketone having the formula $C_{11}H_{10}O_4$ (II), (2) karanjic acid, $C_9H_6O_4$ (III), (3) karanjol, $C_8H_6O_2$ (IV) and (4) benzoic acid. Karanjol could be obtained by the decomposition of karanjic acid and could be easily converted into the acid by boiling aqueous sodium bicarbonate. It was considered to be 4-hydroxy-coumarone and this idea was confirmed by synthesis. The constitution of karanjin was therefore represented as that of 3-methoxy-flavono-7:8-furan (I)





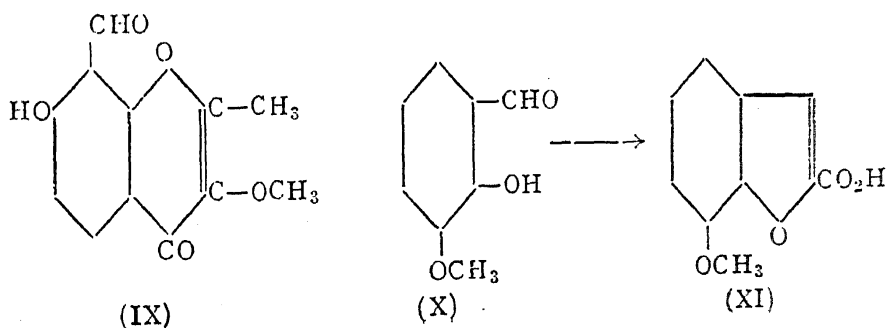
Recently Manjunath *et al*³ have published in detail the reactions and decomposition products of karanjin. They have placed the above constitution beyond doubt by degrading karanjic acid into well-known products. They obtained the hydroxy-ketone (II) as the main product of the action of alcoholic potash on karanjin and they were able to convert the ketone into the original karanjin by the method of Allan and Robinson thereby definitely proving that karanjin is a flavone.

Having prepared the aldehydes of 7-hydroxy-chromones and flavones⁴ we have been engaged for some time on the conversion of these into chromono- and flavono-furans. Since Limaye had indicated his proposed route to the synthesis of karanjin through karanjol² we intended to obtain it by a different way from 3-methoxy-7-hydroxy-flavone-8-aldehyde (V). Though we have not been completely successful in our efforts, in view of the announcement of Manjunath *et al* that they are making attempts to effect a complete synthesis of karanjin we have to record in this paper the results of our experiments leading to the synthesis of 3-methoxy-flavono-7:8-furan- α -carboxylic acid (VIII) which can be called karanjin- α -carboxylic acid.



As the first stage in our synthesis of karanjin the hydroxy-flavone-aldehyde (V) had to be condensed with a halogeno-acetic ester to yield the carbethoxymethyl ether (VI). The methods adopted by Späth and Pailer⁵ and Limaye *et al*⁶ in analogous cases of coumarin compounds were examined. They heated a mixture of the sodium derivative of the hydroxy-compound with iodo-acetic ester or bromo-acetic ester and obtained good yields of the condensation product. Though this was successful when we employed 2-methyl-3-methoxy-7-hydroxychromone-aldehyde (IX) it failed in the case of the corresponding flavone compound. After examining different methods it was discovered that by simply heating a mixture of the hydroxy-aldehyde and bromoacetic ester in benzene solution in the presence of potassium carbonate the condensation went remarkably well and gave rise to a good yield (70%) of the product (VI). It was noted that in the case of simpler aldehydes this treatment though successful did not give rise to such a good yield.

For the hydrolysis of the ester hot alcoholic potash that had been employed in analogous cases was not successful. There was considerable decomposition resulting in very poor yields. The most satisfactory method was to employ aqueous potash and to boil the mixture till solution was effected. But the interesting part of the hydrolysis was that it was accompanied by ring-closure giving rise to 3-methoxyflavono-7:8-furan- α -carboxylic acid (VIII) instead of the expected aldehydo-acid (VII). The above-mentioned workers on the coumarin series obtained simple hydrolysis by means of alcoholic potash and there was no ring-closure which had to be subsequently effected by heating with acetic anhydride and sodium acetate. The experiments of Reichstein *et al*⁷ who obtained 7-methoxy-coumarone-2-carboxylic acid (XI) by boiling *ortho*-vanillin (X) with bromoacetic ester in the presence of sodium ethoxide show that there exists the possibility of the furan ring-closure under these conditions. That the furan-carboxylic acid is obtained by the hydrolysis of the aldehydo-ester is not only supported by the analytical data but is further confirmed by a study of the absorption spectra of karanjin (I), of the carboxylic acid (VIII) and of the carbethoxy-methyl ether (VI). The first two resembled each other very closely and differed markedly from the last.



The final stage in the synthesis, *i.e.*, the decarboxylation of the acid (VIII) has been found to be difficult. It is quite stable under conditions which have been ordinarily found useful to remove the carboxyl group. On strong heating it undergoes a complex change giving rise to products which do not melt. Further attempts to effect this decarboxylation are in progress.

Experimental

The sodium salt of 2-methyl-3-methoxy-7-hydroxy-chromone-8-aldehyde (IX).—The hydroxy-aldehyde was dissolved in the least possible quantity of hot anhydrous methyl alcohol and the hot solution treated with the calculated quantity (1 mol.) of sodium methoxide in alcohol. A solid began to separate in the course of a few minutes. The mixture was cooled and treated with excess of anhydrous ether to precipitate all the sodium salt which was then filtered with suction, washed with ether and dried in a vacuum desiccator.

Carbethoxymethyl ether of 2-methyl-3-methoxy-7-hydroxychromone-8-aldehyde (IX).—The sodium salt (0.4 g.) was heated with ethyl bromoacetate (3–4 c.c.) for 8 hours in an oil-bath at 170–75°, the liquid being kept gently boiling. Excess of the ester was then removed by distillation under reduced pressure. The solid residue was treated with water, left exposed to the open air for a day to get rid of the last traces of the bromoacetic ester and then filtered and washed. It was subsequently stirred with cold dilute alkali and washed again with water. The resulting solid was a pale yellow powder which was quite crystalline and melted sharply at 180° (m.p. of the parent compound 180°, mixed m.p. 150–52°). When recrystallised from alcohol the carbethoxymethyl ether came out as very thin rectangular and rhombic plates, the melting point being the same as before. (Found: C, 60.2; H, 5.3; $C_{16}H_{16}O_7$ requires C, 60.0, H, 5.0%). The compound gave no colour with alcoholic ferric chloride (the original hydroxy-aldehyde gave a blood-red colour). Yield—80%.

Carbethoxymethyl ether (VI) of 3-methoxy-7-hydroxy-flavone-8-aldehyde (V).—The hydroxy-flavone-aldehyde (0.5 g.) was dissolved in a slight excess of hot benzene (40 c.c.) that had been dried over calcium chloride and treated with ethyl bromoacetate (4 c.c.) and freshly ignited potassium carbonate (2 g.). The mixture was kept gently boiling under reflux for 16 hours in a water-bath. The clear hot benzene solution was then carefully decanted into a crystallising dish and left exposed to a current of air for slow evaporation. The solvent and excess of bromoacetic ester were lost in a few hours and a colourless crystalline solid (flakes) remained behind. This when washed with a little ether to remove the last traces of bromoacetic ester melted at 115–16° and was sufficiently pure for further hydrolysis. For analysis the sample

was crystallised from methyl alcohol from which it separated as prismatic needles melting at 116–17°. (Found: C, 66.1; H, 4.7; $C_{21}H_{18}O_7$ requires C, 66.0; H, 4.7 %). Yield—0.4 g.

The compound was highly soluble in methyl and ethyl alcohols and insoluble in cold dilute alkali and it gave no colouration with alcoholic ferric chloride. It melted smoothly during combustion but decomposed slowly when strongly heated and the decomposition product could only be burnt very slowly.

Hydrolysis to 3-methoxyflavono-7: 8-furan- α -carboxylic acid (VIII).—When the foregoing ethyl ester (1 g.) was heated with 5% aqueous potash (50 c.c.) on a wire-gauze most of it went into solution before the boiling point was reached and the little solid that remained was also got into solution by boiling for about a minute. The hot solution which was orange in colour was set aside for half an hour, after which it was cooled under the tap and shaken with ether to remove any non-acid impurities. The lower alkaline layer was filtered through a fluted filter paper and the clear filtrate acidified with hydrochloric acid. A pale yellow fluffy solid separated slowly when the acidic mixture was left in the ice-chest for half an hour. This was filtered and washed with water.

The above crude acid on being ground in a mortar with cold saturated sodium carbonate solution was mostly transformed into a crystalline yellow solid (the sodium salt). This was filtered from the orange-red solution. The filtrate gave on acidification a very small quantity of a coloured solid which was discarded. The residue on the filter paper when washed with water first became colourless and then readily dissolved to give an almost colourless solution. When this was acidified with a few drops of acid it gave a perfectly colourless precipitate which after filtration and washing with water was crystallised from alcohol. The flavono-furan- α -carboxylic acid was thus obtained as narrow rectangular plates melting at 224–26°. (Found: C, 68.2; H, 4.0; $C_{19}H_{12}O_6$ requires C, 67.9; H, 3.6 %). Yield—20%.

The acid was sparingly soluble in water from which it separated in the form of needles and moderately soluble in alcohol. With 2N sodium hydroxide and concentrated sodium carbonate solutions most of the acid separated out as the sparingly soluble sodium salt. This behaviour is very common with benzofuran-carboxylic acids. The acid had a marked tendency to sublime unchanged giving rise to shining needles.

Summary

2-Methyl-3-methoxy-7-hydroxychromone-8-aldehyde formed a sodium derivative which readily condensed with bromoacetic ester to form the

corresponding carbethoxy-methyl ether. This reaction did not take place satisfactorily with 3-methoxy-7-hydroxyflavone-aldehyde. The condensation was, however, smoothly effected in boiling benzene solution in the presence of potassium carbonate. When hydrolysed with aqueous potassium hydroxide, simultaneous ring-closure took place to yield 3-methoxyflavono-7 : 8-furan- α -carboxylic acid which is considered to be karanjin- α -carboxylic acid.

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