

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part VII. Some Stages in the Synthesis of Karanjin

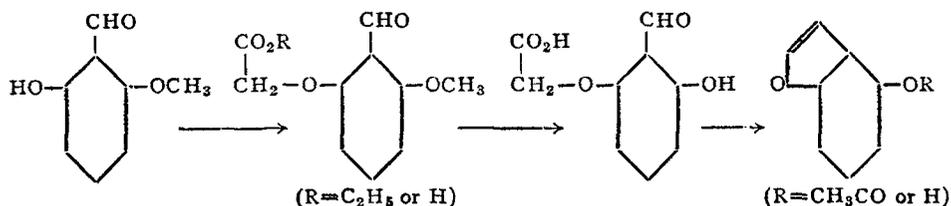
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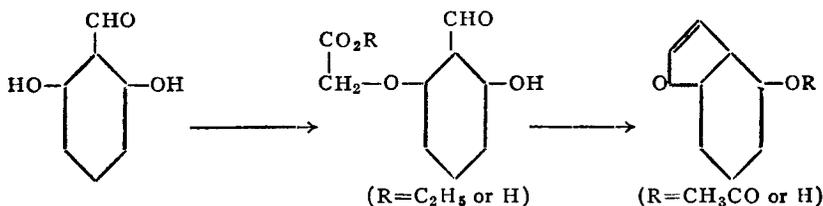
Received November 12, 1942

EXPERIMENTS relating to the synthesis of the karanjin skeleton starting from 7-hydroxy-3-methoxy-flavone were described in Parts I and II¹ of this series of papers. Karanjin itself could not be obtained through them. The alternative route which involves the building up of the flavone ring system from the required hydroxy-coumarone worked smoothly and this was described in Part IV.² Karanjic acid was converted into ω -methoxy-acetyl karanjol and from this ketone karanjin could be obtained by condensation with benzoic anhydride and sodium benzoate. The earlier stages leading to the synthesis of karanjic acid are examined in this communication and a new convenient procedure is described.

4-Hydroxycoumarone (karanjol) was first prepared by Reichstein³ who heated together an intimate mixture of freshly distilled furfural, dried sodium succinate and acetic anhydride. Besides other compounds he could obtain as one of the products 4-hydroxycoumarone in low yield. Subsequently Limaye⁴ adopted a more direct method; in his short note on this subject details of the preparations are not given. The monomethyl ether of γ -resorcylic aldehyde was condensed with ethyl bromoacetate in the presence of sodium ethoxide. The phenoxyacetic ester thus obtained was hydrolysed to form the corresponding acid and subsequently demethylated. This product was cyclised to form karanjol. Demethylation was effected at the phenoxy acetic acid stage since it was not possible after ring closure. The stages are represented below.



This procedure seemed to be capable of simplification. The more easily accessible γ -resorcylic aldehyde⁵ could be used directly and thus methylation and subsequent demethylation involving large losses could be avoided. It has now been condensed with bromoacetic ester in the presence of sodium ethoxide under controlled conditions. The synthesis may be represented as follows :—



The phenoxyacetic ester was hydrolysed to the acid and ring closure and decarboxylation were effected by boiling the acid with acetic anhydride. Karanjol acetate was thus produced and hydrolysed to karanjol. For the preparation of karanjic acid from karanjol two methods were adopted by previous workers. Limaye⁶ heated the hydroxy compound with aqueous sodium bicarbonate in a sealed tube. Harper⁶ treated it with sodium methoxide and methyl alcohol in a distilling flask and heated the mixture in a rapid current of carbon dioxide to 170°. The second method is found to be not only more convenient to operate, but it gives rise to a good yield of a pure sample of the acid.

Experimental

Condensation of γ -resorcylic aldehyde with ethyl bromoacetate: Ethyl-2-aldehydo-3-hydroxyphenoxy-acetic acid.— γ -resorcylic aldehyde (1.0 g., 1 mol.) dissolved in absolute ethyl alcohol (20 c.c.) was treated with sodium ethoxide in alcohol (0.167 g. of sodium-1 atom-in 20 c.c. of alcohol) and ethyl bromoacetate (0.9 c.c.) and the mixture refluxed for 3 hours. At the end of this period, it was found that the solution was practically neutral to litmus. The contents were then transferred to a basin and the solvent and unreacted ethyl bromoacetate allowed to evaporate slowly at the laboratory temperature. The brown viscous liquid left behind did not crystallise when kept in the ice chest and was insoluble in aqueous sodium carbonate. It gave a reddish brown colour with alcoholic ferric chloride and regenerated the colour of the Schiff's reagent. From these it could be concluded to be the required ester having free phenolic and aldehydo groups ortho to each other. It was directly subjected to hydrolysis without further purification.

Hydrolysis of the ester: 2-Aldehydo-3-hydroxy-phenoxy-acetic acid.—Boiling with caustic soda solution was found to be unsuitable since resinification took place and there was almost complete loss. The following

procedure was therefore adopted. The above ester was treated with excess of cold sodium hydroxide (20 c.c. of 10% solution) and allowed to stand at room temperature for about 45 hours. The clear reddish brown solution was treated with excess of dilute hydrochloric acid at 0° C. A light brown solid product separated out. However, the whole mixture was repeatedly extracted with ether. The ether extract was then shaken up with aqueous sodium bicarbonate (4% solution) till no more could be extracted. The acid was regenerated from the aqueous solution by the addition of excess of hydrochloric acid and was again extracted with ether. Much of the impurities could be removed by the above treatment with bicarbonate. However, on evaporating the ether solution a light brown liquid was obtained and it could not be crystallised easily. Further purification was therefore effected by the following method: The viscous liquid was dissolved in dry acetone (10 c.c.) and petroleum ether (B.P. about 60° C.) was then added to the solution until the supernatant liquid was clear and colourless. It was decanted from the brown deposit of impurities and was allowed to evaporate slowly when a light yellow crystalline solid began to separate out. Final crystallisation was effected from alcohol when the acid came out in the form of colourless rectangular plates melting at 176-77°, the melting point given by Limaye for the same being 175°. The acid gave the same colour reactions as the ester. (Found : C, 55.3 ; H, 4.3 ; $C_9H_8O_5$ requires C, 55.1 ; H, 4.1%.) The yield of acid from 1 g. of γ -resorcylic aldehyde was 0.6 g.

4-Hydroxy-Coumarone.—The above acid (1.0 g.) was mixed with a anhydrous sodium acetate (3.0 g.) and acetic anhydride (8.0 g.) and the mixture heated under reflux for about 20 minutes at a temperature of 150°. It was then cooled in ice and diluted with water. The brown liquid product that separated out was extracted with ether. After evaporation of the ether, the residue was treated with sodium hydroxide solution (10 c.c. of 5% solution) and just heated to boiling. The resulting clear solution was then cooled in ice and acidified with excess of dilute hydrochloric acid, when a light brown liquid began to separate out. It was ether extracted; the ether solution was dried over anhydrous calcium chloride and dry petroleum was added until no more coloured impurity separated and the solution was clear. On evaporating the solvents, a pale brown highly viscous liquid separated out which set into a mass of crystals on standing for several weeks. The yield was 0.46 g. and the sample could be directly used for conversion into karanjic acid according to the procedure adopted by Harper.⁷ But it was still contaminated with a little coloured impurity. Further purification could be effected by adopting one of the following

processes : (1) distillation *in vacuo* yields a pure product, but it is not suitable for small quantities ; (2) pressing on a porous tile removed impurities and colourless crystals were left, but the loss was great; (3) recrystallisation using low boiling petroleum ether was effected by extracting the coloured sample with the boiling solvent and evaporating the solution almost to dryness. The liquid residue obtained from (3) was almost colourless and crystallised on standing for a few days. The solid melted at 58·5-59° and the melting point was not depressed by admixture with a sample of karanjol obtained by the decomposition of karanjic acid. It gave a pink colour with alcoholic ferric chloride.

Summary

The initial stages in the synthesis of karanjin have been reinvestigated. A new synthesis of karanjol starting from γ -resorcylic aldehyde is described. The aldehyde is condensed with bromoacetic ester (1 mol.) in the presence of sodium alcoholate and the product hydrolysed and eventually converted into 4-hydroxy-coumarone by well-known stages. The preparation of karanjic acid from karanjol is made best through the action of sodium methoxide and carbon dioxide. Further stages leading to the synthesis of karanjin have already been described.

REFERENCES

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