SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part XVII. Some Isoflavono-7 : 8-Furans

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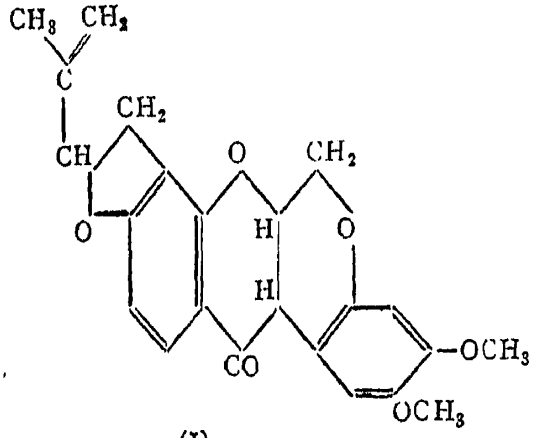
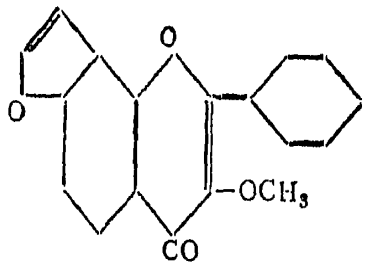
Rotenone (I) is one of the most powerful of the natural insecticides. It is a complex molecule containing five rings and it is not yet clear which parts of the molecule are intimately connected with its remarkable properties. According to Lauger and co-workers,[1] the group —CO—CH = CH—O— present in the chromanone part is a toxophore. But simpler molecules such as karanjin (II), 7-methoxy flavone (III) and flavanone (IV) and 7-methoxy-2-methyl-isoflavone (V) containing this group are considerably less efficient as fish poisons.[2]



(I)



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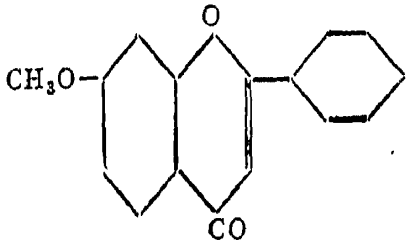

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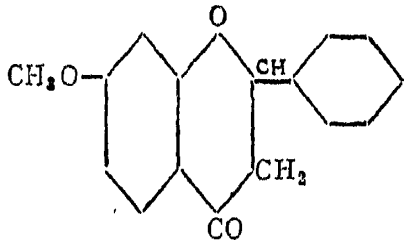

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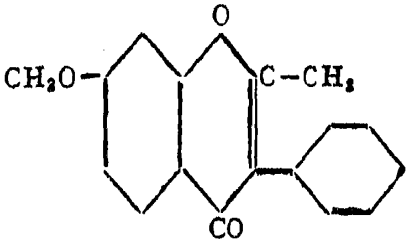
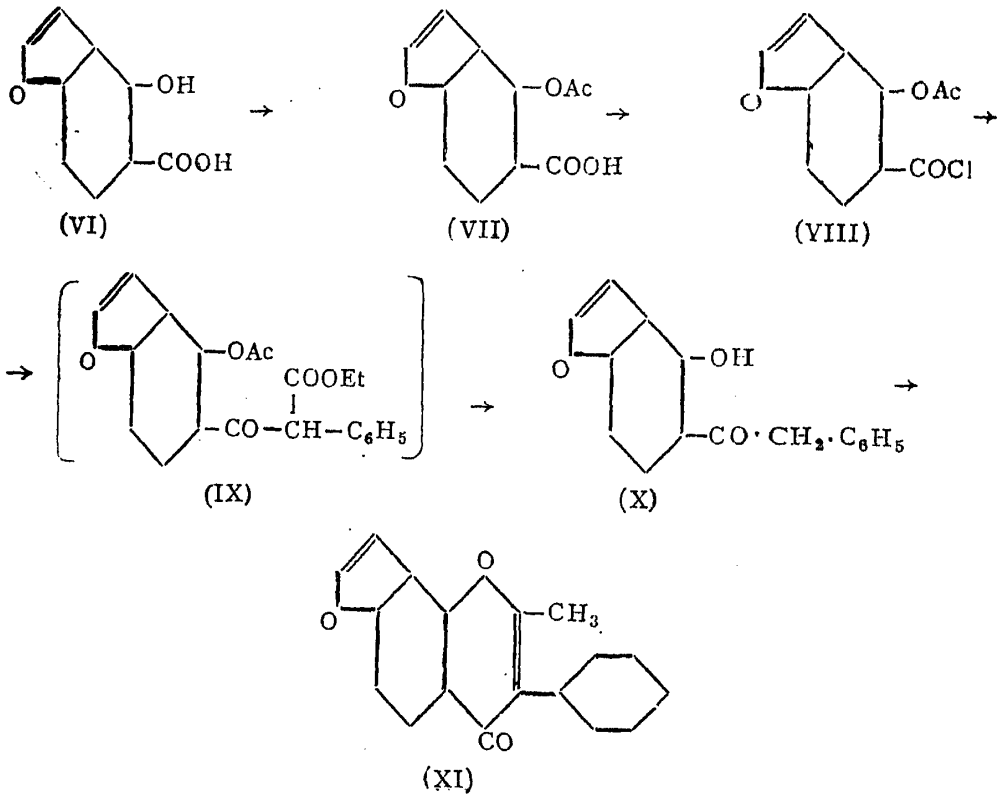


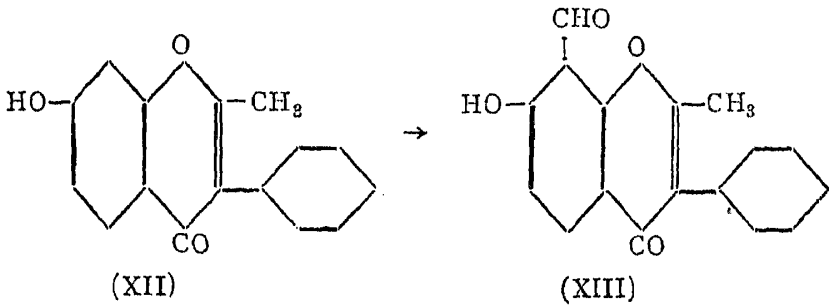
In attempts to gather more information on the effect of structure on toxic properties in the rotenone group, the synthesis of isoflavono-furans of the angular type has now been carried out. For this purpose two possible methods have been explored. The first starts with a suitable coumarone derivative and builds up the isoflavone structure on it; the second alternative begins with an isoflavone skeleton and builds up a furan ring on it. Both these methods have been previously employed in the synthesis of the flavono-furan, karanjin[3] (II).

For the first method karanjic acid (VI) which is fairly easily obtained as a product of hydrolysis of karanjin (II) is the starting material. Its synthesis has been worked out earlier by several groups of workers.[4] It is converted into its acetate (VII) and subsequently the acid chloride (VIII) and condensed with the sodium derivative of phenyl acetic ester. Subsequent hydrolysis and decarboxylation of the intermediate (IX) which is not isolated, yields benzyl-karanjyl-ketone (X). The isoflavone (XI) is obtained by boiling (X) with sodium acetate and acetic anhydride. A 2-methyl derivative is preferred since it is more closely related to rotenone than a compound unsubstituted in position 2.

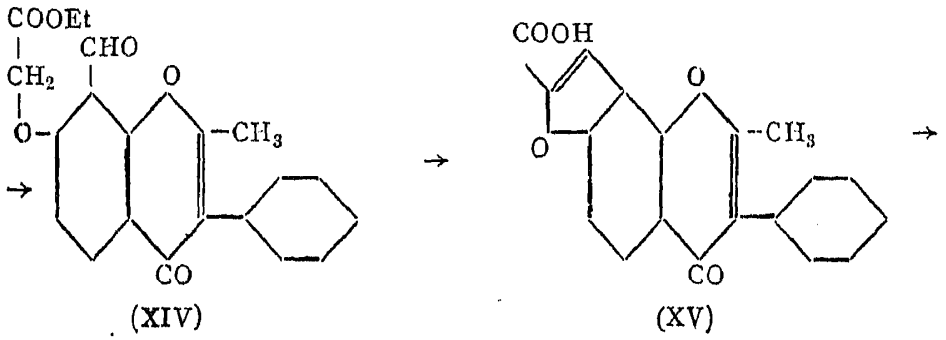


The second alternative method is found to give serious difficulties just as in the synthesis of karanjin (II). The starting material is 2-methyl-7-

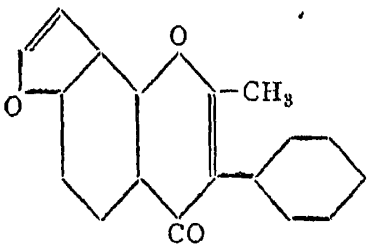
hydroxy-isoflavone (XII) which readily yields the corresponding 8-aldehyde (XIII) by the hexamine method. The next step involving condensation with bromacetic ester to yield the aldehydo-ester (XIV) also proceeds smoothly. Action of aqueous alkali, besides hydrolysing the ester, further brings about conversion into the furan-α-carboxylic acid (XV). This feature was first noticed in karanjin synthesis. The acid (XV) can be obtained more readily pure along with a small quantity of its own ester, by the action of alcoholic sodium ethoxide on the aldehydo ester (XIV). Final decarboxylation of the acid gives the corresponding furan (XVI) in poor yields only.



(XII) (XIII)



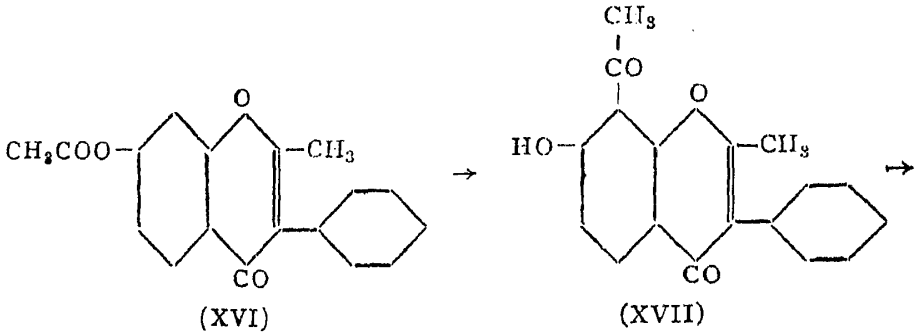
(XIV) (XV)

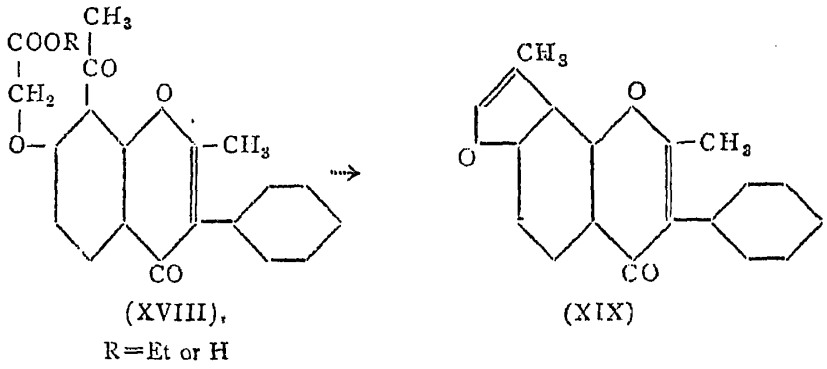


(XVI)

These difficulties are eliminated when a small modification in the synthesis is introduced. Instead of using 7-hydroxy-2-methyl isoflavone-8-aldehyde (XIII) the corresponding ketone (XVII) is made by the Fries migration of (XVI) and subjected to the series of reactions for building up the furan ring. Then every step proceeds smoothly, the carbethoxy-methyl ether (XVIII, R = Et) undergoes hydrolysis to give the corresponding ketonic acid (XVIII, R = H) and when this is boiled with sodium acetate and acetic anhydride ring closure and decarboxylation are effected and a good yield of 2: β-dimethyl-isoflavono-7: 8-furan (XIX) is obtained. Probable explanation of

this difference may be (1) the lower reactivity of a ketone group as compared with an aldehyde and (2) greater stability conferred on the furan structure by the presence of the β-methyl group.





Experimental

O-*Acetyl karanjic acid* (*VII*)

Karanjin required for this preparation was isolated from the oil of *Pongamia glabra* following the improved method of Rao, Rao and Seshadri.[5] Karanjic acid was obtained from it using the method of the same authors but it was not found necessary to keep an inert atmosphere in the reaction vessel. The presence of air did not affect the yields. For the preparation of the acetyl derivative of this acid the following modification of the original method[3] is found to be more convenient.

A solution of karanjic acid (1 g.) in anhydrous pyridine (3 c.c.) was cooled in ice-salt mixture and then treated with acetyl chloride (0·8 c.c.) drop by drop while stirring. After 30 minutes, the mixture was treated with crushed ice and dilute hydrochloric acid (10 c.c.). The acetyl derivative rapidly separated out as a colourless solid. It was filtered and crystallised from alcohol when it came out as colourless elongated prisms, m.p. 172–73°. Yield, 0·8 g.

4-*Hydroxy-coumarone*-5-*benzyl ketone* (*X*)

In an earlier paper[3] the acid chloride of acetyl karanjic acid was made using phosphorous pentachloride. This preparation has now been affected using thionyl chloride instead.

Well dried acetyl karanjic acid (1 g.) was treated with thionyl chloride (5 c.c.) and heated on a water-bath. In the course of a few minutes all the acid went into solution which was green coloured. The unreacted thionyl chloride was removed by distillation and the residue treated with carbon tetrachloride and filtered. The solvent was distilled off from the filtrate and the residual acid chloride was washed thrice with petroleum ether (5 c.c. each time). It was then obtained as a colourless viscous liquid which was directly employed for the next stage.

Freshly distilled ethyl phenyl acetate (1 c.c.) in anhydrous ether (25 c.c.) was treated with thin slices of metallic sodium (0·2 g.) and kept for 2 hours with occasional shaking. A profuse pale yellow precipitate of the sodium derivative appeared. It was fluffy and could with care be decanted along with ether into another flask thus separating it from the unreacted sodium metal. To this was added with stirring an ethereal solution of the acid chloride of acetyl karanjic acid. There was immediate reaction and the mixture became warm. After leaving overnight, it was gently refluxed for three hours and the ether was distilled off. The residue was next refluxed with 3% methyl alcoholic potash (30 c.c.) for two hours more. Alcohol was then removed under reduced pressure and water added. A dark brown solution was obtained. On acidification with hydrochloric acid, a pale yellow coloured solid separated out. It was filtered, agitated with 5% sodium bicarbonate solution to remove any karanjic acid that might have been formed and again filtered, washed with a little water and crystallised from alcohol when the coumarone ketone was obtained as rectangular plates melting at 105–6°. Yield, 0·4 g. (Found: C, 75·9; H, 5·0; $C_{16}H_{12}O_3$ requires C, 76·2 and H, 4·8%.) The ketone was easily soluble in alcohol, ether, benzene, acetone and ethyl acetate. It gave a violet blue colouration with alcoholic ferric chloride. It dissolved in aqueous alkali readily.

2-Methyl-isoflavono-7 : 8-furan (XI)

The coumarone-benzyl ketone (X) (0·5 g.) was refluxed with acetic anhydride (10 c.c.) and freshly fused sodium acetate (2 g.) for 12 hours. The excess of acetic anhydride was then decomposed by adding alcohol. Next day the mixture was distilled to remove alcohol and ethyl acetate and the residue taken up in ether. The ethereal extract was washed thrice with 5% aqueous sodium hydroxide and then with water. After drying over magnesium sulphate, ether was removed by evaporation. The residue quickly solidified on scratching with a glass rod. It was crystallised from alcohol when the isoflavono-furan (XI) was obtained as pale yellow stout prisms melting at 95–6°. Yield, 0·2 g. (Found: C, 78·1; H, 4·6; $C_{18}H_{12}O_3$ requires C,

78·3 and H, 4·3%.) It was easily soluble in alcohol, ether, acetone, benzene and ethyl acetate. It developed no colour with alcoholic ferric chloride. It did not go into solution in warm 5% aqueous alkali.

7-Hydroxy-8-formyl-2-methyl-isoflavone (XIII)

A mixture of 7-hydroxy-2-methyl-isoflavone[6] (2 g.), hexamine (8 g.) and glacial acetic acid (24 c.c.) was heated under anhydrous conditions on a vigorously boiling water-bath for six hours. The hot reddish brown liquid was then treated with 1 : 1 hydrochloric acid (24 c.c.) and heated again on the water-bath for about 5 minutes. After dilution with water (40 c.c.) it was allowed to remain overnight. There was a yellow precipitate which was collected, washed with water and dried in an air oven. The dry solid was extracted with hot benzene (25 c.c.) twice and the residue rejected. On concentrating the benzene extract, the hydroxy aldehyde (XIII) crystallised out as stout rectangular prisms melting at 164–5°. Yield, 1·0 g. It was easily soluble in aqueous alkali yielding a bright yellow solution. With ferric chloride a wine red colouration was obtained in alcoholic solution. (Found: C, 72·8; H, 4·4; $C_{17}H_{12}O_4$ requires C, 72·9 and H, 4·3%.)

7-Carbethoxy-methyl ether (XIV)

The above aldehyde (XIII) (2·8 g.) in anhydrous acetone (75 c.c.) solution was treated with ethyl bromo-acetate (1·2 c.c.) and anhydrous potassium carbonate (5 g.). After refluxing for six hours, the mixture was filtered and the filtrate distilled to recover acetone. The residue was treated with water and extracted thrice with ether. The ether extract was dried over anhydrous magnesium sulphate and the ether removed by distillation. The residue contained traces of ethyl bromo-acetate and was therefore washed thrice with small quantities of petroleum ether. It then solidified quickly when scratched with a glass rod. It was recrystallised twice from alcohol when the carbethoxy-methyl ether was obtained as colourless rectangular prismatic rods melting at 124–5°. Yield, 0·9 g. (Found: C, 68·6; H, 5·1; $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%.)

The potassium salts residue left after filtering off the acetone solution, was dissolved in a little water and acidified with hydrochloric acid. A white solid precipitate (1·4 g.) was obtained which was found to be identical with 7-hydroxy-8-formyl-2-methyl isoflavone.

2-Methyl-isoflavono-7 : 8-furan-α-carboxylic acid (XV)

A suspension of carbethoxymethyl ether (XIV) (1 g.) in absolute alcohol (6 c.c.) was treated with sodium ethoxide (0·1 g. of sodium in 4 c.c. of alco-

hol). On stirring vigorously a yellow precipitate separated out. After 45 minutes the mixture was diluted with ether (50 c.c.), agitated and carefully decanted. Very little was present in the ether solution. The ether-insoluble solid residue dissolved in water (20 c.c.). On the addition of hydrochloric acid (2 c.c.) a bright yellow precipitate separated out. It did not crystallise well from ethyl or methyl alcohol, acetone or ethyl acetate. It was purified by dissolving in sodium carbonate (effervescence) and reprecipitating with hydrochloric acid. It melted at 253–5° (decomp.). Yield, 0·8 g. It gave no colour with ferric chloride in alcoholic solution. (Found: C, 70·9; H, 4·0; $C_{19}H_{12}O_5$ requires C, 71·3 and H, 3·8%.)

Esterification of acid (XV)

The carboxylic acid (0·5 g.) was dissolved in absolute alcohol (25 c.c.) and refluxed for eight hours after adding concentrated sulphuric acid (1 c.c.). When the solution was concentrated, the ester came out in the form of microcrystals melting at 225–7°. It was thus different from the original ester (XIV). (Found: C, 72·2; H, 4·8; $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%.)

Decarboxylation of (XV) to 2-methyl isoflavono-7: 8-furan (XVI)

(*a*) Boiling the carboxylic acid (XV) with acetic anhydride and sodium acetate for two hours produced no appreciable change.

(*b*) The dry carboxylic acid (1·0 g.) was heated at 290–300° in a pyrex round-bottomed flask for 15 minutes. The cooled mass was broken up and warmed with 4% aqueous sodium hydroxide. The turbid dark reddish brown solution was repeatedly extracted with ether. The ethereal extract was washed with water and dried over calcium chloride and evaporated to dryness. A brown solid was left behind which was crystallised from acetone-petroleum ether mixture. The isoflavono-furan (XVI) separated out in the form of pale yellow stout prisms melting at 95–6°. Mixed m.p. with the sample prepared from karanjic acid was undepressed. Yield, 45 mg.

(*c*) A mixture of the dry carboxylic acid (0·5 g.) and copper bronze (0·5 g.) in absolute quinoline (25 c.c.) was refluxed for 45 minutes. It was cooled, diluted with ether (100 c.c.) and filtered. The filtrate was successively extracted with 1 : 1 hydrochloric acid (five times—25 c.c. each time), with 4% aqueous sodium hydroxide (thrice—20 c.c. each time) and finally with water. It was then dried over calcium chloride and evaporated to dryness. A pale yellow residue was obtained. It crystallised from acetone-petroleum ether as pale yellow prisms melting at 95–6°. Yield, 60 mg.

The isoflavono-furan dissolved in cold concentrated sulphuric acid to give a pale brownish yellow solution which on warming with a drop of ferric chloride solution turned dark brownish red.

The alkali washings from (*a*) or (*b*) on acidification gave rise to uncrystallisable products.

7-Hydroxy-8-acetyl-2-methyl-isoflavone (XVII)

An intimate mixture of 7-acetoxy-2-methyl-isoflavone[6] (XVI) (3·0 g.) and anhydrous aluminium chloride (5·5 g.) was heated at 170–80° in a conical flask protected from atmospheric moisture. At first, the contents melted into a dark coloured liquid but gradually solidified. After an hour and a half, it was cooled and treated with crushed ice and dilute hydrochloric acid (1 : 1, 75 c.c.). The dark solid slowly disintegrated when kept overnight. It was then heated on a wather-bath for 30 minutes and filtered hot. The solid residue was washed thoroughly with dilute hydrochloric acid and then with water. It was crystallised from alcohol twice when it was obtained as colourless star-like clusters of needles melting at 204–5°. Yield, 2·5 g. (Found: C, 73·2; H, 5·0; $C_{18}H_{14}O_4$ requires C, 73·5 and H, 4·7%.) It was soluble in alcohol, acetone and ether but only sparingly in benzene. It dissolved in dilute sodium hydroxide to give a pale yellow solution. With alcoholic ferric chloride, a brownish red colour was obtained. It dissolved in concentrated sulphuric acid to give brownish yellow solution with no fluorescence.

7-Carbethoxy-methyl ether (XVIII, $R = C_2H_5$)

A solution of (XVII) (2·0 g.) in dry acetone (120 c.c.) was treated with ethyl bromo-acetate (0·85 c.c.) and anhydrous potassium carbonate (5 g.) and refluxed for six hours. The inorganic salts were filtered off and washed with a little warm acetone. The filtrate was distilled to recover acetone and the residue taken up in ether. The ethereal extract was shaken twice with 2% aqueous alkali and then twice with water. After drying over anhydrous sodium sulphate, removal of ether gave a colouriess, viscous liquid, which solidified only after a few days. It crystallised from alcohol, as colourless prismatic crystals melting at 123–4°. Yield, 1·3 g. (Found: C, 69·2; H, 5·5; $C_{22}H_{20}O_6$ requires C, 69·5 and H, 5·4%.) It was easily soluble in alcohol, ether, acetone and benzene; but sparingly soluble in light petroleum. It did not dissolve in aqueous alkali and gave no colour with alcoholic ferric chloride.

7-Carboxy-methyl-ether (XVIII, R = H)

The above carbethoxy-methyl ether (1 g.) was treated with 3% aqueous potash (75 c.c.) and heated to 80° on a water-bath till all the solid went into solution (30 mts.). The resulting red solution was cooled and extracted with ether to remove any unhydrolysed material. On acidification, a colourless compound was obtained. It crystallised from acetone-petroleum ether mixture in the form of colourless prismatic crystals melting at 156-8°. Yield, 0·7 g. (Found: C, 68·0; H, 4·7; $C_{20}H_{16}O_6$ requires C, 68·2 and H, 4·5%.) It dissolved easily in sodium bicarbonate solution with effervescence and gave no colour with alcoholic ferric chloride.

β: 2-Dimethyl-isoflavono-7: 8-furan (XIX)

The above carboxylic acid (1·0 g.) was refluxed with freshly distilled acetic anhydride (15 c.c.) and fused sodium acetate (2 g.) for two hours. The excess of acetic anhydride was decomposed by pouring the cooled mixture into alcohol (45 c.c.). After leaving it overnight, the alcohol and the ethyl acetate were removed by distillation and the residue taken up in ether. The ethereal extract was thoroughly washed with 2% aqueous alkali to remove any unconverted carboxylic acid. It was dried over calcium chloride and distilled to remove ether. A colourless viscous liquid was obtained which did not crystallise even after three days. It was then taken up in acetone and petroleum ether added to turbidity. After some time the clear solution was carefully decanted and allowed to crystallise. Further crystallisation from alcohol yielded colourless needles melting at 170-1°. Yield, 0·4 g. (Found: C, 78·3; H, 5·1; $C_{19}H_{14}O_3$ requires C, 78·6 and H, 4·8%.) The substance was easily soluble in alcohol, ether and acetone. It was insoluble in aqueous alkali and developed no colour with ferric chloride.

Summary

Two methods of synthesising isoflavonofurans of the angular type are examined. Starting from karanjic acid (VI) and passing through the intermediate (X), 2-methyl-isoflavono-7: 8-furan (XI) is easily obtained. The alternative method which starts with 2-methyl-7-hydroxy-isoflavone (XII) and builds up the furan ring through the 8-aldehyde (XIII) is beset with difficulties. However if instead of the aldehyde, the corresponding ketone (8-acetyl derivative XVII) is employed the difficulties are eliminated and good yield of 2: β-dimethyl-isoflavono-7: 8-furan (XIX) is secured.

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