NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXIII. A Synthesis of Kellin*

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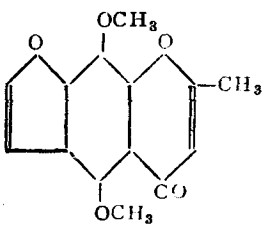
Kellin is the most important chemical component of the fruits of *Ammi Visnaga*, a plant belonging to the family Umbelliferæ. It is found in Egypt and the neighbouring Mediterranean countries. The crude drug has been used for a long time as a cure for leucoderma. Recently, Kellin has been found to be very useful in the treatment of spasmodic conditions like asthma and intestinal colic and also for certain diseased conditions of the heart. Its constitution was established by Späth and Gruber[1] as 2-methyl-5: 8-dimethoxy-7: 6-furano-chromone (I). For working out its synthesis, two ways are possible: (1) building up the furan ring on the required chromone system, and (2) building up the pyrone ring on the appropriate coumarone. Both these were examined in the case of the synthesis of karanjin[2]; the latter was found to be eventually successful. In a recent publication Robertson



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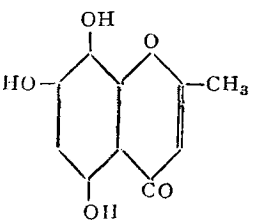

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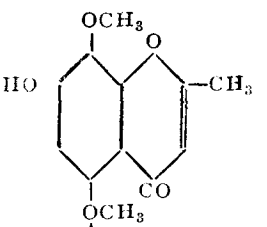

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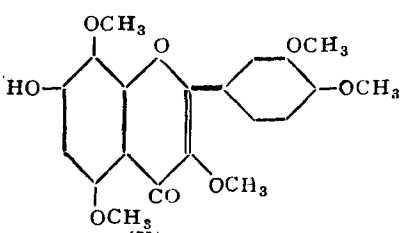

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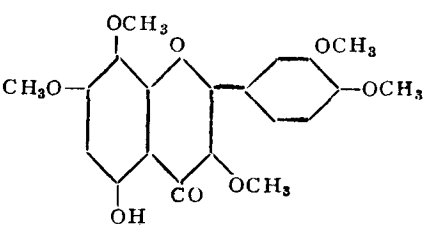

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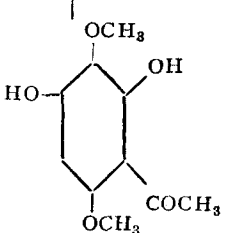

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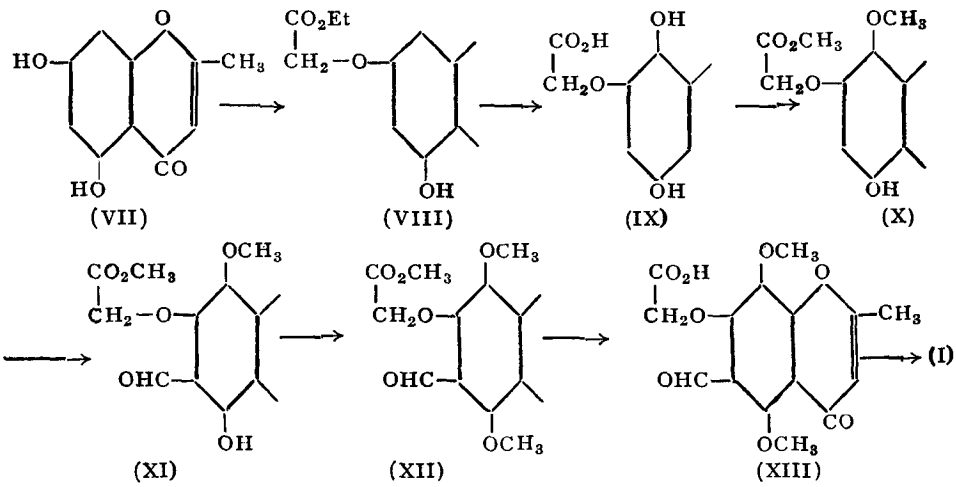
* A preliminary note was submitted to the Editor, *J.S.I.R.*, on 25—4—1949.

and co-workers[3] also have expressed the opinion that the second procedure is the more feasible of the two, particularly for the synthesis of the linear furano-chromones. But in the course of our recent work on nuclear oxidation in flavones and related compounds, there were indications that method I could be successful in the synthesis of kellin.

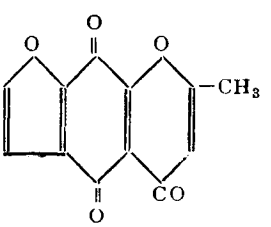
From the structure of kellin as given by Späth and Gruber, it is a derivative of 2-methyl-5: 7 : 8-trihydroxy chromone (II). The 5: 8-dimethyl-ether of this compound (III) could be directly made from 2 : 4-dihydroxy-3: 6-dimethoxy acetophenone (IV) which is known.[4] If an aldehydo group could be put into the 6-position of the ether (III) the synthesis of kellin could be readily achieved. But exploratory experiments[5] using the more readily available gossypetin pentamethyl ether with the 7-hydroxyl free (V) showed that the 6-position was not reactive. On the other hand, the isomeric 5-hydroxy compound (VI) reacted readily. It was, therefore, concluded that a free hydroxyl in the 5-position is necessary for the success of the synthesis. The procedure described below is based on these considerations and also conveniently utilizes alkaline persulphate oxidation which has been extremely successful for the (para) nuclear oxidation of flavones.



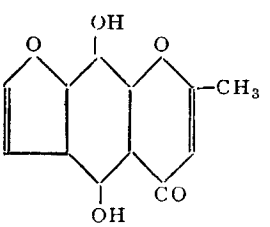
2-Methyl-5: 7-dihydroxy-chromone (VII)[6] is the starting point and its preparation has been effected by a modified process giving rise to improved yields. It is condensed with one mole of bromacetic ester using anhydrous potassium carbonate in acetone medium. The reactive hydroxyl in the 7-position takes part. The resulting phenoxy-acetic ester (VIII) is subjected to para-oxidation with alkaline persulphate. This introduces a hydroxyl in the 8-position (*cf.* oxidation of tectochrysin[7]) and at the same time the ester group undergoes hydrolysis yielding the dihydroxy acid (IX). This acid

is rather too unstable to be used directly for aldehyde synthesis. Methylation using two moles of dimethyl sulphate in acetone in the presence of potassium carbonate converts it into the 8-methoxy-phenoxy acetic ester (X) the resistant 5-hydroxyl being left out. This compound undergoes condensation with hexamine in glacial acetic acid solution yielding the 6-aldehyde (XI). Final methylation with excess of dimethyl sulphate gives the dimethoxy aldehydo-ester (XII). Gentle hydrolysis with alkali provides the required carboxylic acid (XIII) which when boiled with acetic anhydride and sodium acetate forms the furan ring with the simultaneous evolution of carbon dioxide. The product (I) melts at 154–55° and has the same crystal form as natural kellin. Previous workers[1] have recorded that it crystallises as colourless needles but it is now noted that on slow crystallisation it comes out as stout rectangular prisms though rapid crystallisation produces needles. The mixture of the natural and synthetic products does not exhibit any depression in melting point.

For a more thorough comparison of the natural and synthetic samples a readily available derivative was needed. This has been found in the oxidation of kellin with nitric acid whereby oxidative demethylation[1,8] takes place yielding the orange-yellow quinone (XIV). This melts at 215–16° with decomposition and has been used for comparison. The natural and synthetic samples are found to be identical. Further, reduction of the quinone with sulphur dioxide in alcoholic solution yields the corresponding quinol (XV) melting at 285–87° with decomposition. That this is the correct nor-kellin is proved by methylating it to kellin.



(XIV)



(XV)

EXPERIMENTAL

5 : 7-*Dihydroxy-2-methyl chromone* (*VII*)

This substance was prepared earlier by Joachum and Kostanecki and also by Gulati, Seth and Venkataraman.[6] The following modified procedure gives rise to better yields of a purer product.

Dry phloracetophenone (6 g.) was dissolved in acetic anhydride (25 c.c.) and freshly fused sodium acetate (10 g.) added. The mixture was

gently refluxed in an oil-bath for 6 hours. The dark brown mixture was cooled in ice-water and the acetic anhydride was decomposed by the addition of alcohol. After the reaction was over the contents were left overnight; the ethyl acetate that was formed was then removed under reduced pressure and the residue treated with water when the chromone acetate gradually separated as a pale-brown crystalline solid. This was filtered, washed with water, suspended in 5% aqueous alcoholic sodium carbonate solution (50 c.c.) and gently refluxed for one hour. The solution was filtered from suspended impurities, and acidified with dilute hydrochloric acid while cooling in ice-water. The chromone was precipitated as a pale yellow solid. It crystallised from alcohol-ethyl acetate mixture as very pale yellow stout prisms melting at 279–80°. Yield, 2·5 gm.

5-Hydroxy-7-O-carbethoxymethyl-2-methyl-chromone (VIII)

The dihydroxy chromone (2·4 g.) was dissolved in dry acetone (200 c.c.) and freshly ignited potassium carbonate (10 g.) and ethyl bromo-acetate (2·0 c.c.) were added and the mixture refluxed for 8 hours. The acetone solution was filtered, the solvent removed by distillation and the product crystallised from alcohol-petroleum ether mixture when it was obtained as colourless tiny prisms melting at 123–4°. It gave a violet-red ferric chloride colour turning brown-red with excess of the reagent and showed a weak green fluorescence in alcoholic solution. Yield, 1·5 g. (Found: C, 60·7; H, 5·3; $C_{14}H_{14}O_6$ requires C, 60·4; and H, 5·0%.)

5: 8-Dihydroxy-7-O-carboxymethyl-2-methyl chromone (IX)

The above compound (VIII) (1·0 g.) was dissolved in aqueous sodium hydroxide (2 g. in 50 c.c. of water) and a solution of potassium persulphate (3 g. in 50 c.c. of water) added slowly in 4 hours. During the addition the contents were cooled in ice-water and mechanically stirred. The red solution was allowed to stand overnight, then acidified to congo-red with hydrochloric acid and filtered from a small amount of fluffy matter that separated out. After an extraction with ether a further quantity (15 c.c.) of concentrated hydrochloric acid and sodium sulphite (5 g.) were added and the mixture heated on a boiling water-bath for half an hour. On cooling, a yellow powder separated which was filtered, washed free from acid and crystallised from alcohol-ether mixture when the quinol-acid (IX) was obtained as yellow rectangular prisms. The compound darkens at 220° and melts with decomposition at 229°-31°. It dissolves in 5% aqueous sodium carbonate to give a yellow solution; the colour gradually changes to pink-brown and fades. With ferric chloride in alcoholic solution, the compound gives a bluish-green colour changing to green with excess and

finally turning red; a dark brown precipitate separates on standing. (Found: C, 54·4; H, 3·9; $C_{12}H_{10}O_7$ requires C, 54·1 and H, 3·8%.)

5-Hydroxy-8-methoxy-7-O-carbomethoxymethyl-2-methyl chromone (X)

The dihydroxy-acid (IX) (0·5 g.) was methylated in dry acetone solution (30 c.c.) with freshly distilled dimethyl sulphate (0·4 c.c., 2 moles) in the presence of potassium carbonate (5 g.) by refluxing for 6 hours. The product crystallised from methyl alcohol as colourless needles melting at 137–8° and gave a pink-brown ferric chloride colour. Yield, 0·3 g. (Found: C, 56·9; H, 5·0; $C_{14}H_{14}O_7$ requires C, 57·1 and H, 4·8%.)

5-Hydroxy-8-methoxy-7-O-carbomethoxymethyl-2-methyl-chromone-6-aldehyde (XI)

The above ether-ester (X) (0·6 g.) was dissolved in glacial acetic acid (20 c.c.), hexamine (2 g.) added and the mixture heated in a boiling water-bath for 6 hours. A mixture of fuming hydrochloric acid and water (1 : 1; 10 c.c.) was then added and heating continued for half an hour more. The reaction mixture was diluted with water, neutralized with sodium bicarbonate and extracted with a large volume of ether. On distilling off the ether, the aldehyde was obtained as a yellow solid. It crystallised from rectified spirit as yellow flat needles and narrow rectangular plates melting at 149–50°. It gave a brown colour with ferric chloride in alcoholic solution. Yield, 0·1 g. (Found: C, 56·2; H, 4·7; $C_{15}H_{14}O_8$ requires C, 55·9 and H, 4·4%.)

5:8-Dimethoxy-7-O-carbomethoxymethyl-2-methylchromone-6-aldehyde (XII)

The hydroxy-aldehyde (XI) (0·3 g.) was completely methylated in acetone solution (25 c.c.) with dimethyl sulphate (0·2 c.c.) and potassium carbonate (5 g.) by refluxing for 30 hours. The product crystallised from alcohol as colourless prismatic needles melting at 142–3°. Yield, 0·2 g. (Found: C, 57·4; H, 5·1; $C_{16}H_{16}O_8$ requires C, 57·2 and H, 4·8%.)

2-Methyl-5: 8-dimethoxy-7-O-carboxymethyl-chromone-6-aldehyde (XIII)

The methyl ester (0·5 g.) was suspended in 2% potassium hydroxide (10 c.c.) and heated on a water-bath for 10 minutes. The solution was filtered, cooled in ice-water, acidified with dilute hydrochloric acid and extracted with a large volume of ether. The ether extract was dried over anhydrous sodium sulphate and the solvent distilled off. A viscous oil was left behind and it solidified on cooling. It crystallised from methyl alcohol as small colourless prisms melting at 179–80°. Yield, 0·3 g. (Found: C, 56·2; H, 4·6; $C_{15}H_{14}O_8$ requires C, 55·9; and H, 4·4%.)

Kellin (I)

The above aldehydo-acid (XIII) (0·2 g.) was dissolved in acetic anhydride (5 c.c.), fused sodium acetate (2 g.) added and the mixture gently refluxed in an oil-bath for 2 hours. It was then treated with ice-water, neutralized with sodium bicarbonate and the product extracted with ether. Some amount of sparingly soluble resinous matter was filtered off. The ether extract was washed with 5% sodium bicarbonate solution and water and the solvent evaporated. A pale yellow solid remained behind which on crystallisation from methyl alcohol appeared as thick, long, rectangular prisms melting at 154–55°. The mixed melting point with a sample of natural kellin was undepressed. Yield, 50 mg. (Found: C, 64·9; H, 4·8; $C_{14}H_{12}O_5$ requires C, 64·6 and H, 4·6%.)

Nitric acid oxidation of kellin to kellin-quinone (XIV)

Kellin (0·5 g.) was treated with nitric acid (d., 1·2; 5 c.c.) while cooling in ice and stirring with a glass rod. The substance dissolved with a deep red colour and immediately the quinone separated as an orange solid. After 15 minutes, water was added, the solid product filtered and washed free from acid and crystallised from alcohol in which it was moderately soluble. The quinone (XV) separated as orange-yellow needles and narrow rectangular prisms melting at 215–16° with decomposition. It was identical in all respects with a sample of the quinone obtained from natural kellin. (Found: C, 63·0; H, 2·9; $C_{12}H_6O_5$ requires C, 62·6 and H, 2·6%.)

Reduction to nor-kellin (XV)

Kellin-quinone (0·2 g.) was suspended in alcohol (20 c.c.) and sulphur dioxide was passed for half an hour. The quinone went into solution which gradually assumed a yellow colour. When concentrated the quinol came out as a crystalline solid. Further recrystallisation from alcohol yielded stout yellow rectangular prisms melting at 285–87° with decomposition. It gave a deep green colour with alcoholic ferric chloride, changing to red with excess. With *p*-benzoquinone in alcoholic solution, it produced a deep-red colour. (Found: C, 62·5; H, 3·8; $C_{12}H_8O_5$ requires C, 62·1; and H, 3·5%). Methylation with excess of dimethyl sulphate and potassium carbonate in dry acetone medium regenerated kellin.

Summary

Kellin (I) has been synthesised starting from 2-methyl-5: 7-dihydroxy-chromone (VII). The stages are as follows: (1) treatment with bromacetic ester (VIII); (2) oxidation with alkaline persulphate in which the ester group gets hydrolysed (IX); (3) partial methylation with 2 moles of dimethyl

sulphate (X); (4) condensation with hexamine to introduce an aldehyde group in the 6-position (XI); (5) complete methylation (XII); (6) gentle alkali hydrolysis to aldehydo-acid (XIII); and (7) final boiling with acetic anhydride and sodium acetate. Kellin-quinone and nor-kellin have been prepared as convenient derivatives.

We are further employing this method for the synthesis of the isomers and analogues of kellin.

Our thanks are due to Professors A. Schönberg and R. B. Fahmy of Cairo for samples of natural kellin.

Note added in Proof.—After submitting this paper for publication we received the issue of the *J.C.S.* containing the paper of Clarke and Robertson on the " Synthesis of Kellin and related Compounds (1949, 302) " Their method is different from ours. Following earlier work in this line they have first prepared kellinone, an ortho-hydroxy ketone having the coumarone ring system and subsequently built up the *r*-pyrone part to get kellin. By the ordinary method of demethylation using hydriodic acid they did not succeed in obtaining nor-kellin since the reaction was accompanied by isomeric change.

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