

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part X. Synthesis of Carthamidin and Iso-Carthamidin

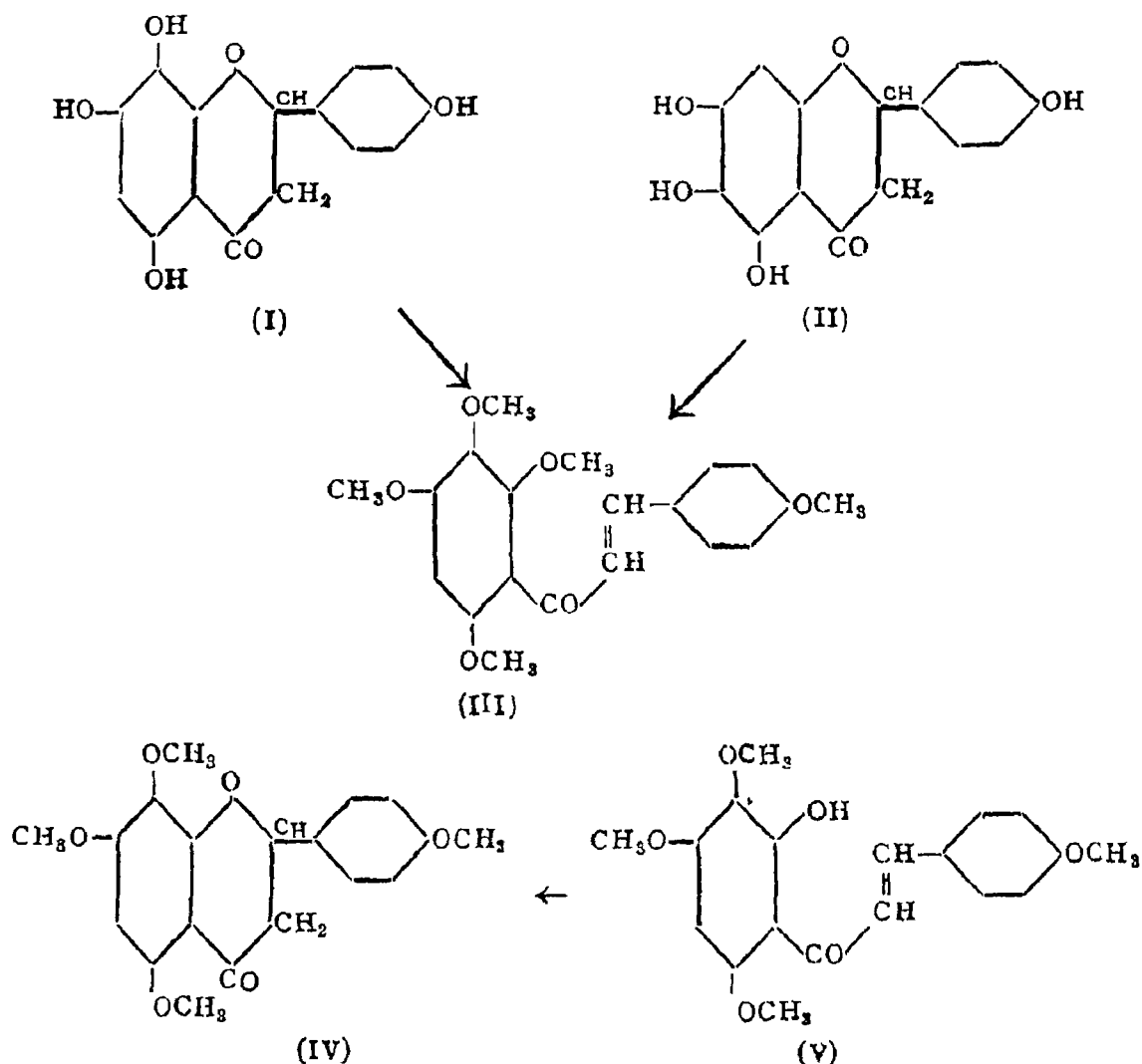
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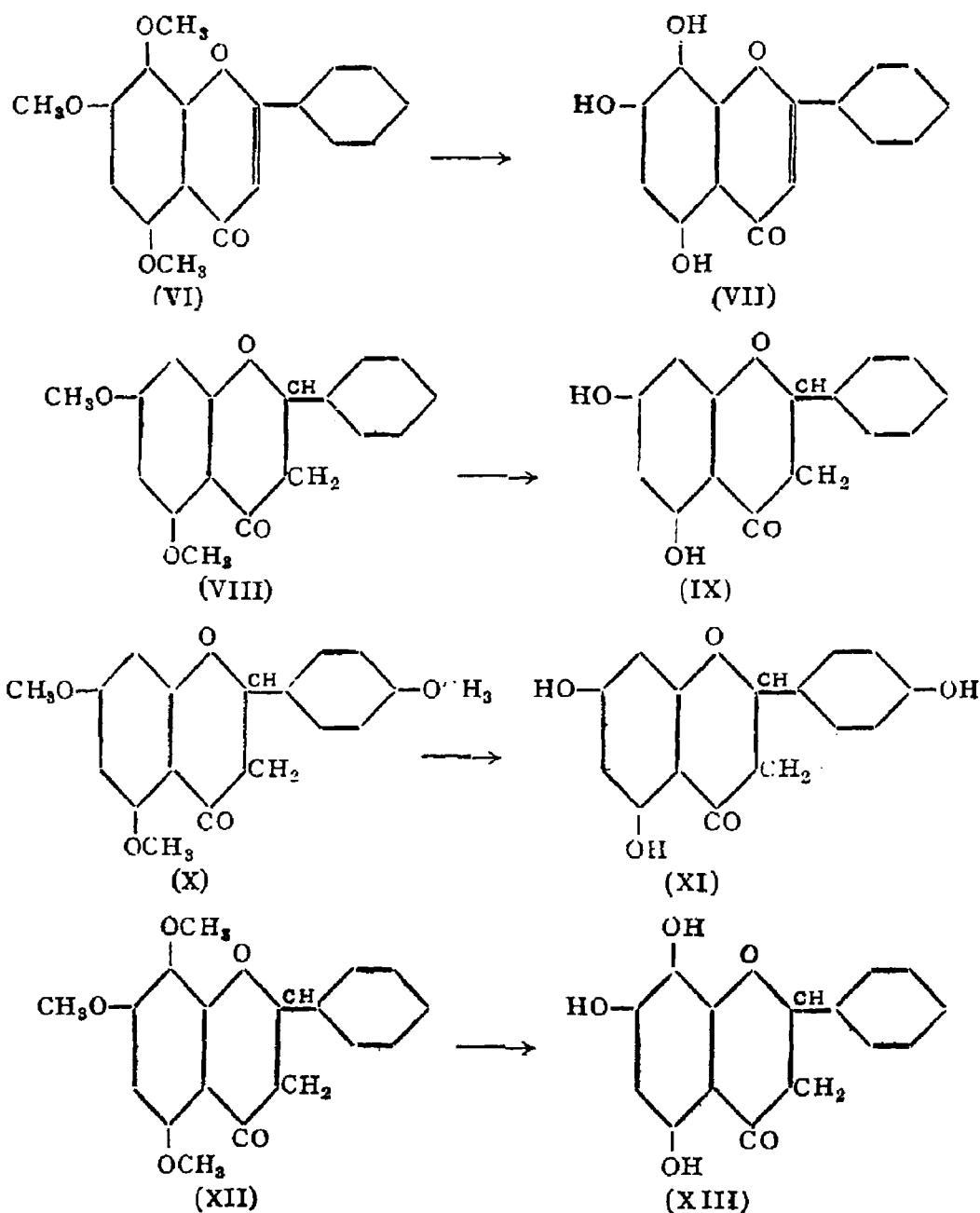
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CARTHAMIN, the red colouring matter of safflower has not only been used as a dye but is also believed to have remarkable medicinal properties. It is a glucoside which is most conveniently hydrolysed with phosphoric acid. Two aglucones carthamidin (I) and iso-carthamidin (II) are formed and they could be separated by means of moist chloroform. They were investigated in detail by Kuroda¹ who represented them by the formulæ (I) and (II). They are isomers with distinctive properties. In support of these constitutions she was able to show that by acetylation both of them gave rise to the same β -acetyl carthamidin which could be methylated by Freudenberg's method. The product, β -carthamidin pentamethyl ether (III), was found to be identical with synthetic 2:3:4:6:4'-pentamethoxy chalkone. Later Bargellini² described the synthesis of what could be considered to be carthamidin tetramethyl ether (flavanone IV) from the corresponding chalkone tetramethyl ether (V) by ring closure. Its relationship to carthamidin does not seem to have been established. There has been no report that this tetramethyl ether could be prepared from carthamidin by methylation or could be demethylated to carthamidin.

In earlier publications³ from this laboratory the use of anhydrous aluminium chloride in nitrobenzene solution for the partial demethylation of flavanones and chalkones has been described. Hydrobromic acid is also suitable for this purpose but it brings about loss by excessive resinification. In attempts to effect complete demethylation, hydriodic acid is found to be unsatisfactory since it seems to produce some other ununderstood complicated changes besides demethylation. This reaction is being investigated separately. The use of anhydrous aluminium chloride in benzene solution seemed to offer better chances of success. Successful use of it was made in the demethylation of wogonin dimethyl ether (VI) to norwogonin⁴ (VII). A more relevant example for the present purpose is the demethylation of the 5:7-dimethoxy flavanone (VIII) to the corresponding dihydroxy



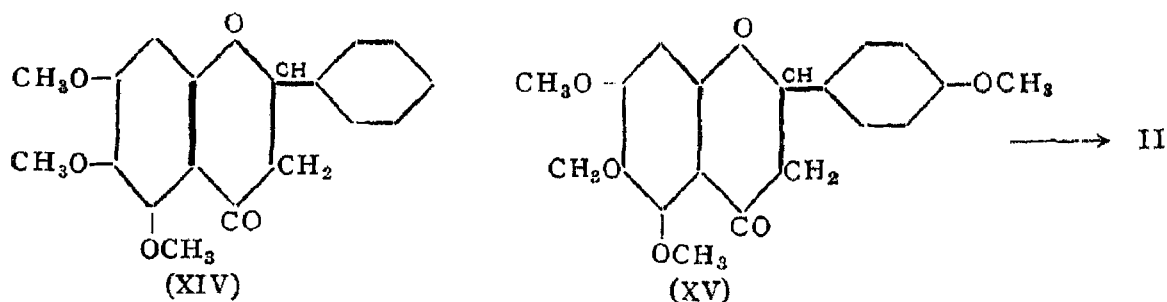
compound (IX).⁵ This showed that besides the 5-position, the 7-position also could be successfully demethylated. As the next step naringenin trimethyl ether⁵ (X) has now been examined. It easily yields naringenin (XI) and hence it could be concluded that this reagent is suitable for the 4'-position also. Before extending the work to carthamidin tetramethyl ether the simpler case of 5:7:8-trimethoxy flavanone (XII) was taken up. It also underwent smooth demethylation yielding a product which had all the properties that could be expected for 5:7:8-trihydroxy flavanone (XIII). When a similar product was obtained from 5:7:8:4'-tetramethoxy flavanone (IV) it could safely be considered to be the corresponding 5:7:8:4'-tetrahydroxy flavanone (I). Its properties and reactions closely agreed with those already recorded in the literature for carthamidin.¹ Though it has not been possible for us so far to secure a genuine sample of carthamin paste and isolate carthamidin from it or secure an authentic sample from Miss Kuroda, the agreement is so close that it could be safely stated that the synthesis of carthamidin has now been effected and that it supports the constitution given for it by Kuroda.



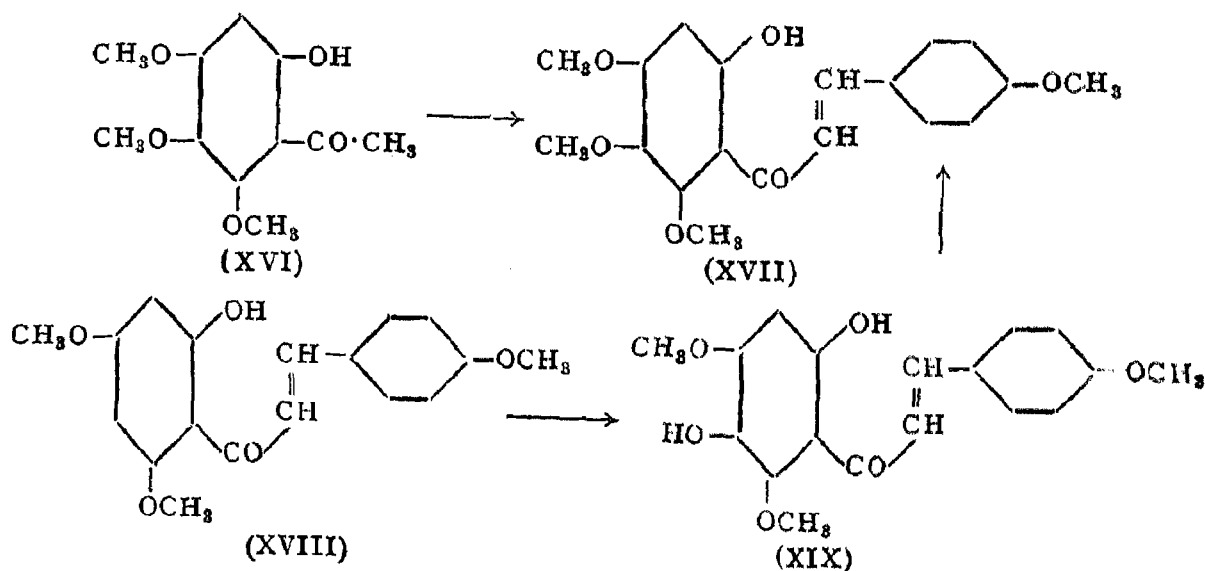
That no isomeric change takes place during the above demethylation to carthamidin is confirmed by the methylation of the product with 4 moles of dimethyl sulphate and anhydrous potassium carbonate in acetone medium. This method of methylation eliminates the difficulties experienced by previous workers. In the present case the product is a chalcone tetramethyl ether (V) which could be subsequently cyclised to carthamidin tetramethyl ether (IV). The course of the reaction is in agreement with similar cases reported recently.⁵

The above experimental technique has been further extended to the demethylation of 5:6:7-trimethoxy flavanone (XIV) and 5:6:7:4'-tetramethoxy flavanone (XV). Both get completely demethylated. The product from the latter agreed very closely in its properties with isocarthamidin (II).

Thus this constitutes a synthesis of this tetrahydroxy flavanone and a confirmation of its constitution.



Among the ethers required for the above work, the synthesis of carthamidin tetramethyl ether (IV) was reported by Bargellini.² The lower member, 5:7:8-trimethoxy flavanone (XII) has now been prepared by adopting a similar procedure. The preparation of the required chalcone was reported recently by Rao and Seshadri.⁶ The synthesis of 5:6:7-trimethoxy flavanone (XIV) has also been described by Rajagopalan and Seshadri.⁷ The required 2-hydroxy-chalcone was originally isolated only as a liquid. It has now been possible to crystallise it. The preparation of the higher member, 5:6:7:4'-tetramethoxy flavanone (XV) is now reported. It has now been prepared in two ways as indicated in the following diagrams. In the second method involving persulphate oxidation of the 2-hydroxy-chalcone (XVIII), the quinol-chalcone (XIX) is conveniently obtained as an intermediate.



In the reactions of the flavanones studied in the course of this work two points require special mention. (1) Bargellini's test with sodium amalgam which is characterised by the formation of green flocs in the case of 5:6:7-hydroxy flavones like baicalein, scutellarein, quercetagenin and other members of the series, produces only a green solution followed by a brown precipitate in the case of the corresponding flavanones. (2) The

bright red colour or a related shade which is readily given by most flavanones when treated with magnesium and hydrochloric acid in alcoholic solution is not produced by those members which are devoid of a hydroxyl or methoxyl group in the side-phenyl nucleus.

EXPERIMENTAL

Demethylation of 5:7:4'-trimethoxy flavanone (X)

A solution of 5:7:4'-trimethoxy flavanone (0.5 g.) in benzene (10 c.c.) was refluxed with anhydrous aluminium chloride (2 g.) for 2 hours. Benzene was then distilled off and the complex decomposed with ice and hydrochloric acid. The solid that separated was filtered and washed with ice-cold hydrochloric acid. It crystallised from dilute alcohol in the form of short needles melting at 244–45° alone or in admixture with an authentic sample of naringenin (XI).

5:7:8-Trimethoxy flavanone (XII)

A solution of 2-hydroxy 3:4:6-trimethoxy chalcone⁶ (1 g.) in alcoholic sulphuric acid (100 c.c., 4%) was refluxed on a water-bath for 24 hours. It was concentrated to 20 c.c. when the unreacted chalcone separated out. This was then filtered and the filtrate diluted with an equal volume of water when a colourless solid crystallised out. It was filtered and washed with small quantities of ether to remove the traces of the chalcone. On recrystallisation from benzene, 5:7:8-trimethoxy flavanone was obtained as colourless narrow rectangular prisms melting at 156–7°. Yield, 0.4 g. It gave no colour with ferric chloride in alcoholic solution and was insoluble in cold aqueous alkali. (Found: C, 68.4; H, 6.1; C₁₈H₁₈O₅ requires C, 68.7; H, 5.8%.)

5:7:8-Trihydroxy flavanone (XIII)

To a solution of 5:7:8-trimethoxy flavanone (0.5 g.) in benzene (10 c.c.) anhydrous aluminium chloride (1.5 g.) was added and the mixture refluxed on a water-bath for 2 hours. Benzene was then removed by evaporation and the complex decomposed with ice and hydrochloric acid when a pale yellow solid separated out. The mixture was then heated on a water-bath for a few minutes to complete the decomposition and after cooling was extracted with ether. On evaporating the ether solution a pale yellow solid was obtained. It crystallised from ethyl acetate-benzene mixture in the form of pale yellow prisms melting at 208–10°. It gave a dark reddish brown colour with ferric chloride in alcoholic solution and with *p*-benzoquinone gave a reddish brown colouration. Yield, 0.25 g.

(Found: C, 66.0; H, 4.6; $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%.) It did not give any red colour with magnesium and hydrochloric acid, but in all other reactions it very closely resembled carthamidin.

5:7:8:4'-Tetrahydroxy flavanone (carthamidin) (I)

A solution of 5:7:8:4'-tetramethoxy flavanone² (IV) (0.5 g.) in benzene (10 c.c.) was treated with anhydrous aluminium chloride (2 g.) and the reaction carried out as before. The product crystallised from aqueous chloroform as pale yellow broad rectangular prisms melting at 216–18°. It dissolved in aqueous alkali (2 N) to give a blue colour changing to reddish brown. Its alcoholic solution gave (1) with a drop of ferric chloride a green colouration changing rapidly to reddish brown, (2) with magnesium and hydrochloric acid a magenta colour, (3) a deep blue colour with aqueous barium hydroxide and (4) with lead acetate a yellow precipitate changing to green. Thus it agreed with carthamidin in all its properties. Yield, 0.2 g. (Found: C, 55.1; H, 5.2; $C_{15}H_{12}O_6, 2H_2O$ requires C, 55.5; H, 5.0%.)

Methylation

Carthamidin (0.2 g.) was dissolved in acetone (20 c.c.), dimethyl sulphate (0.3 c.c.; 4.4 mols.) and anhydrous potassium carbonate (1 g.) were added and the mixture refluxed on a water-bath for 8 hours. It was then filtered and the potassium salts washed with hot acetone. On evaporating the acetone solution a bright yellow solid was left. It crystallised from alcohol as bright orange yellow rectangular plates and prisms melting at 144–5°. It gave a deep reddish brown colour with ferric chloride in alcohol and was identical with 2-hydroxy-3:4:6:4'-tetramethoxy chalkone (V). The mixed melting point with a synthetic sample obtained from 2-hydroxy-3:4:6-trimethoxy acetophenone and anisaldehyde² was undepressed. On boiling with alcoholic sulphuric acid for 24 hours it was converted into carthamidin-tetramethyl ether (IV).

2-Hydroxy-4:5:6-trimethoxy chalkone

This was first prepared as a viscous liquid by Rajagopalan and Seshadri.⁷ When a concentrated alcoholic solution is allowed to stay in the refrigerator for two days it comes out as a crystalline solid. Recrystallisation from alcohol yields yellow broad rectangular plates melting at 132–3°. It gives a deep reddish brown colour with ferric chloride in alcohol. (Found: C, 69.0; H, 5.6; $C_{18}H_{18}O_5$ requires C, 68.7; H, 5.8%.) It could be cyclised into 5:6:7-trimethoxy flavanone, m.p. 154–55° (XIV).

5:6:7-Trihydroxy flavanone

5:6:7-Trimethoxy flavanone (XIV) (0.2 g.) was refluxed in benzene solution with anhydrous aluminium chloride (1 g.) for 2 hours and the product worked up. It crystallised from benzene-chloroform mixture as colourless tiny prisms melting at 226–27°; yield 0.1 g. It was easily soluble in alcohol, less in benzene and insoluble in chloroform. It gave a deep brown colour with ferric chloride in alcohol. It dissolved in aqueous sodium hydroxide forming a green solution which rapidly changed to yellow. Barium hydroxide gave a similar green solution. An alcoholic solution of the substance produced a deep green colour with sodium amalgam; this rapidly changed to brown and finally a brown precipitate was formed. Lead acetate in methyl alcoholic solution gave a green precipitate. (Found: C, 66.4; H, 4.0; $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%.) This substance resembled closely in its colour reaction isocarthamidin except in the lack of red colour when treated with magnesium and hydrochloric acid in alcoholic solution.

2-Hydroxy-4:5:6:4'-tetramethoxy chalkone (XVII)

2-Hydroxy-4:5:6-trimethoxy acetophenone⁹ (2 g.) was dissolved in alcohol (50 c.c.) and anisaldehyde (4 g.) added. A solution of potassium hydroxide (5 g.) in water (10 c.c.) was then introduced during the course of fifteen minutes, the temperature being maintained below 5°. The reaction was allowed to proceed at the laboratory temperature for 4 days, the solution being kept out of contact with air. The mixture was then diluted with water (100 c.c.) and extracted twice with ether to remove any unreacted aldehyde. The solution was then acidified while cooling under the tap when the hydroxy chalkone was precipitated as a slightly sticky reddish brown solid. It was collected, washed and taken up in ether. The ether solution was washed with dilute aqueous sodium carbonate to remove anisic acid. Distillation of ether yielded the chalkone as an orange yellow crystalline solid. Yield 1.5 g. On recrystallisation from alcohol it was obtained as deep yellow elongated rhombohedrons and melted at 141–42°. It was moderately soluble in alcohol and ether and dissolved more readily in acetone. It dissolved in aqueous sodium hydroxide with an yellow colour and gave a reddish brown colouration with ferric chloride in alcoholic solution. Its alcoholic solution developed no colour with magnesium and hydrochloric acid. (Found: C, 66.4; H, 5.7; $C_{19}H_{20}O_6$ requires, C, 66.3; H, 5.8%.)

2:5-Dihydroxy-4:6:4'-trimethoxy chalkone (XIX)

2-Hydroxy-4:6:4'-trimethoxy chalkone (XVIII)⁹ (1 g.) was dissolved in a solution of sodium hydroxide (2 g. in 25 c.c. water). The solution was

cooled to 15–20° and kept continually stirred. A solution of potassium persulphate (1.5 g.) in water (40 c.c.) was introduced dropwise during the course of 2 hours, the temperature being maintained at 15–20° throughout the reaction. After allowing to stand for 24 hours the dark brown reaction mixture was rendered distinctly acid to litmus by adding concentrated hydrochloric acid. The recovered unreacted chalkone was filtered and the filtrate extracted twice with ether. The clear solution was treated with sodium sulphite (1 g.) and concentrated hydrochloric acid (20 c.c.) and heated on a boiling water-bath for ½ hour. On cooling under the tap a reddish yellow crystalline mass of the oxidation product separated. It was filtered and washed with water; some more of it was obtained by extracting the filtrate with ether. The dihydroxy-trimethoxy chalkone crystallised from alcohol in red glistening prisms melting at 190–91°; yield, 0.3 g. It gave a deep reddish brown colour with ferric chloride in alcoholic solution and dissolved in aqueous alkali forming a deep red solution. (Found: C, 66.0; H, 5.5; C₁₈H₁₈O₆ requires C, 65.5; H, 5.6%)

Partial methylation

The above dihydroxy chalkone (XIX) (0.2 g.) was methylated by boiling with dimethyl sulphate (0.1 c.c.) and anhydrous potassium carbonate (0.5 g.) in dry acetone (15 c.c.) for 6 hours. It was filtered and the potassium salts washed with acetone. On distilling off acetone a yellow crystalline solid was obtained. It crystallised from alcohol as elongated rhombohedrons and melted at 141–42°. It was soluble in cold aqueous sodium hydroxide and gave reddish brown colour with alcoholic ferric chloride. The mixed melting point with the sample of 2-hydroxy-4:5:6:4'-tetramethoxy chalkone (XVII) described above was undepressed.

5:6:7:4'-Tetramethoxy flavanone (Isocarthamidin tetramethyl ether) (XV)

The hydroxy-tetramethoxy chalkone (XVII) (1 g.) was refluxed for 24 hours with alcoholic sulphuric acid (100 c.c.; 4%). The solution was concentrated under reduced pressure to 10 c.c. and the unreacted chalkone that separated on cooling filtered. The filtrate was diluted with an equal volume of water and left overnight. The colourless crystalline solid now produced was filtered and crystallised from dilute alcohol. Yield, 0.3 g. The tetramethoxy flavanone was obtained as colourless rhombohedral prisms melting at 124–25°. It was insoluble in cold dilute alkali and gave no colour with ferric chloride in alcoholic solution. With magnesium and concentrated hydrochloric acid its alcoholic solution developed a red colour. (Found: C, 66.2; H, 6.0; C₁₉H₂₀O₆ requires C, 66.3; H, 5.8%)

5 : 6 : 7 : 4'-Tetrahydroxy flavanone (Isocarthamidin) (II)

As in the previous cases the tetramethoxy flavanone (XV) (0.5 g.) was dissolved in benzene, treated with anhydrous aluminium chloride (2 g.), refluxed on a water-bath for 2 hours and the product worked up. It was first crystallised from acetone chloroform mixture and then from dilute methyl alcohol when it was obtained in the form of yellow prisms melting at 239–40° (Kuroda gave m.p. 240°); yield 0.2 g. It gave a deep brown colour when rubbed with aqueous alkali (2 N). Its alcoholic solution gave (1) a bluish green colour changing to reddish brown with ferric chloride, (2) a magenta colour when reduced with magnesium and hydrochloric acid, (3) a green colour with aqueous barium hydroxide, (4) a green precipitate with lead acetate and (5) with sodium amalgam a green colour fading rapidly with the formation of a brown precipitate. Thus the product agreed in all its properties with isocarthamidin described by Kuroda.¹ (Found: C, 62.2; H, 4.5; C₁₅H₁₂O₆ requires C, 62.5; H, 4.2%.)

SUMMARY

The method of demethylation using aluminium chloride in benzene medium is shown to be applicable to polymethoxy flavanones. 5:7:4', 5:7:8- and 5:6:7-trimethoxy flavanones yield the corresponding trihydroxy compounds. Similarly carthamidin and isocarthamidin are obtained from their tetramethyl ethers whose synthesis is described. This work provides synthetic confirmation of the constitution of these tetrahydroxy flavanones proposed by Kuroda. That no isomeric change takes place in the preparation of carthamidin is established by its methylation to its tetramethyl ether.

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