SYNTHESIS OF ISOCARAJURETIN HYDROCHLORIDE

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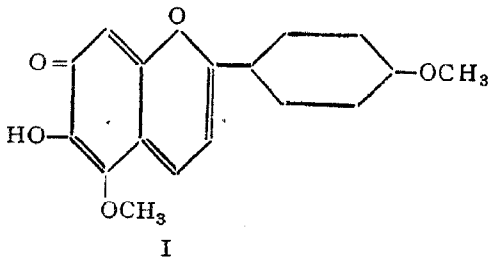
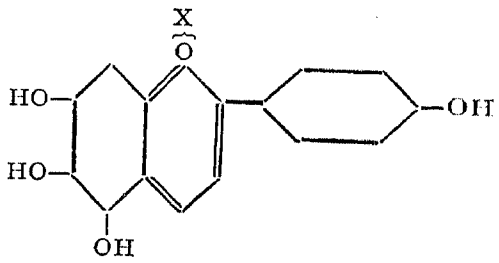
IN an earlier publication[1] on the synthesis of carajurin, the main constituent of the cosmetic pigment 'carajura', the work of Chapman, Perkin and Robinson[2] on the constitution of carajurin was reviewed. Carajurin was considered to be the colour-base of 5:4′-dimethoxy-6:7-dihydroxy flavylium chloride (I). The most important evidence for the above constitution was derived from the demethylation of carajurin with hydriodic acid. The product, carajuretin hydriodide (II) was converted into the corresponding hydrochloride (III) which was found to be the same as scutellareinidin chloride (III).



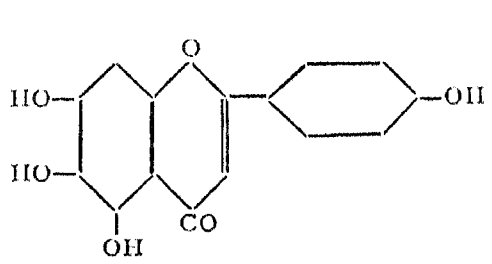
I



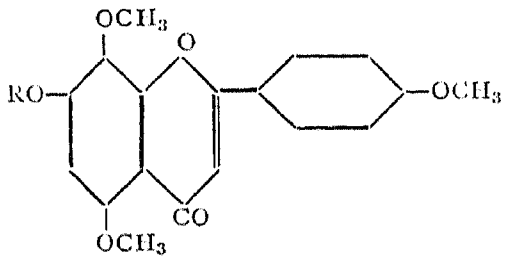
II, X=I
III, X=Cl

As we have mentioned earlier[1] the capacity of hydriodic acid to bring about isomeric change of 5:7:8-trihydroxy flavones into 5:6:7-trihydroxy compounds has an important bearing on the nature of the above demethylation. Scutellarein (IV) itself has been prepared by the demethylation of 5:8:4′-trimethoxy-7-hydroxy flavone (V *a*)[3] and 5:7:8:4′-tetramethoxy flavone (V *b*)[4]. Besides causing demethylation, hydriodic acid opens out the heterocyclic ring of the flavone molecule producing as a probable intermediate the diketone (VI). Subsequent ring closure involves the hydroxyl which forms part of the quinol unit and hence scutellarein results.

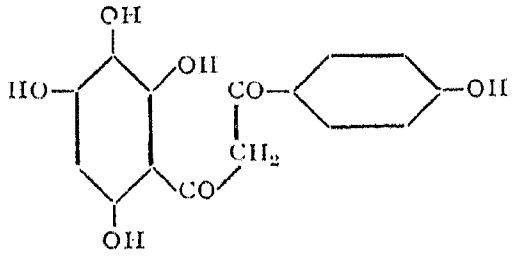
The phenomenon of ring isomerisation in flavones and related compounds was discussed in detail in a recent paper by Mukerjee, Seshadri and Varadarajan.[5] While flavones undergo ready isomeric change in the presence of boiling hydriodic acid, flavonols do not. The possibility of a similar isomeric change in the flavone type of anthocyanidins (*e.g.*, carajuridin)



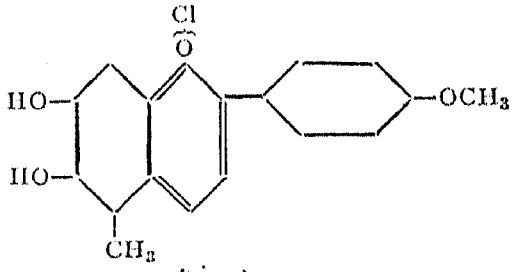
IV



V *a*, R = H
V *b*, R = CH_3



VI



(VI *a*)

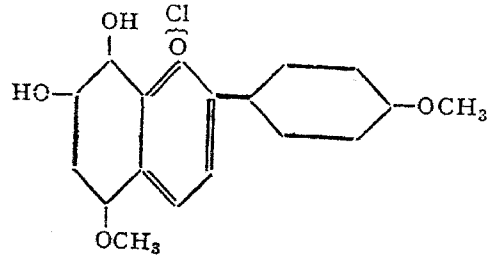
has not so far been investigated. Based on the analogy with flavones mentioned above, carajuridin chloride could be considered to have the alternative constitution of 5 : 4′-dimethoxy-7 : 8-dihydroxy flavylium chloride (VII) undergoing isomeric change during demethylation to yield carajuretin chloride. Evidence against this constitution was supplied in part in our previous communication[1] in which we pointed out the marked difference in the colour reactions exhibited by 6 : 7 and 7 : 8-dihydroxy flavylium salts. 6 : 7-Dihydroxy-4′-methoxy flavylium chloride exhibited reactions very similar to those of carajuridin whereas 7 : 8-dihydroxy-4′-methoxy flavylium chloride was very different. As a more appropriate example of 6 : 7-dihydroxy type of flavylium salts, 5-methyl-6 : 7-dihydroxy-4′-methoxy flavylium chloride (VI *a*) has now been prepared by the condensation of 2 : 4 : 5-trihydroxy-6-methyl benzaldehyde with *p*-methoxy acetophenone. This product also exhibits properties very similar to carajuridin. Obviously a methoxyl, a methyl group and a hydrogen atom in the 5 position are equivalent as far as colour reactions are concerned. Although on the basis of these observations, we could eliminate the possibility of carajuridin having the alternative structure (VII) no conclusive proof was provided for the view that 5 : 4′-dimethoxy-7 : 8-dihydroxy flavylium chloride could not undergo isomeric change on demethylation.

This question has now been settled by studying the demethylation of the closely related compound, 5 : 8 : 4′-trimethoxy-7-hydroxy flavylium chloride (VIII), with hydriodic acid. The compound (VIII) has now been prepared by condensing 2 : 4-dihydroxy-3 : 6-dimethoxy benzaldehyde with *p*-methoxy

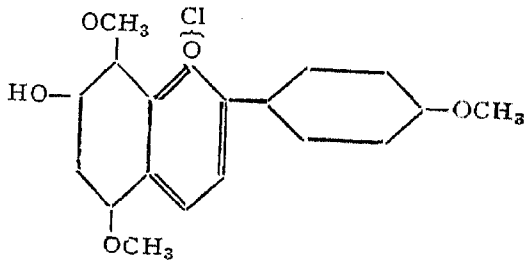
acetophenone. The product has been demethylated with hydriodic acid in the usual way. The resulting flavylium iodide (IX) has been isolated and its colour reactions recorded. It has been converted into the corresponding colour-base and finally into the flavylium chloride according to the method adopted by Pratt and Robinson.[6] The colour-base as well as its hydrochloride are markedly different from carajuretin and carajuretin hydrochloride respectively (*see* table); in ferric chloride colour and colour of solutions they are very similar to 7:8-dihydroxy-4′-methoxy flavylium chloride and its colour-base. The product of demethylation of 5:8:4′-trimethoxy-7-hydroxy flavylium chloride should therefore by 5:7:8:4′-tetrahydroxy flavylium chloride (XI), an isomer of carajuretin hydrochloride; the colour-base (X) has been given the name ' isocarajuretin '. The properties of carajuretin and isocarajuretin have been compared and the results are embodied in the table given below:—

TABLE

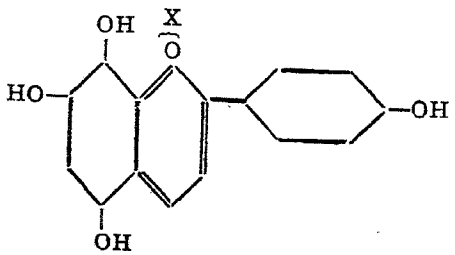
	Carajuretin (Chapman, Perkin and Robinson)	Isocarajuretin (Present work)
1 Heating ..	Turns black and decomposes at about 330° ; does not have any melting point	Melts with decomposition at 239–40°
2 Colour of solutions ..	Gives red solution in alcohol	Gives purple coloured solutions in alcohol and ethyl acetate
3 Ferric-reaction ..	Deep purple	Brilliant emerald green



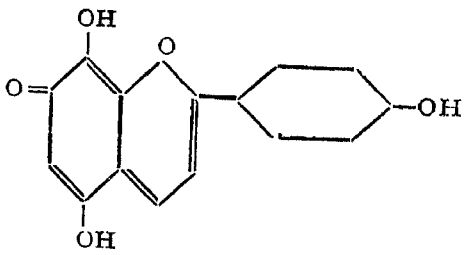
VII



VIII



IX, X=I
XI, X=Cl



X

The above experiments lead to the conclusion that the heterocyclic ring of the anthocyanidin molecule does not open under the influence of boiling hydriodic acid and confirm the constitution of Carajurin given by Chapman, Perkin and Robinson.

EXPERIMENTAL

5-Methyl-6 : 7-dihydroxy-4′-methoxy flavylium chloride (VI a)

2 : 4 : 5-Trihydroxy-6-methyl benzaldehyde (0·5 g.) the preparation of which by the nuclear oxidation of orcylaldehyde will be described elsewhere,[8] and *p*-methoxy acetophenone (0·9 g.) were dissolved in glacial acetic acid (30 c.c.) and the solution saturated with dry hydrogen chloride at 25°. After standing for 2 days, the precipitated flavylium chloride (0·45 g.) was filtered off and washed with ether thoroughly and crystallised from hydrochloric acid (10%). Excess of ether was added to the remaining acetic acid solution when a further quantity (0·5 g.) was precipitated. The crystallised flavylium chloride formed glistening orange red needles which melted with decomposition at 223–24° (Found: C, 56·9; H, 5·3. $C_{17}H_{15}O_4$ Cl, $2H_2O$ requires C, 57·5; H, 5·4%). It gives a dull violet colour with aqueous sodium carbonate and forms a brownish orange solution in aqueous sodium hydroxide. Its orange red amyl alcoholic solution becomes deep red on the addition of sodium acetate and a drop of ferric chloride changes the red to deep purple. It leaves a red stain on the skin; is stable in the oxidation test and is almost completely extracted by the cyanidin reagent.

5 : 8 : 4′-Trimethoxy-7-hydroxy flavylium chloride (VIII)

2 : 4-Dihydroxy-3 : 6-dimethoxy benzaldehyde[7] (3·0 g.) and *p*-methoxy acetophenone (4·5 g.) were dissolved in glacial acetic acid (100 c.c.) and saturated with dry hydrogen chloride at room temperature (25°). The reaction mixture was allowed to stand for 2 days, when a portion of the flavylium chloride formed, crystallised out. It was filtered off and the remainder obtained from the acetic acid solution by precipitation with ether. It was crystallised from 10% alcoholic hydrochloric acid when small aggregates of needles were obtained (Found: C, 57·3; H, 4·9. $C_{18}H_{17}O_5$ Cl, 1·5 H_2O requires C, 57·5; H, 5·3%). It formed a deep red solution in aqueous sodium carbonate, a crimson red solution in aqueous sodium hydroxide and gave no colour with ferric chloride. Extraction by cyanidin reagent was fairly high.

5 : 7 : 8 : 4′-Tetrahydroxy flavylium iodide (IX)

5 : 8 : 4′-Trimethoxy-7-hydroxy flavylium chloride (2·5 g.) was mixed with phenol (12·5 g.) and hydriodic acid (90 c.c., *d*, 1·7) and heated by

means of a glycerol bath in an atmosphere of carbon dioxide for 2 hours. After the evolution of methyl iodide had completely stopped, the reaction vessel was removed from the glycerol bath, cooled and a little water (25 c.c.) and much ether (75 c.c.) were added to the reaction mixture and left in the refrigerator for a day. A deep red (almost black) microcrystalline solid separated out. The flavylium iodide (2·4 g.) thus obtained was filtered and washed thoroughly with ether. It gave a deep red solution in amyl alcohol, which became violet on the addition of solid sodium acetate. A drop of ferric chloride changed the violet to a brilliant green.

Isocarajuretin (*X*)

The above flavylium iodide (2 g.) was ground well with aqueous sodium acetate and then filtered. The colour-base (1·5 g.) thus obtained, was crystallised from ethyl acetate when glistening brownish purple rectangular plates were obtained (Found: C, 67·1; H, 4·2. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). It melted with decomposition at 239–40°, was sparingly soluble in alcohol and ether, dissolved in amyl alcohol forming a deep purple solution, gave a rich green colour with ferric chloride in alcohol and did not stain the skin.

Isocarajuretin hydrochloride (*XI*)

Isocarajuretin (0·2 g.) was boiled with 3% aqueous hydrochloric acid (15 c.c.) for 15 minutes and then cooled. The solid was filtered off and crystallised twice from alcoholic hydrochloric acid (5%) when purplish red short stout rectangular prisms (0·1 g.) melting with decomposition at 239–40° were obtained (Found: C, 59·1; H, 4·1. $C_{15}H_{11}O_5Cl$ requires C, 58·7; H, 3·6%). Like the colour-base, it dissolved sparingly in aqueous sodium carbonate giving a brownish red colour and formed a deep green solution in aqueous sodium hydroxide which became brownish yellow on standing. Its extractability by the cyanidin reagent was poor.

SUMMARY

7-Hydroxy-5:8:4′-trimethoxy flavylium chloride has now been prepared and subjected to demethylation with hydriodic acid. The resulting flavylium iodide and the colour-base (Isocarajuretin) and the flavylium chloride obtained from it, are different from carajuretin and its salts. Hence it is concluded that no isomeric change takes place during the demethylation of derivatives of 5:7:8-hydroxy-flavylium salts related to flavones, supporting the constitution of carajurin, given by Chapman, Perkin and Robinson.

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5. Mukerjee, Seshadri and Varadarajan *Proc. Ind. Acad. Sci.*, 1953, **37A**, 127.
6. Pratt and Robinson .. *J.C.S.*, 1925, **173**.
7. Baxter *et al.* .. *Ibid.*, 1949, **S**, 30.
8. Aghoramurti and Seshadri .. Under publication.