

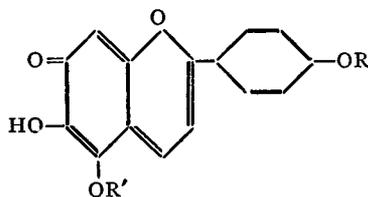
A SYNTHESIS OF CARAJURONE HYDROCHLORIDE

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CHAPMAN, PERKIN AND ROBINSON¹ found that the cosmetic pigment 'Carajura' contained along with carajurin (I), another crystallisable component carajurone in small quantities. The main difference in properties between them was the solubility of the former in benzene as compared to the insolubility of the latter and this was made use of for their separation. The benzene insoluble portion, when crystallised twice from acetone, yielded an indefinitely crystalline mass melting at 183–86°. Its molecular formula was found to be $C_{16}H_{12}O_5$. It contained one methoxyl group and gave a ferric reaction very similar to carajurin and carajuretin (III). Therefore carajurone was considered to be a monomethyl ether of carajuretin. The amount of pigment obtained was too little to permit a detailed investigation of its constitution through degradation experiments and preparation of derivatives. However, the perceptible odour of *p*-acetylanisole obtained when carajurone was boiled with concentrated aqueous potassium hydroxide led the authors to believe that the pigment was closely related carajurin and that the methoxyl group was situated in the side phenyl nucleus as in carajurin. It was therefore given the constitution (II).



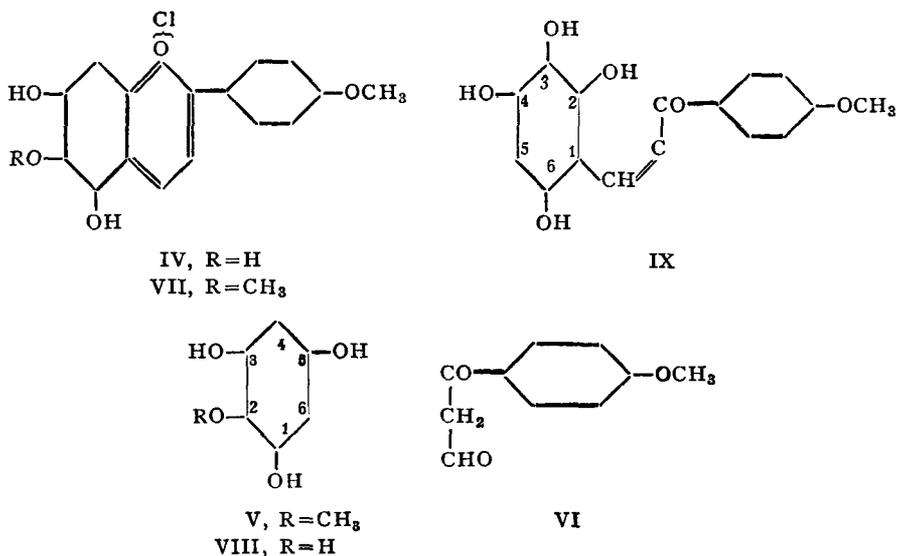
I, $R=R'=\text{CH}_3$

II, $R=\text{CH}_3$; $R'=\text{H}$

III, $R=R'=\text{H}$

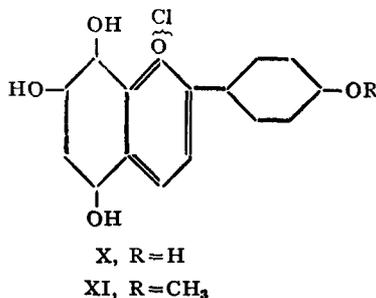
For the synthesis of 5:6:7-trihydroxy-4'-methoxy flavylum chloride (IV) (carajurone hydrochloride) the method of Bulow² has now been adopted. In connection with the use of this method, particular mention should be made of the work of Chapman, Perkin and Robinson.¹ They condensed iretol (V) with anisoyl acetaldehyde (VI), and obtained 5:7-dihydroxy-6:4'-dimethoxy flavylum chloride (VII). By analogy with this reaction, a

synthesis of carajurone hydrochloride seemed to be possible by the condensation of 1:2:3:5-tetrahydroxy benzene (VIII) with anisoyl acetaldehyde (VI). The intermediate stage would be 2:3:4:6-tetrahydroxy-4'-methoxy chalcone represented by (IX) and the subsequent ring closure may take place in two ways, one in which the 2-hydroxyl is involved and the other in which the 6-hydroxyl takes part. The exact course of the reaction would be expected to be guided by the relative reactivities of the two hydroxyl groups. The greater reactivity of the 5-hydroxyl group as compared with the 3-hydroxyl in derivatives of 1:2:3:5-tetra hydroxy benzene (VIII) is indicated by the study of several reactions of different types (see Mukerjee, Seshadri and Varadarajan³ for a recent consolidated account).

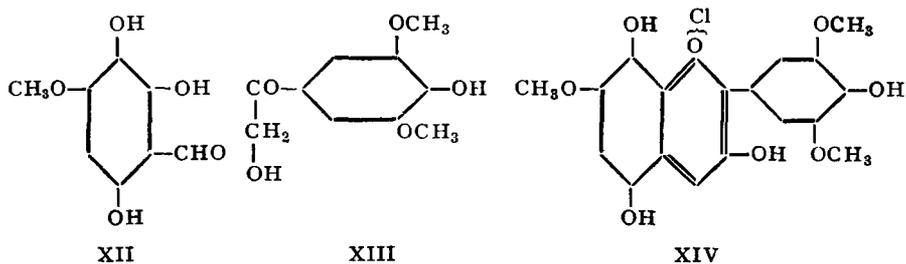


1:2:3:5-Tetrahydroxy benzene (VIII) was originally prepared by Oettinger⁴ by hydrolysing the hydrochloride of trihydroxy amino benzene with water. Posternack⁵ reported its preparation by an entirely different method from inosose, a cyclose obtained from mesoinositol. The demethylation of 2:6-dimethoxy quinol with hydriodic acid appeared to be a convenient method of preparing it; but the product obtained was extremely difficult to purify and the action of hydriodic acid seemed to bring about other changes besides demethylation. Next, demethylation with aluminium chloride was attempted. The above quinol was unsuitable for this purpose owing to its insolubility in benzene. However, 1:2:3:5-tetramethoxybenzene was easily soluble in this solvent and the demethylation proceeded smoothly. The tetrahydroxy benzene so obtained was in the form of a pale brown solid which gave all the characteristic reactions previously recorded for it. It was

however difficult to purify fully, owing to its instability. An ethereal solution of the crude compound was therefore dried over anhydrous sodium sulphate and directly condensed with anisoyl acetaldehyde. The resulting flavylum salt required careful purification and was eventually obtained in a crystalline condition. It did not exhibit any of the characteristic properties of carajuretin and carajurone hydrochlorides. But its reactions were very similar to those of isocarajuretin hydrochloride (X) and 7:8-dihydroxy-4'-methoxy flavylum chloride.⁶ It gave a violet colour-base on the addition of sodium acetate and a prominent green ferric reaction. It did not stain the skin. Consequently, it should have the constitution of 5:7:8-trihydroxy-4'-methoxy flavylum chloride (XI). Thus the behaviour of the above tetrahydroxy benzene is not according to expectation based on the reactivities of similar compounds, particularly iredol.

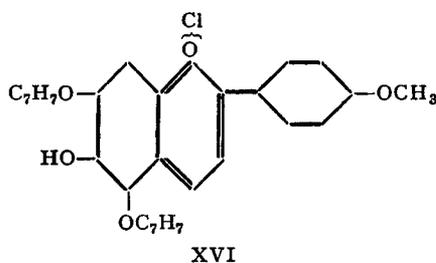
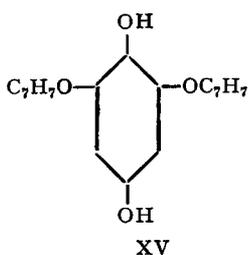


However, such types of ring closure leading to 5:7:8-hydroxy compounds are not unknown. Robinson and Vasey⁷ reported that 2:3:6-trihydroxy-4-methoxy benzaldehyde (XII), on condensation with ω :4-dihydroxy-3:5-dimethoxy acetophenone (XIII) yielded 3:5:8:4'-tetrahydroxy-7:3':5'-trimethoxy flavylum chloride which gave no ferric reaction. More recently, Baker *et al.*⁸ have observed a similar mode of reaction in the new isoflavone condensation using ethyl oxalyl chloride.



Since the tetrahydroxy benzene failed to yield the desired product, it appeared that either a benzoyl or benzyl derivative in which the 3-hydroxyl

is protected and the 5-hydroxyl is free should be used for the condensation, in order to enable the reaction to take place only in the desired direction. One such derivative is the readily accessible 2:6-dibenzoyloxy quinol (XV). It appeared at first sight to be unsuitable because of the possibility of debenzoylation taking place in the course of the condensation giving rise to complications. It had been reported earlier,⁹ that 2:6-dibenzoyloxy-1:4-dimethoxy benzene undergoes debenzoylation in the course of Gattermann and Hoesh condensations in which zinc chloride is also used. In the synthesis of malvidin and hirsutidin by Bradley *et al.*¹⁰ using formic acid as solvent, a similar debenzoylation was noticed. On the other hand in the synthesis of pelargonidin-5-methyl ether employing ethyl acetate as solvent, Leon *et al.*¹¹ found the condensation product to retain the benzyl group. Hence the suitability of using dibenzoyloxy quinol as the starting material for the present synthesis has been tested. When condensed with anisoyl acetaldehyde using ether as solvent it yields a product which gives no colour with ferric chloride and the analytical values agree with the requirements of a dibenzoyloxy compound. It does not form a colour-base on the addition of sodium acetate. The formation of a colour-base should be expected even if partial debenzoylation has taken place. Hence it has been given the constitution of 5:7-dibenzoyloxy-6-hydroxy-4'-methoxy flavylum chloride (XVI). The above constitution is further supported by its debenzoylation by means of a mixture of glacial acetic acid and hydrochloric acid whereby 5:6:7-trihydroxy-4'-methoxy flavylum chloride (IV) is obtained. The marked difference in properties between the isomeric 5:7:8 and 5:6:7-hydroxy compounds has already been emphasised and hence there is no doubt about the mode of ring closure in XVI.



When crystallised from alcoholic hydrochloric acid carajurone hydrochloride is obtained as short red rectangular prisms which do not melt or decompose below 300°. It forms an orange red solution in amyl alcohol which becomes deep red on the addition of sodium acetate; a drop of ferric chloride solution changes it to a deep brownish purple. It causes a red stain on the skin. All these properties are characteristic of 6:7-dihydroxy flavylum

salts. In circular filter paper chromatography, using as solvent the aqueous phase of butanol-acetic acid-water mixture, it has an R_f value 0.56, a value in accordance with its structure (see R_f value of carajurin hydrochloride¹²). Its absorption maximum in 1% aqueous hydrochloric acid has been determined in Beckmann's spectrophotometer and lies at 450 $m\mu$.

When treated with aqueous sodium acetate the above flavylum chloride forms a bright red colour-base which when crude, melts with decomposition between 140–60°. After two crystallisations from acetone the decomposition point is raised to 170–86°. Further recrystallisation from pyridine-ethyl acetate mixture has resulted in a product which does not decompose below 300°. It gives a deep brown-violet colour with ferric chloride. This colourbase could be converted into the original flavylum chloride (IV) by boiling with aqueous 3% hydrochloric acid.

EXPERIMENTAL

1:2:3:5-Tetrahydroxy benzene (VIII)

1:2:3:5-Tetramethoxy benzene (5 g.) was dissolved in dry benzene (30 c.c.), anhydrous aluminium chloride (20 g.) added and the mixture refluxed for 2 hours. The solvent was then distilled off and ice and concentrated hydrochloric acid were added to the residue. The product was then extracted with ether and the dull brownish red solution dried over anhydrous sodium sulphate and directly employed for condensation. It gave a deep red colour with ferric chloride which became brown on standing; on dilution with water, a characteristic bluish violet colour was produced. The same bluish violet colour was produced even when an aqueous solution was diluted further with water.

5:7:8-Trihydroxy-4'-methoxy flavylum chloride (XI)

An ethereal solution containing 1:2:3:5-tetrahydroxy benzene (about 2 g.) was mixed with an ethereal solution of anisoyl acetaldehyde (from 2.9 g. of copper derivative) and saturated with dry hydrogen chloride at 0°. The deep red reaction mixture, after standing for 2 days deposited a deep red crystalline flavylum salt. It was filtered off and digested with a small quantity of methyl alcoholic hydrochloric acid. It then became extremely sticky, but when digested with concentrated hydrochloric acid it became a definite solid. The flavylum salt could not be directly crystallised from dilute hydrochloric acid. It was therefore converted into the colour base by grinding with aqueous sodium acetate. The precipitated resinous colour-base was extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous sodium sulphate and then distilled to

remove the solvent. This colour-base was then reconverted into the hydrochloride by heating with 3% aqueous hydrochloric acid. The portion that readily dissolved during the above treatment was decanted off from the remaining solid, allowed to cool and filtered. To the filtrate a small quantity of concentrated hydrochloric acid (5 c.c.) was added, when a portion of the flavylum chloride separated out. It was filtered and washed with a little ether. This product was deep red (almost black) in colour but had a definite crystalline appearance. Under the microscope, it appeared as clusters of deep red tiny prisms (Found: C, 60.4; H, 4.7; $C_{18}H_{13}O_5Cl$ requires C, 60.0; H, 4.1%).

When heated, it decomposes at 235–36°; forms a violet colour-base on the addition of sodium acetate and gives a rich pure green colour with ferric chloride. It is moderately extracted by the cyanidin reagent and is quite stable in the oxidation test. It gives a deep olive green colour with aqueous sodium hydroxide.

5:7-Dibenzoyloxy-6-hydroxy-4'-methoxy flavylum chloride (XVI)

2:6-Dibenzoyloxy quinol (3 g.) and anisoyl acetaldehyde (from 2.35 g. of copper derivative) were dissolved in a mixture of dry ether (400 c.c.) and ethyl acetate (20 c.c.) and cooled to 0°. Dry hydrogen chloride was passed for 12 hours. The reaction mixture became deep red and on keeping for 3 days deposited a deep brown red crystalline solid (2.5 g.). It was filtered off, washed with small quantities of methyl alcohol and recrystallised twice from methyl alcoholic hydrochloric acid (5%) when glistening orange red clusters of rectangular prisms were obtained (Found: C, 66.7; H, 5.2; $C_{30}H_{25}O_5Cl, 2H_2O$ requires C, 67.1; H, 5.4%). When heated, it decomposes at 105–07°. It gives an orange red solution in amyl alcohol the colour of which does not change on the addition of sodium acetate. It does not give any positive ferric reaction.

5:6:7-Trihydroxy-4'-methoxy flavylum chloride (carajurone hydrochloride) (IV)

The above dibenzoyloxy compound (1 g.) was suspended in glacial acetic acid (200 c.c.) and concentrated hydrochloric acid (100 c.c.) was added and the mixture gently refluxed on a wire-gauze for an hour. The benzoyloxy pyrylium chloride dissolved during the first 15 minutes. It was then allowed to stand overnight and the solvent was distilled off until a red solid began to separate. On the addition of dry ether a scarlet red crystalline pyrylium salt separated out (0.55 g.). It was then recrystallised from methyl alcoholic hydrochloric acid (2%) when deep brownish red carajurone hydrochloride crystals were obtained. The product appeared to be short red

prisms under the microscope. It does not decompose below 300°. It forms a deep orange red solution in amyl alcohol which becomes deep red on the addition of sodium acetate. A drop of ferric chloride changes the red to deep brown violet. It is largely extracted by the cyanidin reagent and is partly destroyed in the oxidation test. It causes a deep red stain on the skin (Found: C, 56.5; H, 4.6; $C_{16}H_{13}O_5Cl$, H_2O requires C, 56.7; H, 4.4%). The absorption maxima of a solution of carajurone hydrochloride in 1% hydrochloric acid lies at 450 $m\mu$. In circular filter paper chromatography using the aqueous phase of butanol-acetic acid-water mixture as solvent it has an R_f value of 0.56.

Carajurone (II)

The brownish red hydrochloride (IV) was digested with a saturated aqueous solution of sodium acetate. The deep red colour-base was filtered off and washed with a little water and small quantities of alcohol. When crude, it melted with decomposition at 140–60°. When crystallised once from acetone in which it was easily soluble it melted with decomposition at 170° with sintering at 160°. A second crystallisation from acetone raised the decomposition point to 170–86°. This product was still impure and did not analyse satisfactorily. A third crystallisation from a mixture of pyridine and ethyl acetate gave a product which was in the form of deep red prisms. It did not melt below 300°. It gave a deep brown violet colour with ferric chloride and stains the skin.

SUMMARY

The condensation of 1:2:3:5-tetrahydroxy benzene with anisoyl acetaldehyde takes place in an abnormal way and gives rise to 5:7:8-trihydroxy-4'-methoxy flavylum chloride. By using 2:6-dibenzoyloxy quinol, 5:7-dibenzoyloxy-6-hydroxy-4'-methoxy flavylum chloride is obtained and subsequent debenzoylation yields carajurone hydrochloride; by the action of sodium acetate, the colour-base carajurone is obtained.

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