NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLV. A Synthesis of Carajuridin Chloride and Carajurin

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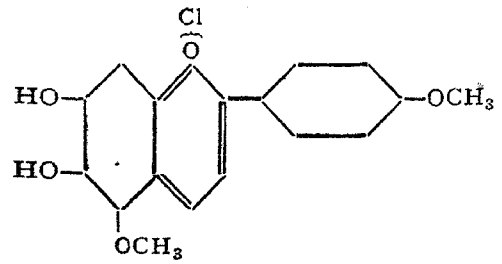
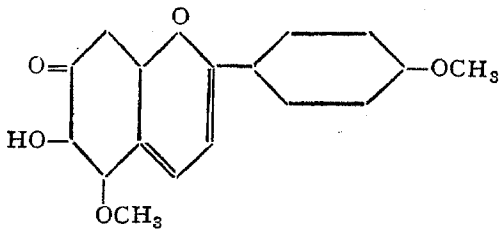
IN Part XLII of this series,[1] an account was given of exploratory work intended to lead to the synthesis of carajuridin chloride. In the course of this preliminary investigation, the preparation of polyhydroxy benzaldehydes using the method of nuclear oxidation with potassium persulphate was studied, a number of 6-hydroxy pyrylium salts of the gesneridin type were made and their properties recorded. The synthesis of carajuridin chloride itself has now been accomplished and forms the subject-matter of the present communication.

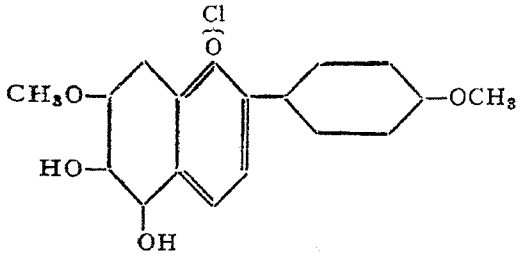
Carajura is the name of a rare cosmetic pigment used by the natives of the Orinoco. This was investigated by Chapman, Perkin and Robinson[2] who found that the main constituent is carajurin, the colour base of carajuridin. Carajurin had the molecular formula $C_{17}H_{14}O_5$ and readily formed the corresponding pyrylium salt, carajuridin chloride $C_{17}H_{15}O_5Cl$. Unlike the other naturally occurring anthocyanidins, carajuridin exhibited no tendency to pass into a pseudobase and hence was considered to have no hydroxyl in the 3-position. It was found to contain two methoxyl groups and yield *p*-acetoxy anisole when boiled with concentrated aqueous alkali and *p*-hydroxy benzoic acid on fusion with caustic potash; but no other identifiable product was obtained. On demethylation, it gave a tetrahydroxy flavylium chloride which was identified as scutellareinidin chloride (III) and which could be synthesised by the condensation of antiarol aldehyde and *p*-methoxy acetophenone and subsequent demethylation. The fact that *p*-acetoxy anisole was produced on boiling carajurin with aqueous concentrated alkali indicated that one of the methoxyl groups was situated in the 4′-position of the side-phenyl nucleus. Carajurin gave a brown-violet colour with ferric chloride indicating the presence of vicinal hydroxyl groups in the molecule. The constitutional formula for carajuridin chloride could therefore be either (I) or (II). Structure (II) would give rise to a violet or blue colour base and would be characterised by instability whereas structure (I) would form a stable red colour base. Hence the constitution for carajuridin was represented by (I) and the colour base carajurin by (I *a*).



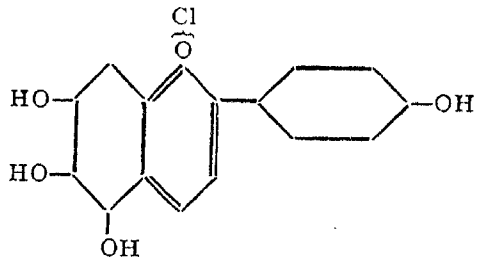
(I)



(I*a*)

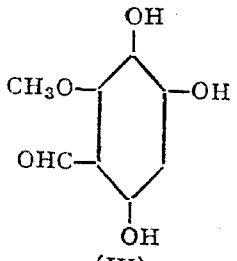


(II)

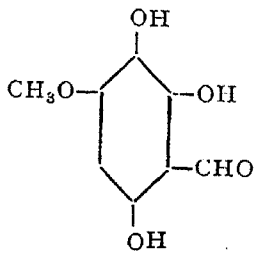


(III)

Vasey and Robinson[3] attempted to synthesise 2 : 4 : 5-trihydroxy-6-methoxy benzaldehyde (IV) which on condensation with *p*-methoxy acetophenone should yield carajuridin. They subjected 1 : 2 : 5-trihydroxy-3-methoxy benzene to the Gattermann condensation and instead of the expected aldehyde (IV), obtained a different product which condensed with *p*-methoxy acetophenone to form a flavylium salt which did not give any colour with ferric chloride. Hence it was concluded that the aldehyde was 2 : 3 : 6-trihydroxy-4-methoxy benzaldehyde, represented by formula (V) and the ring closure involved the 2-hydroxyl and not the 6-hydroxyl. Hence the synthesis of carajuridin could not be accomplished.



(IV)



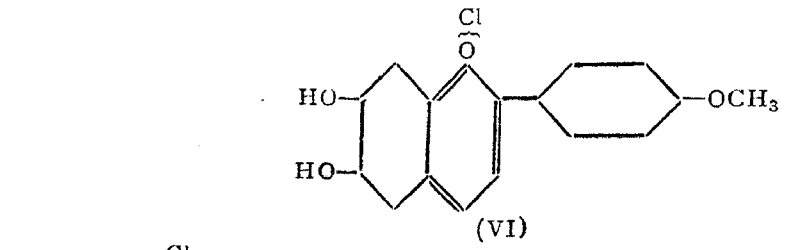
(V)

For carrying out an unambiguous synthesis of 5 : 4′-dimethoxy-6 : 7-dihydroxy flavylium chloride, 6-O-methyl phloroglucinaldehyde has now been used as the starting material and it has been prepared from monomethyl phloroglucinol.

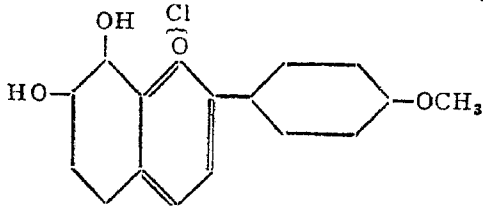
Herzig and Wenzel[4] subjected O-monomethyl phloroglucinol to the Gattermann condensation. They reported the formation of an aldehyde (m.p. 170°) which was considered to be 4-O-methyl phloroglucinaldehyde.

Karrer and Bloch[5] obtained two isomers (m.p. 203° and m.p. 139–40°) by partial methylation of phloroglucinaldehyde with diazomethane and separated them by fractional crystallisation from benzene. They studied their constitutions and showed that the higher melting substance was the 6-methyl ether and the lower melting one the 4-methyl ether. Leon, Robertson, Robinson and Seshadri[6] obtained 6-O-methyl phloroglucinaldehyde by methylation of 2:4-dibenzoyl phloroglucinaldehyde and subsequent debenzoylation. The same product melting at 208° was also prepared by them from monomethyl phloroglucinol by the Gattermann condensation. However in this reaction, the formation of small amounts of 4-O-methyl phloroglucinaldehyde is unavoidable and cannot be ignored. The resulting product which melts at about 170° is best purified by repeated fractional crystallisation from water containing sulphur dioxide. The pure sample (m.p. 208°) of 6-O-methyl phloroglucinaldehyde thus obtained is subjected to nuclear oxidation with potassium persulphate when 2:4:5-trihydroxy-6-methoxy benzaldehyde is produced. In its properties it closely resembles hydroxy quinol aldehyde. When condensed with *p*-methoxy acetophenone in glacial acetic acid medium at 25°, carajuridin chloride is obtained. The synthetic sample has been compared and found to be identical with a natural sample of carajuridin chloride kindly provided by Professor Sir Robert Robinson. The details of the comparison are given in the experimental part. Particular mention may be made of the capacity of carajuridin chloride to stain the skin a brilliant red shade. This property is also possessed by the simpler analogue, 6:7-dihydroxy-4′-methoxy flavylium chloride (VI) described in an earlier paper[1] which gives also most of the colour reactions exhibited by carajuridin. In contrast to this 7:8-dihydroxy-4′-methoxy flavylium chloride (VII) prepared according to the method of Robinson and Vasey[3] shows marked difference. It gives with ferric chloride a brilliant emerald green colour, forms a deep bluish purple colour base on treatment with sodium acetate and does not stain the skin. This marked difference is of some significance, since it definitely eliminates a further possibility for the constitution of carajuridin. It may be pointed out that the production of carajuretin (III) by the demethylation of carajuridin with hydriodic acid is an important consideration on which the constitution of carajurin is based. In the case of flavones, the possibility of 5:7:8-trihydroxy compounds undergoing change into 5:6:7-trihydroxy isomers during demethylation with hydriodic acid has been definitely established.[7] Though no experimental data are available in regard to the related flavylium salts, the possibility of this isomeric change could be visualised and carajuridin could then have the possible structure of 5:4′-dimethoxy-7:8-dihydroxy flavylium chloride

(VIII). The abovementioned ferric reaction of 7: 8-dihydroxy-4′-methoxy flavylium chloride rules out this possibility.



(VI)



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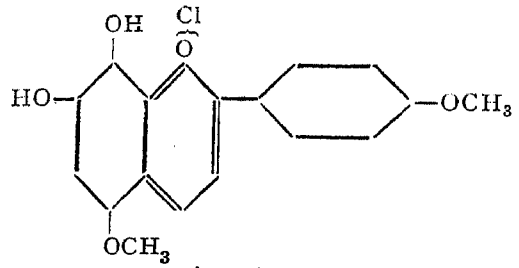

(VIII)

Another point that should be relevantly noted here is the wide range of colour of the ferric reaction encountered in the study of anthocyanidins. In the case of the commonly occurring anthocyanidins which are structurally related to flavonols and have *o*-dihydroxy groups only in the side phenyl nucleus, a positive ferric reaction is a blue colour. But this is different with the flavone analogue carajuridin which has *o*-dihydroxy groups in the 6: 7-positions of the condensed benzene ring and the positive reaction here is a purple colour; with the 7 : 8 disposition of the ortho hydroxy groups, this colour changes to emerald green.

EXPERIMENTAL

For the preparation of monomethyl phloroglucinol, the method of Robertson and Subramanian[9] has been employed with small modifications. Saturation of the methyl alcoholic solution of phloroglucinol with hydrogen chloride leads to the formation of dimethyl phloroglucinol mostly. Hence hydrogen chloride was passed at a slower rate (approximately 200 bubbles per minute) keeping the temperature between 20° and 25°. The methyl alcohol employed should also be quite pure. Even with these precautions, yields of the monomethyl ether were never consistent and varied according to the extent of saturation, though the total yield of the two ethers (mono and dimethyl ethers) was usually high.

2: 4-*Dihydroxy-6-methoxy benzaldehyde*

The product (7·5 g.) of the Gattermann condensation of monomethyl phloroglucinol using hydrogen cyanide was subjected to repeated fractional

crystallisation from water containing sulphur dioxide. After six crystallisations, the more sparingly soluble part consisting of 6-O-methyl phloroglucinaldehyde (2·2 g.) melted with decomposition at 208–10° with sintering at 202°.

2 : 4 : 5-*Trihydroxy-6-methoxy benzaldehyde* (*IV*)

6-O-Methyl phloroglucinaldehyde (2·2 g.) was dissolved in aqueous potassium hydroxide (3·75 g. in 38 c.c. of water) and the solution cooled to 10°. Potassium persulphate solution (3·6 g. in 100 c.c. of water) was added dropwise, in the course of 2 hours, while the mixture was kept continuously stirred. It was allowed to stand for 2 days at room temperature and then acidified to congo red and finally extracted repeatedly with ether to remove all the unchanged monomethyl phloroglucinaldehyde. To the aqueous solution, concentrated hydrochloric acid (60 c.c.) was added and the mixture was heated in a water-bath at 80° for 30 minutes. It was then cooled and extracted with ether. The ether solution was dried over sodium sulphate and the solvent distilled off. A dark viscous oil (about 200 mg.) was left behind, which could not be conveniently crystallised on account of its instability. However, it readily formed its 2 : 4-dinitro-phenylhydrazone which when crystallised twice from ethyl alcohol and once from ethyl acetate formed clusters of prismatic needles melting at 228–29° (Found: C, 46·1; H, 3·6; $C_{14}H_{12}O_8N_4$ requires C, 46·2; H, 3·3%).

Carajuridin chloride (*I*)

2 : 4 : 5-Trihydroxy-6-methoxy benzaldehyde (about 200 mg.) and *p*-methoxy acetophenone (300 mg.) were dissolved in glacial acetic acid (50 c.c.) and the solution saturated with dry hydrogen chloride at room temperature (25°). It was allowed to stand at room temperature for two days, excess of ether added and the precipitated pyrylium chloride filtered off. When allowed to stand in contact with a small amount of 1% hydrochloric acid, it became a definite crystalline looking solid (200 mg.). It was then extracted with hot 1% hydrochloric acid and the concentration of acid in the solution gradually raised to about 5% by adding concentrated hydrochloric acid. The portion that separated out during this process was not pure and hence filtered off. Hydrogen chloride gas was then passed into the filtrate till the solution became slightly turbid. On standing, it deposited glistening purplish red crystals of carajuridin chloride (25 mg.). On slow heating it softened at 129° and melted with decomposition at 202–04° (Found in air-dried sample: C, 54·9; H, 5·5; $C_{17}H_{15}O_5Cl$, $2H_2O$ requires C, 55·1; H, 5·1%. Found in a sample dried *in vacuo* at 80° for 6 hours: C, 61·2; H, 4·7; $C_{17}H_{15}O_5Cl$ requires C, 61·0; H, 4·5%). Under the microscope, both synthetic as well as natural carajuridin appeared as clusters

of prismatic needles. The synthetic sample consisting of bigger crystals was darker in colour, but when allowed to crystallise rapidly on the microscope slide from ethyl alcoholic hydrochloric acid, both synthetic as well as natural carajuridin appeared in the form of deep red leaflets. They dissolved in 1% hydrochloric acid to form identically coloured orange yellow solutions. A solution of the chloride in ethyl alcohol (orange) gives a dark brown colour on the addition of a drop of ferric chloride. The ferric reaction is best carried out following the procedure of Robinson and Robinson[8] for flower extracts. A dilute solution of carajuridin in 1% hydrochloric acid (golden yellow) was shaken well with amyl alcohol which extracts the pigment largely, forming an orange solution. Addition of sodium acetate renders amyl alcoholic solution deep crimson and the aqueous layer colourless. Ferric chloride changes the crimson colour to deep purple which is stable for several hours; excess of reagent does not make any change. The synthetic sample and the natural sample behaved similarly in the above treatment. Complete extraction with amyl alcohol from 1% hydrochloric acid has been considered to be characteristic of anthocyanidins. It is true in the case of anthocyanidins of the flavonol type, *e.g.*, peonidin. But carajuridin as well as other flavylium salts of the flavone type undergo incomplete extraction, although it is quite high. The aqueous layer definitely retains a small part of the salt.

In circular filter-paper chromatography,[10] using as solvent the aqueous phase of butanol-acetic acid-water mixture synthetic and natural carajuridin gave the same R_F value 0·60 at 29°. In a mixed chromatogram using two spots side by side a single ring was obtained confirming identity.

The absorption spectra of dilute solutions of synthetic as well as natural carajuridin have been studied using Beckmann spectrophotometer in the visible region; they are found to be identical, the absorption maxima being at 460 *mμ*. From solutions in 1% hydrochloric acid both samples are easily extracted almost completely by the cyanidin reagent. They cause identical shades of a red stain on the skin.

Carajurin (I a)

Carajuridin chloride (5 mg.) was boiled with water (50 c.c.) for 2 hours under a layer of boiling benzene (50 c.c.). The benzene layer was then separated, dried over sodium sulphate and concentrated when brownish red prisms of carajurin were obtained (m.p. 180-85°). It was again dissolved in a small quantity of benzene (20 c.c.) and an equal volume of petroleum ether was added; the solution deposited on standing a brownish red crystalline solid which was filtered off and washed with a little benzene when pure

in was obtained as garnet coloured prisms. It melted with decom- at 200°. (The natural sample sintered at 200° and melted with de- ition at 202–04°; admixture with the synthetic sample did not the melting point.) Its alcoholic solution was orange in colour and brown-violet colour with a drop of ferric chloride and it turned deep with excess of the reagent. The violet colour was more prominent myl alcohol was used. It was sparingly soluble in aqueous sodium de forming an orange red solution. In all these reactions the natural behaved quite similarly. When treated with alcoholic lead acetate, ıthetic and natural carajurin formed crimson coloured solutions which leposited red needles. In circular filter-paper chromatography, using ent the aqueous phase of butanol-acetic acid-water mixture, both e same R_F value 0·56 at 29°.

Summary

e synthesis of carajuridin chloride and carajurin has been carried rting with 6-O-methyl phloroglucinaldehyde, preparing 2:4:5-tri--6-methoxy benzaldehyde as an intermediate and condensing the ith *p*-methoxy acetophenone. Identity with the natural products n established by direct comparison using melting points, chromato- and colour reactions. This synthesis confirms the constitution pro- y Chapman, Perkin and Robinson for carajurin. 6:7-Dihydroxy- oxy flavylium chloride exhibits colour reactions very similar to cara- and the isomeric 7:8-dihydroxy-4′-methoxy flavylium chloride s very different properties thus excluding other possibilities for the tion of carajuridin.

thanks are due to Professor Sir Robert Robinson for a supply of carajurin and carajuridin chloride which has enabled us to make nd full comparison with the synthetic samples.

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