NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLII. A Synthesis of 6-Hydroxy Pyrylium Salts of the Gesneridin Type

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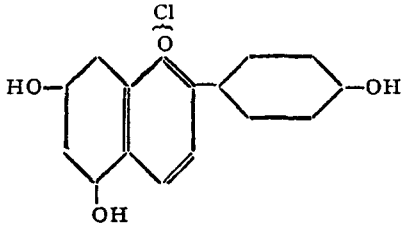
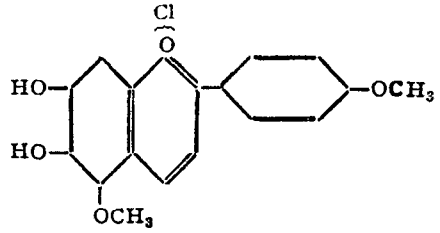
Received September 29, 1952

THE widely occurring and important anthocyanidins are pyrylium salts related to the flavonols, and have a hydroxyl in the 3-position. Members belonging to the flavone type are rare, gesneridin (I) and carajuridin (II) being the only two representatives of this group occurring in nature. The former is found as its glucoside 'gesnerin' in the orange coloured flowers of *Gesnera fulgens*, whereas the latter was discovered as its colour base 'carajurin' in the rare cosmetic pigment 'carajura' which is considered to originate from an anthocyanin similar to gesnerin. In fact, carajuridin is the 5:4'-dimethyl ether of carajuretin having the constitution of 6-hydroxy gesneridin.



I

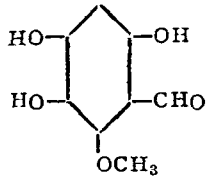


II

The synthesis of gesneridin[1] was accomplished by the condensation of O-benzoyl phloroglucinaldehyde with *p*-methoxy acetophenone, and by the subsequent debenzoylation and demethylation of the intermediate product. But, the synthesis of carajuridin has been proved to be very difficult, and has not been accomplished so far. However, in the course of the investigation on the constitution of carajuridin, the synthesis of a number of 6-hydroxy pyrylium salts of the gesneridin type was achieved by Chapman, Perkin and Robinson.[2] They condensed antiarol aldehyde with *p*-methoxy acetophenone and obtained 5:6:7:4'-tetramethoxy flavylium chloride which they demethylated to carajuretin chloride. Further, the condensation of iretol and 2:6-dimethoxy quinol was carried out with anisoyl acetone to obtain 5:7-dihydroxy-6:4'-dimethoxy-4-methyl flavylium chloride and

5: 7: 4'-trimethoxy-6-hydroxy-4-methyl flavylium chloride respectively. Both were demethylated to give the corresponding hydroxy compounds. Even earlier, 2-hydroxy-5-methoxy benzaldehyde was condensed with *p*-methoxy acetophenone and acetoveratrone, and the products demethylated.[3]

The main difficulty in the synthesis of carajurin lies in the presence in the molecule of a hydroxyl group in the 6-position along with a methoxyl in the 5-position. In general, the synthesis of partial methyl ethers offers some difficulty, but carajurin represents the only example, where the difficulties have not yet been surmounted. Methods of partial methylation and demethylation, which have been so very successful in the synthesis of partial methyl ethers of anthoxanthins, have not been shown to be possible in the case of anthocyanidins. Direct synthesis, using the required aldehyde and ketone components, seems to be the only available method, with the exception of benzoylation and benzylation, which could be employed for the temporary protection of certain reactive hydroxyl groups of the aldehyde component. For the synthesis of carajurin, there was need therefore to work out a satisfactory method of preparing 2: 4: 5-trihydroxy-6-methoxy benzaldehyde (III), or a suitable derivative of it, and also the most satisfactory conditions for effecting its condensation with *p*-methoxy acetophenone.

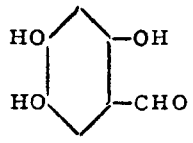


III

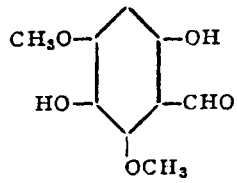
As part of exploratory work, a synthesis of simpler 6-hydroxy pyrylium salts of the 'gesneridin' type has now been carried out. Since nuclear oxidation with persulphate of monomethyl phloroglucinaldehyde was expected to provide the most convenient method of obtaining aldehyde (III), this method has been used for obtaining the simpler aldehydes required in the preliminary work. No detailed investigation of the application of this method for the preparation of polyhydroxy benzaldehydes seems to have been made before.

Gentisic aldehyde[4] and 2 : 5-dihydroxy-3-methoxy benzaldehyde[5] have already been prepared from salicylaldehyde and ortho-vanillin respectively, by persulphate oxidation. In a similar way, the otherwise tedious preparation of hydroxy-quinol aldehyde (IV) has now been made easy, by the oxidation of the readily accessible β-resorcylaldehyde. Though the yield is not good, the simplicity of the method more than provides compensation, and

it is quite suitable for the ready preparation of small amounts of the aldehyde. Further, 2: 6-dimethoxy quinol aldehyde (V) has now been prepared from 4: 6-O-dimethyl phloroglucinaldehyde. These are condensed with *p*-hydroxy and *p*-methoxy acetophenones, the two ketones needed for the synthesis of pyrylium salts related to gesneridin and carajuridin.



IV



V

In a polyhydroxy aldehyde, the reactivity of the aldehyde group is known to be considerably diminished, especially when there is a free hydroxyl group in the para position with respect to the aldehyde group.[6] In the course of earlier work, difficulties were experienced on account of the adverse effect of too many free hydroxyl groups in the aldehyde component, and so, either partial benzoylation or benzylation was resorted to in order to prevent failure of the condensation, or to obtain higher yields. For example, in the synthesis of 5-O-methyl pelargonidin,[7] monomethylphloroglucinaldehyde was not directly used for the condensation, but was first converted into its monobenzyl derivative; similarly, hydroxy quinol aldehyde was first benzoylated before being used for pyrylium salt condensation.[8] In the course of the present work, it is found that the pyrylium salt preparation can be carried out successfully with a number of free hydroxyl groups in the aldehyde component without loss of yields.

Hill and Melhuish[9] have reported that 4-phenacyl pyrylium salts are also formed when pyrylium salt condensation is carried out with *p*-methoxy acetophenone in ether solution and that this does not happen in acetic acid medium. In the course of the experiments, described in this paper, it is found that *p*-methoxy acetophenone requires a higher temperature (30°) for its successful condensation, and hence ether could not be used as solvent; glacial acetic acid gives good results. Further, this solvent prevents the formation of phenacyl pyrylium salts.

EXPERIMENTAL

6: 4'-*Dihydroxy flavylium chloride*

It was prepared earlier by Ridgway and Robinson[3] by demethylating the product of condensation of 2-hydroxy-5-methoxy benzaldehyde with *p*-methoxy acetophenone. It has now been made directly from gentisic aldehyde.

Gentisic aldehyde (0·8 g.) obtained by the nuclear oxidation of salicylaldehyde was dissolved in dry ethyl acetate (80 c.c.), *p*-hydroxy acetophenone (1·1 g.) added, and the mixture cooled to 10° and saturated with dry hydrogen chloride. After keeping for 48 hours, excess of ether was added, and the brown red crystals of the pyrylium chloride (1 g.) were collected, and recrystallised from 5% hydrochloric acid when reddish brown glistening plates were obtained (Found: C, 61·2; H, 4·8; Cl, 11·3. $C_{15}H_{11}O_3Cl$, H_2O requires C, 61·5; H, 4·4; Cl, 12·1%). It decomposes at 240–41°, gives a brilliant bluish red colour with aqueous sodium carbonate, a purple colour with sodium hydroxide, and a marked green fluorescence in concentrated sulphuric acid; it is highly stable in the oxidation test and its extraction by the cyanidin reagent is poor.

6-Hydroxy-4'-methoxy flavylium chloride

Gentisic aldehyde (0·6 g.) and *p*-methoxy acetophenone (1·2 g.) were dissolved in glacial acetic acid (50 c.c.) and saturated with dry hydrogen chloride at room temperature (30°). The reaction mixture was allowed to stand for 48 hours, excess of ether added, and the precipitated pyrylium salt (0·9 g.) filtered, washed with ether, and recrystallised from 5% hydrochloric acid, when fine wedge-shaped purplish red crystals were obtained (Found: C, 60·9; H, 4·9. $C_{16}H_{13}O_3Cl$, 1·5 H_2O requires C, 60·9; H, 5·1%. Found in a sample dried *in vacuo* for 7 hours: C, 66·7; H, 4·8. $C_{16}H_{13}O_3Cl$ requires C, 66·6; H, 4·5%).

It decomposes between 143° and 146°, gives with aqueous sodium carbonate a crimson colour which becomes wine red on the addition of sodium hydroxide, exhibits a strong green fluorescence in concentrated sulphuric acid; is highly stable in the oxidation test, and forms no colour base. Its extractability by the cyanidin reagent is very poor.

6: 4'-Dihydroxy-8-methoxy flavylium chloride

2: 5-Dihydroxy-3-methoxy benzaldehyde (0·5 g.) obtained by the nuclear oxidation of *o*-vanillin and *p*-hydroxy acetophenone (0·8 g.) were dissolved in dry ethyl acetate (100 c.c.), cooled to 5°, and saturated with dry hydrogen chloride. The mixture was allowed to stand for two days at room temperature, excess of ether added, and the pyrylium salt that had separated out (1 g.) was filtered and recrystallised from 5% hydrochloric acid, when brick red tiny prisms were obtained (Found: C, 56·0; H, 5·2. $C_{16}H_{13}O_4Cl$, $2H_2O$ requires C, 56·4; H, 5·0%). It gives a deep bluish red colour in aqueous sodium carbonate, a purple colour in aqueous sodium hydroxide and an extremely weak green fluorescence in concentrated

sulphuric acid. It forms a colour base, is stable in the oxidation test and is not extracted by the cyanidin reagent.

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

β-Resorcylaldehyde (13·8 g.) was dissolved in aqueous sodium hydroxide (10%, 200 c.c.) and the solution cooled to 10°. A solution of potassium persulphate (27·2 g. in 500 c.c. of water) was slowly introduced into it in the course of 4 hours with continuous stirring, the temperature being kept always below 20°. After allowing to stand for 24 hours, the solution was made neutral with dilute hydrochloric acid, and then extracted with ether to remove the unchanged aldehyde (6 g.); sodium sulphite (10 g.) and concentrated hydrochloric acid (120 c.c.) were then added to the aqueous solution, and it was heated in a water-bath at 80° for 20 minutes. The solution was cooled and repeatedly extracted with ether. The ether extract was dried over anhydrous sodium sulphate and finally distilled to remove ether. Hydroxy-quinol aldehyde (1·2 g.) separated out in the form of colourless rectangular plates (m.p. 220°) which turned brown on exposure to air.

6:7:4′-*Trihydroxy flavylium chloride*

Hydroxy-quinol aldehyde (1·5 g.) and *p*-hydroxy acetophenone (1·15 g.) were dissolved in dry ether (300 c.c.) and the solution saturated with dry hydrogen chloride at 0°. The reaction mixture was left in the ice-chest for a day, fresh ether added, and the dark red crystals of the pyrylium chloride (2·5 g.) which separated out were filtered, washed with ether, and recrystallised from 5% hydrochloric acid, when orange red aggregates of needles of the pyrylium chloride were obtained (Found: C, 59·0; H, 4·2. $C_{15}H_{11}O_4Cl$, H_2O requires C, 58·4; H, 4·2%. Found in a sample dried *in vacuo* for 14 hours: C, 62·2; H, 4·3. $C_{15}H_{11}O_4Cl$ requires C, 62·0; H, 3·8%). It darkens at 210° and decomposes between 246° and 248°, gives a purple colour with aqueous sodium carbonate, a green fluorescence in alcohol as well as in concentrated sulphuric acid and a dark brown violet colour with ferric chloride in alcoholic solution and forms a red colour base. Its extractability by the cyanidin reagent is rather poor.

6:7-*Dihydroxy*-4′-*methoxy flavylium chloride*

Hydroxy quinol aldehyde (1·0 g.) and *p*-methoxy acetophenone (1·7 g.) were dissolved in glacial acetic acid (110 c.c.) and saturated with dry hydrogen chloride at room temperature (30°). After two days, excess of ether was added, when a maroon red crystalline solid (2 g.) separated out. It was recrystallised from dilute hydrochloric acid (5%), when reddish brown

rectangular prisms were obtained (Found: C, 58·2; H, 5·3; Cl, 9·1 $C_{16}H_{13}O_4Cl$, 1·5 H_2O requires C, 57·9; H, 4·8; Cl, 10·7%. Found in a sample dried *in vacuo* for 5 hours: C, 63·2; H, 4·4. $C_{16}H_{13}O_4Cl$ requires C, 63·1; H, 4·3%). It darkens at 190°, partly fuses at 224° and decomposes at 241°. It gives a pinkish orange colour with aqueous sodium carbonate, a strong green fluorescence in concentrated sulphuric acid and a dark purple colour with ferric chloride, forms a colour base, is fairly stable in the oxidation test and is largely extracted by the cyanidin reagent.

2: 5-*Dihydroxy*-4: 6-*dimethoxy benzaldehyde* (*V*)

4: 6-Dimethyl phloroglucinaldehyde (10 g.) (m.p. 78°) was dissooved in aqueous sodium hydroxide (10%, 110 c.c.) and the solution cooled to 10°. Potassium persulphate (16·5 g. in 300 c.c. of water) was gradually introduced over a period of 4 hours with continuous stirring. When worked up as already described for a similar case, 2: 5-dihydroxy-4: 6-dimethoxy benzaldehyde (0·9 g.) melting at 136° was obtained. It was identical with a sample prepared from 2: 6-dimethoxy quinol through the Gattermann reaction and the mixed melting point was undepressed.

5: 7-*Dimethoxy*-6: 4′-*dihydroxy flavylium chloride*

2: 5-Dihydroxy-4: 6-dimethoxy benzaldehyde (0·9 g.) and *p*-hydroxy acetophenone (1·1 g.) were dissolved in dry ethyl acetate (100 c.c.) and the solution saturated with dry hydrogen chloride at 10°. After two days, the dark red product (0·7 g.) was filtered, washed with ethyl acetate, and recrystallised from dilute hydrochloric acid (5%) when brick red rhombic prisms were obtained (Found: C, 54·3; H, 4·4. $C_{17}H_{15}O_5Cl$, H_2O requires C, 54·9; H, 4·8%). It gives a red violet colour with aqueous sodium carbonate, exhibits a feeble green fluorescence in concentrated sulphuric acid and is fairly stable in the oxidation test; its extractability by the cyanidin reagent is very poor.

5: 7: 4′-*Trimethoxy*-6-*hydroxy flavylium chloride*

2: 5-Dihydroxy-4: 6-dimethoxy benzaldehyde (0·2 g.) and *p*-methoxy acetophenone (0·19 g.) were dissolved in glacial acetic acid (75 c.c.) and saturated with dry hydrogen chloride at 30°. After keeping for two days at room temperature, excess of ether was added and the solid that had separated was filtered, washed with ether, and recrystallised from dilute hydrochloric acid (5%), when purplish red long rectangular prisms (0·1 g.) were obtained (Found: C, 55·9; H, 5·9. $C_{18}H_{17}O_5Cl$, $2H_2O$ requires C, 56·1; H, 5·5%). It darkens at 160° and melts with decomposition at 184°, gives a very feeble green fluorescence in concentrated sulphuric acid and an

orange colour with aqueous sodium carbonate which becomes deep red on the addition of sodium hydroxide, does not form a colour base and is highly stable in the oxidation test; its extractability by the cyanidin reagent is very poor.

SUMMARY

Polyhydroxy benzadehydes are prepared by nuclear oxidation of *o*-hydroxy benzaldehyde derivatives with alkaline persulphate and condensed with *p*-hydroxy and *p*-methoxy acetophenones to yield 6-hydroxy pyrylium salts.

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