NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XVI. A New Synthesis of Myricetin

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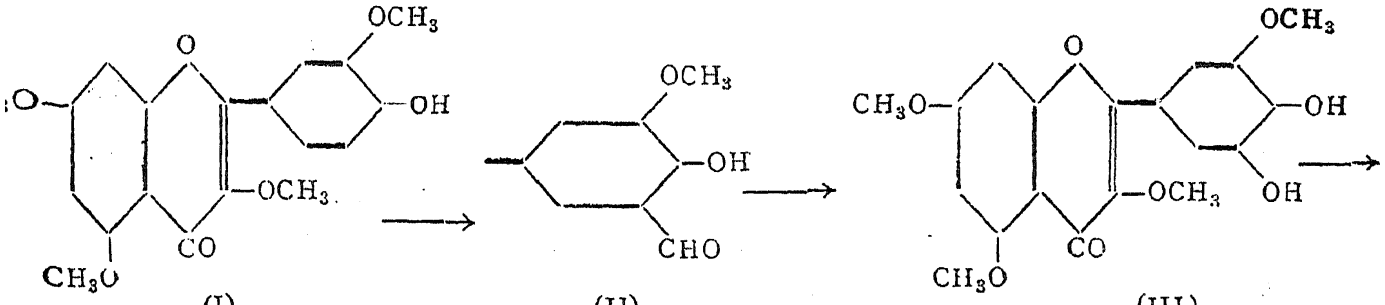
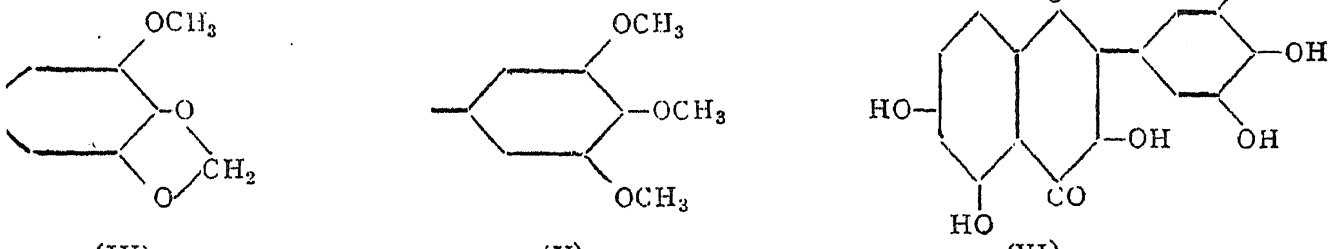
In Part XV[1] it was pointed out that ortho-oxidation in the side phenyl nucleus of flavones does not take place to any appreciable extent with alkaline persulphate and in fact this method of ortho-oxidation is unsatisfactory even in the case of simpler benzene derivatives. The conclusion was therefore drawn that an alternative method of oxidation should be available for this purpose. Persulphate as a reagent has been shown to be very similar to hydrogen peroxide[2] and its action may be considered to be a single stage oxidation process introducing directly a hydroxyl group in a reactive nuclear position. It is quite satisfactory for para oxidations and probably most para oxidations in nature take place by this direct process. For the majority of ortho-oxidations, however, this is unsuitable. They appear to proceed by a multi-stage process involving (1) introduction of an aldehyde group and (2) its replacement by a hydroxyl group. Hexamine and hydrogen peroxide used in the exploratory experiments described in Part XV seem to represent phytochemical reagent closely; this point will be discussed in detail later.

In the exploratory experiments on ortho-oxidation, as the most favourable example, the conversion of 3-methoxy-7-hydroxy flavone into 3-methoxy-7:8-dihydroxy flavone was studied. The results were highly successful and the yields quite good, being about 60% as against a maximum of 20% in the persulphate method. As the most appropriate example from the point of view of biogenesis, the synthesis of myricetin from a quercetin derivative has now been attempted. Quercetin-3:5:7:3′-tetramethylether (I) required for this purpose was described earlier as a stage in the synthesis of rhamnazin.[3] In the course of repetitions of its preparation a colourless by-product insoluble in alkali could be isolated. It is identified as galangin trimethyl ether. Its formation seems to be connected with the behaviour of the benzoyloxy groups in the reagents. In this connection may be mentioned the earlier observation of Allan and Robinson[4] that by heating *ω*-methoxy-phloroacetophenone with *o*-acetoxybenzoic anhydride and sodium

o-acetoxybenzoate, the acetoxy groups alone functioned and that the product was 3-methoxy-5:7-dihydroxy-2-methylchromone. In the present case such reaction seems to proceed only to a minor extent. The quercetin tetramethyl ether reacts with hexamine readily and yields the corresponding 5′-aldehyde (II) which exhibits the characteristic reactions of an ortho-hydroxy aldehyde. Its oxidation with alkaline hydrogen peroxide produces myricetin tetramethyl ether (III) in very good yields. Like other catechols it gives characteristic colour reactions and reacts with methylene sulphate to form a methylene-dioxy compound (IV) analogous to kanugin. This product may be called 5-methoxy-kanugin; its constitution is definitely confirmed by its synthesis from ω:4:6-trimethoxy-2-hydroxy acetophenone and the sodium salt and anhydride of myristicic acid. When, on the other hand, the catechol is methylated myricetin hexamethyl ether (V) and when demethylated myricetin (VI) itself are obtained.



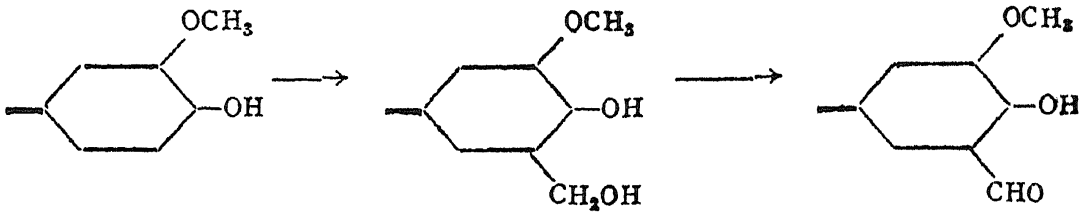
(I) (II) (III)



(IV) (V) (VI)

Besides the experimental verification of the multi-stage theory of ortho-oxidation given above, closely related examples have also been examined successfully and they will be reported as early as possible. It may be useful to discuss here the choice of the reagents and their appropriateness for the theory of biogenesis. Since hexamine could be considered to be a convenient form of formaldehyde, then this aldehyde and hydrogen peroxide are the reagents involved in this type of oxidation and their availability in phytochemical processes can be granted. In regard to the action of formaldehyde it was suggested earlier in connection with the biogenesis of Lichen Acids,[5] that it is responsible for the introduction of the carbinol (CH_2OH), aldehyde (CHO) and related groups in certain active nuclear positions. The first would represent the earliest stage and as well

known laboratory analogies could be mentioned the condensation of formalin with phenol, guaiacol, *p* and *o*-cresols,[6] and with *m*-hydroxy benzoic acid[7] yielding the corresponding benzyl alcohols or their derivatives. The next stage, *i.e.*, conversion of the carbinol into aldehyde can also be brought about by formaldehyde. In the laboratory synthesis with hexamine such an oxidation is evidently involved. A process somewhat analogous to the Meerwein-Pondorff reaction could be suggested for the conversion of alcohol (VIII) into aldehyde (IX) by means of formaldehyde though the possibility of other oxidising agents available in the plant taking part in this oxidation also exists.



(VII) (VIII) (IX)

Regarding phytochemical nuclear oxidation the position could now be stated as follows. The single stage process is quite satisfactory for the para; though it may not be precluded for the ortho it is inefficient. The multi-stage process on the other hand works very well for ortho-oxidation and it seems to be equally available for para oxidation.

Experimental

Condensation of ω:4:6-trimethoxy-2-hydroxy-acetophenone with the anhydride and potassium salt of benzoyl vanillic acid

An intimate mixture of ω:4:6-trimethoxy-2-hydroxy-acetophenone (2 g.), benzoyl vanillic anhydride (8 g.) and potassium benzoyl vanillate (3 g.) was heated under vacuo for 3 hours at 180°. The product was finely powdered and refluxed with 10% alcoholic potash (80 c.c.) for 30 minutes. The solvent was distilled off, the residue treated with water and the solution filtered from an insoluble yellowish grey soild (A). The filtrate on saturation with carbon dioxide gave quercetin 3:5:7:3′-tetramethyl ether (I) (1·6 g.) melting at 200–1°.[3] The solid marked (A) was crystallised from alcohol when it separated out as colourless rectangular prisms melting at 197–8°. It was insoluble in aqueous alkali and did not give any colour with ferric chloride. Mixed melting point with an authentic sample of galangin trimethyl ether was not depressed. Yield 0·4 g.

O-3:5:7:3′-Tetramethylquercetin-5′-aldehyde (II)

A solution of the tetramethyl quercetin (0·5 g.) in glacial acetic acid (6 c.c.) was treated with hexamine (2 g.). The clear pale yellow solution

was kept in a boiling water-bath for 6 hours. At the end the deep yellowish brown solution was treated with a boiling mixture of concentrated hydrochloric acid (3 c.c.) and water (3 c.c.) and heated for 5 minutes. After adding more water (10 c.c.) it was left overnight whereby a greyish yellow solid crystallised out. Yield 0·25 g. It was purified by recrystallisation from a mixture of absolute alcohol and ethyl acetate when it appeared as yellow stout rectangular prisms melting at 217–18°. (Found: C, 62·2; H, 4·8; $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%.) It was sparingly soluble in benzene, ether and ethyl acetate but more easily in alcohol and acetone. Very dilute solutions of the substance in alcohol gave only a pale brown colour with ferric chloride, but more concentrated solutions produced a deep greenish blue which slowly faded. There was no precipitate with alcoholic neutral lead acetate for several hours.

When an alcoholic solution of the substance (0·05 g.) was treated with a solution of 2:4-dinitro-phenyl hydrazine (0·05 g.) in the same solvent (5 c.c.) containing two drops of concentrated hydrochloric acid, there was an almost immediate separation of a bright scarlet red crystalline solid. It was filtered and crystallised from a mixture of pyridine and glacial acetic acid. It formed bright red lance-shaped crystals melting at 270–72° with decomposition.

3:5:7:3′-*O-Tetramethyl myricetin* (*III*)

A solution of the tetramethyl quercetin aldehyde (0·5 g.) in N/2 sodium hydroxide (3·85 c.c.) was treated dropwise with vigorous shaking with 6% hydrogen peroxide (1·95 c.c.). The initial orange yellow solution changed to deep brown and became turbid. Pyridine was added to get a clear solution which was kept at the ordinary temperature for 2½ hours with occasional shaking and adding a few drops of pyridine to keep it clear. It was acidified with dilute hydrochloric acid when a small quantity of a yellow solid separated out. The acid solution was saturated with sodium chloride and shaken with ether when a bulky yellow precipitate was thrown out. It was filtered and washed with water. The ether extract on evaporation gave a little more of the substance. Yield 0·4 g. Crystallisation from a mixture of ethyl acetate and absolute alcohol gave pale yellow broad rectangular plates melting at 220–21°. (Found: C, 60·9; H, 5·1; $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). It was easily soluble in alcohol and acetone. The alcoholic solution gave an olive green colour with ferric chloride and a yellow precipitate with lead acetate. In 5% aqueous sodium hydroxide it dissolved to a bright orange coloured solution.

O-Hexamethylmyricetin (V)

The tetramethylmyricetin (III) (0·2 g.) was methylated in anhydrous acetone (20 c.c.), with dimethyl sulphate (0·5 c.c.) and potassium carbonate (3 g.). After refluxing for 3 hours, the solvent was distilled off, water was added to the residue and the white solid left behind was filtered and washed with water. Crystallisation from alcohol gave colourless flat needles melting at 155–56°. Mixed melting point with an authentic sample of myricetin hexamethyl ether was not depressed.

Myricetin (VI) was obtained by the demethylation of the tetramethyl ether (III) using hydriodic acid and acetic anhydride. The product crystallised from dilute acetic acid as yellow flat needles and rectangular plates, decomposed above 350° and had other properties and colour reactions identical with an authentic sample of myricetin.

3 : 5 : 7 : 3′-*Tetramethoxy*-4′ : 5′-*methylenedioxy-flavone*

(A) *By methylenation.*—A solution of tetramethyl myricetin (III) (0·2 g.) in acetone (20 c.c.) was treated with methylene sulphate (0·5 g.) and potassium carbonate (2 g.). After refluxing for 12 hours the mixture was filtered and the potassium salts washed with hot acetone. The filtrate was distilled off and the residue heated to boiling with 10% sodium hydroxide (10 c.c.). The white solid was filtered after cooling, washed well with water and crystallised from alcohol. It formed colourless rectangular plates melting at 214–15° (Found: C, 61·9; H, 5·0; $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). It was insoluble in aqueous alkali and did not give any colour with ferric chloride. A trace of the substance when heated with concentrated sulphuric acid (2 c.c.) and gallic acid (1 mg.) developed a stable brilliant bluish green colour.

(B) *By synthesis.*—An intimate mixture of ω : 4 :6-trimethoxy-2-hydroxy acetophenone (0·8 g.), myristicic anhydride (2 g.) and sodium salt of myristicic acid (1 g.) was heated under reduced pressure at 180° for 3 hours. The product was refluxed with 10% alcoholic potash (20 c.c.) for 20 minutes. The alcohol was distilled off and the residue treated with water. The undissolved solid was filtered, washed with 5% aqueous alkali followed by water and crystallised from alcohol. It formed colourless rectangular plates melting at 214–15° alone or in admixture with the sample described under (A).

Summary

The most important example of ortho-oxidation from the point of view of the biogenesis of the anthoxanthins is the conversion of quercetin into

myricetin. *O*-3:5:7:3′-Tetramethyl quercetin has now been oxidised to *O*-tetramethyl-myricetin by the two stage process already explored in Part XV. The intermediate O-tetramethyl quercetin aldehyde and the final myricetin tetramethyl ether are obtained in satisfactory yields. From the latter 5-methoxykanugin, hexamethyl myricetin and myricetin have been obtained. These experiments could be taken as support for the multi-stage mechanism of ortho-oxidation. The appropriateness of the reagents from the point of view of biogenesis is discussed.

References

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