NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXVI. Phytochemical Methods of Nuclear Oxidation

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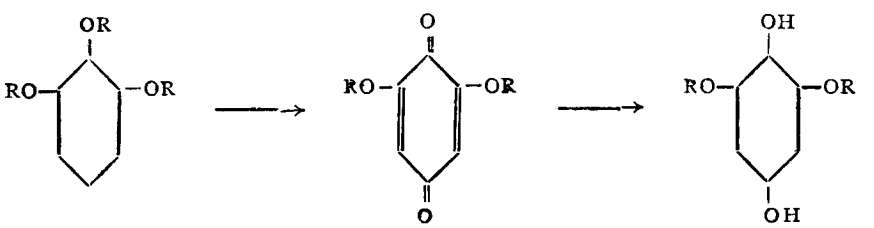
IN Nature as well as in the laboratory oxidation is a fundamentally important process and is employed for a variety of purposes. The term nuclear oxidation has been used[1, 7] for the oxidation of a nuclear position of benzenoid systems resulting in the introduction of a fresh hydroxyl group. It is considered that the word ' hydroxylation ' is not suitable for this purpose because it has been used in a wider sense in the preparation of dye-intermediates and further it does not always signify the use of an oxidising agent. Nuclear oxidation seems to take place fairly freely in Nature and appears to be an essential phytochemical process in the evolution of anthoxanthins.[2] It may be relevant to mention here the view of Szent-Gyorgyi[3] that flavones form part of the oxidation-reduction chain in the plant cell.

A possible method that could be suggested for nuclear oxidation and that was also investigated earlier, involves the use of oxidising agents like chromic and nitric acids. Typical examples[4] are the conversion of pyrogallol-trimethyl and tribenzyl-ethers (I) to 2: 6-dimethoxy and dibenzyloxyquinones (II) which could be subsequently reduced to the quinols (III). However, the application of this method is quite limited and it has been unsuccessful in the case of the anthoxanthins.[5] Further the reagents have no analogy with the phytochemical reagents available in the plants.



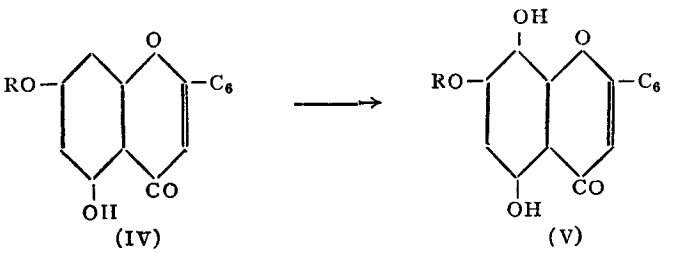
(I) (II) (III)

R = CH_3 or C_7H_7

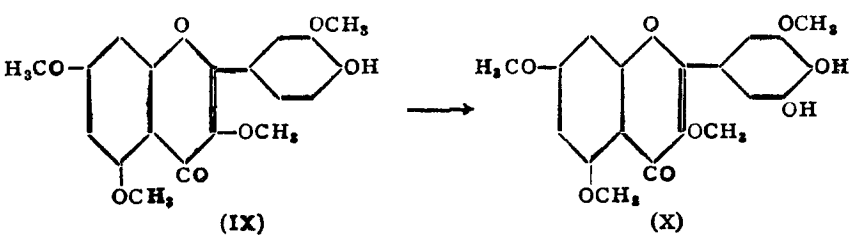
On the other hand, Elbs persulphate oxidation method has been found to be highly useful. The mechanism of this reaction has been recently discussed by Baker and Brown.[6] It introduces a fresh hydroxyl group in a reactive position of the flavone structure quite satisfactorily. The main results obtained are discussed in Part XIII[7] of this series under the headings

(1) Biogenesis of anthoxanthins, (2) Simplified methods of synthesis and (3) Study of chemical constitution. The important point in regard to this process is its directness for introducing a hydroxyl in a nuclear position and its appropriateness from the point of view of biogenesis. Persulphate is very closely analogous in its reaction to hydrogen peroxide[8] which could be accepted as a phytochemical reagent.

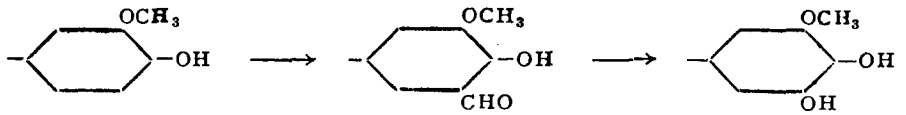
In the above mentioned discussion[7] the question of the variations in the condensed benzene ring of the flavone system was satisfactorily dealt with on the basis that nuclear oxidation involves both the fully closed pyrone compounds (IV) and the related open forms (VI) and that partial protection of the hydroxyl groups is effected earlier leaving a resistant hydroxyl group alone free to activate the concerned position. In these cases only para oxidation was necessary; this takes place readily in the laboratory with persulphate and in nature an analogous single stage process involving hydrogen peroxide could be suggested.



On the other hand, in regard to the side phenyl nucleus, as exemplified by the oxidation of quercetin into myricetin, ortho-oxidation is involved. The parallel case of cyanidin and delpihinidin in the anthocyanins has been discussed in detail by Robinson and his collaborators[9] using genetic evidence and the position is well established. But the oxidation of a quercetin derivative (IX) into (X) could not be achieved with persulphate.[10]

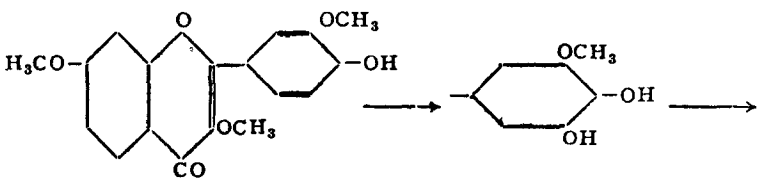


Even in simpler cases ortho-oxidation with this reagent was very unsatisfactory. Consequently an alternative procedure which would be more effective had to be considered. The following two stage process seemed to be suitable.

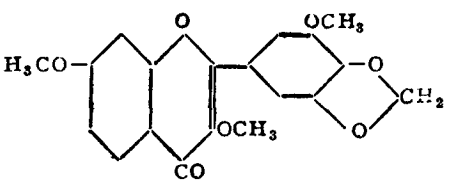


(XI) (XII) (XIII)

This has been confirmed not only by using the most favourable cases[11] of ortho oxidation, but also with the classical example[12] of quercetin oxidation to myricetin. Very satisfactory yields are obtained. For the first stage hexamine is used as the reagent and for the second stage (Dakin's reaction) hydrogen peroxide. The former may be considered to be a convenient form for bringing into reaction formaldehyde. Thus the reagents employed approximate phytochemical reagents closely. Incidentally the intermediate catechols can be conveniently methylenated to yield naturally occurring methylene ethers. As a typical naturally occurring example kanugin (XVI) has been synthesised from fisetin-tri-methyl ether (XIV).[13]

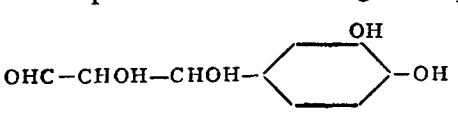


(XIV) (XV)

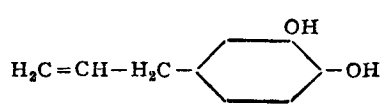


(XVI)

More recently this work has been extended to the components of essential oils which are classified as allyl (XVII) and propenyl benzene derivatives. Robinson[14] has drawn attention to the biogenetic similarity between the 9 carbon systems present in these and in the non-phloroglucinol part of anthocyanins and anthoxanthins. Both are considered to arise from the component B of the biogenetic precursor.

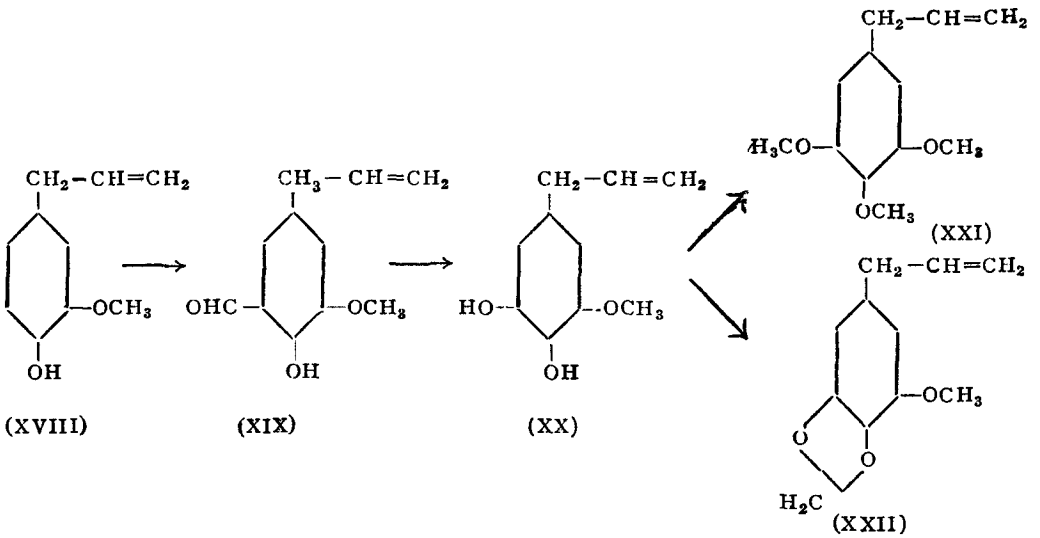


B

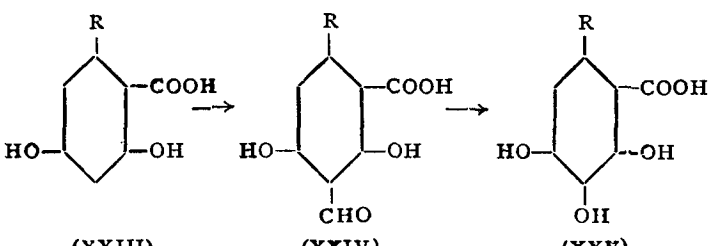


(XVII)

The two stage ortho oxidation process is now found to proceed very satisfactorily with eugenol[15] (XVIII). This has led to a simplified synthesis of elemicin (XXI) and myristicin (XXII).

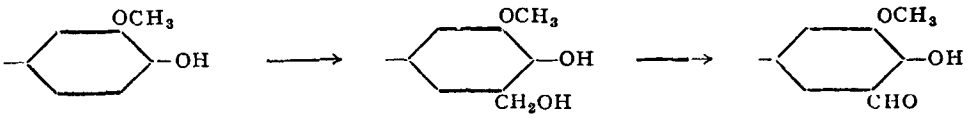


For considering this multi-stage mechanism as valid for phyto-chemical ortho-oxidation, support could be obtained from the study of lichen acids, a group of great chemical as well as physiological interest. In an earlier study of the biogenesis[16] of lichen depsides and depsidones it was suggested that formaldehyde was responsible for the introduction of CH_2OH, CHO and related groups in certain active nuclear positions yielding β-orcinol derivatives and the details were discussed. The important point relevant to the present purpose is that we could get here evidence for the existence of the aldehyde stage as a step in the introduction of a phenolic hydroxyl group. The fundamental units in these lichen acids are orsellinic acid or its homologues (XXIII). The aldehyde stage (XXIV) is found for instance in barbatolic acid and atranorin and corresponding hydroxy units (XXV) are present in sekikaic, homosekikaic, ramalinolic and boninic acids.



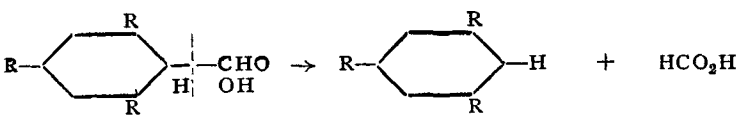
$R = CH_3$, C_3H_7, C_5H_{11}, C_7H_{15} or $CH_2—CO—C_5H_{11}$

In regard to the action of formaldehyde in these processes, the carbinol (XXVII) should represent the earliest stage. As well-known laboratory analogies could be mentioned the condensation of formalin with phenol, guaiacol, para and ortho cresols and *m*-hydroxy benzoic acid yielding the corresponding benzyl alcohols.[17] The next stage, *i.e.*, the conversion of the carbinol into the aldehyde (XXVIII) 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 can be suggested for the conversion of the alcohol (XXVII) into the aldehyde (XXVIII) by means of formaldehyde though the possibility of other oxidising agents available in the plant taking part in this oxidation also exists.

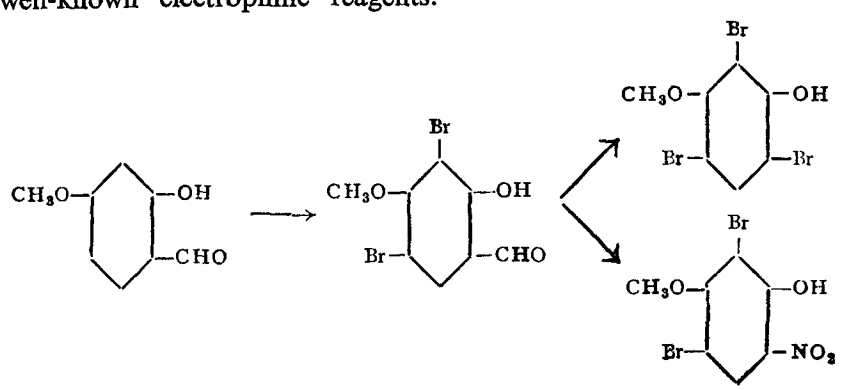


(XXVI) (XXVII) (XXVIII)

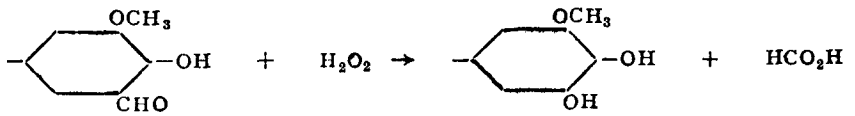
In the next stage the facility with which an aldehyde group is replaced by a phenolic hydroxyl group in Dakin's reaction has to be considered and explained. The same considerations will hold good where an acetyl group is involved instead of an aldehyde. In the first instance the presence of alkali may be expected to encourage the hydrolytic fission of aromatic aldehydes and ketones. The expulsion of a formyl group in warm acid or alkaline media has been considered to be common in polyhydroxy aldehydes.[18]



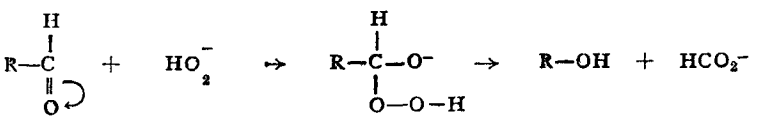
That a bromine atom or a nitro group could replace it more readily is shown by the following example;[19] bromine and nitric acid used in these reactions are well-known electrophilic reagents.



The smoothness of Dakin's reaction may be attributed to the combined effect of alkali and hydrogen peroxide, the former helping the removal of the aldehyde and the latter supplying the hydroxyl group for substitution. That this reagent is also electrophilic in its reaction with phenolic compounds has been recognised.[8]

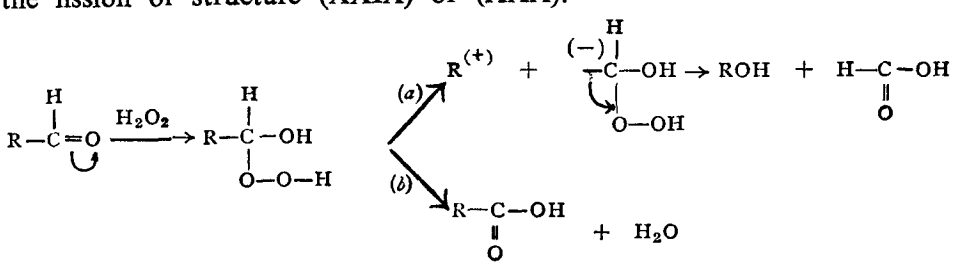


The above simple explanation may not be quite adequate. Recently it has been considered that when reacting with aldehydes in the presence of bases hydrogen peroxide behaves as a nucleophilic reagent, HO_2^- being the active ion.[20] Based on this consideration the reaction can be represented as follows.



(XXIX)

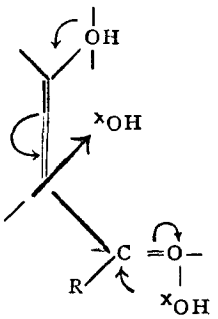
The experiments of Späth, *et al.*[21] would indicate that neither alkali nor a phenolic hydroxyl group is necessary. They have been able to carry out Dakin's reaction with non-hydroxylic aldehydes using an ether solution of hydrogen peroxide. The conditions are not favourable for the formation of the ion HO_2^-. But it has been suggested that structure (XXX) is probably formed as an intermediate. From their results it could be seen that actually benzaldehyde gives a very poor yield of phenol (0·7%) whereas aldehydes containing a number of methoxyls in certain suitable positions give much better yields (14-26%). But in no case is the yield so good as in the normal example using an ortho hydroxy aldehyde and alkaline hydrogen peroxide (about 80%). It would therefore appear that at some stage of the reaction nucleophilic activity of the polymethoxy phenyl system is involved though the beginning may be different. This stage may well be the fission of structure (XXIX) or (XXX).



(XXX)

Another significant result of the above experiments is the formation of the corresponding carboxylic acid as by-product, its yield being high when the yield of the phenol is low and *vice versa*. This is again explicable on the above mechanism. Where electron access to the concerned nuclear position is lacking or insufficient to encourage process (*a*), elimination of water (process *b*) takes place.

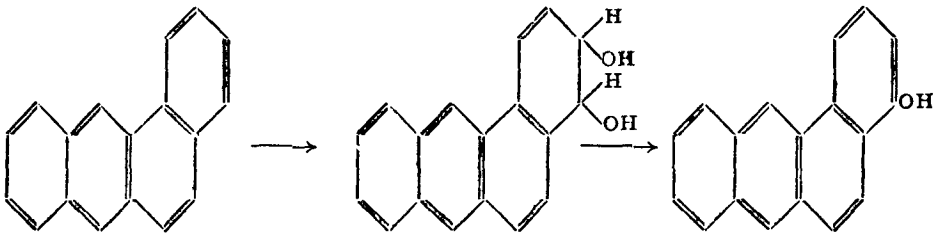
That both cationoid (electrophilic) and anionoid (nucleophilic) centres play their part in Dakin's reaction has earlier been indicated by Sir Robert Robinson in the course of his highly valuable address to the Chemical Society, London, on benzidine transformation and allied topics.[24] Considering hydrogen peroxide as the source of hydroxyl radicals, he has embodied this feature in his representation of the first phase of the reaction.



Summing up the discussion it could be stated that in phytochemical nuclear oxidation more than one process would appear to be employed. The single stage direct process is quite satisfactory for the para; though it may not be precluded for the ortho, it is very inefficient. On the other hand, the multistage process discussed above works very well for ortho oxidation. It may seem to be equally available for para oxidation also; but recent experiments using flavone derivatives[22] indicate that though *p*-hydroxy aldehydes could be obtained in good yields their further conversion into quinols takes place in low yields only.

It will be appropriate to mention here the interesting case of the biochemical nuclear oxidation of polycyclic (including carcinogenic) hydrocarbons in animal system, recently discussed by J. W. Cook and others.[23] This involves an altogether different mechanism. The initial products of metabolism are found to be diols resulting from the addition of two hydroxyl groups to an aromatic double bond (ethylenic activity). These are readily dehydrated to phenolic hydroxy derivatives of the original hydrocarbons. 1 : 2-Benzanthracene (XXXI) is used below as a typical example. The oxidation of these hydrocarbons in the laboratory using osmium tetroxide

resembles biochemical oxidation, but the position of the double bond attacked is found to be different.



(XXXI)

SUMMARY

It is suggested that phytochemical nuclear oxidation involves several processes. (1) A single stage direct process which is satisfactory for the para oxidation of flavones and related compounds, the model being Elbs persulphate oxidation method, has already been discussed in detail in Part XIII. (2) A multistage process, an aldehyde being an intermediate stage which subsequently undergoes oxidation (Dakin's reaction), is illustrated by the recent synthesis of the flavonols, myricetin, robinetin and kanugin and essential oil components, elemicin and myristicin. Support for the existence of the stages can be obtained from a study of lichen acids. The mechanism of this process is discussed; it is quite suitable for ortho oxidations in flavones and related compounds, but the yields are rather poor in para-oxidations. Another multistage process involving ethylenic activity has been shown by Cook and others to be applicable to polycyclic hydrocarbons.

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