BIOGENESIS OF BENZOQUINONES AND RELATED SUBSTANCES

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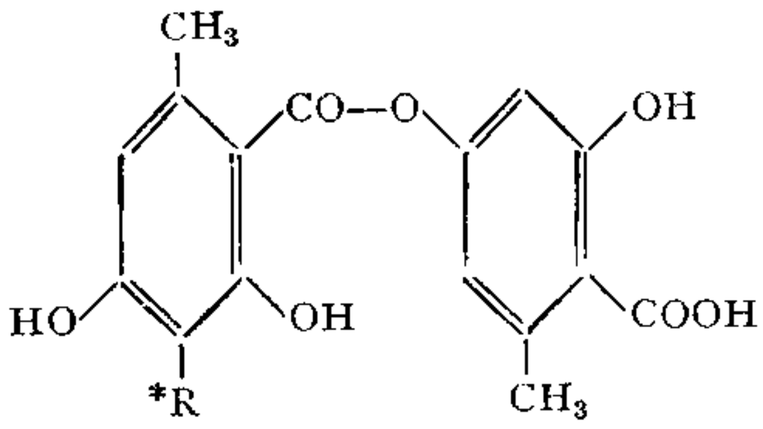
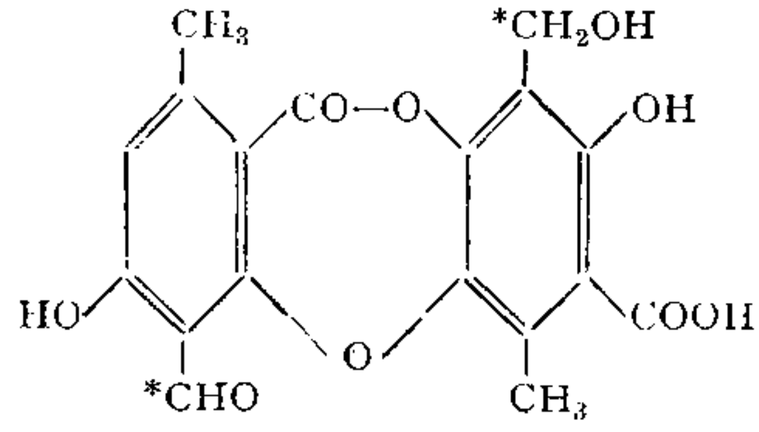
AMONG natural products, benzoquinone derivatives form an important group. They occur widely and a large number of them have been isolated as metabolic products of moulds, fungi, higher plants and insects. Their antibiotic properties are of current interest though the simpler members like fumigatin are known to be toxic. Some of the bigger compounds like embelin are components of drugs and others may have nutritional function (*e.g.*, ubiquinones). They form components of oxidation-reduction systems and can undergo easy reduction to the quinol derivatives which sometimes occur along with the quinones as natural products (*e.g.*, fumigatin and its corresponding quinol). From their large occurrence there is indication of appreciable stability; however they are highly reactive compounds capable of undergoing substitution and also polymerization.

The biogenesis of a large number of benzoquinones seems to have the C_8-unit as the origin. The C_8-unit scheme was first formulated[1] for the large number of depsides (I) and depsidones (II) occurring in lichens. In these compounds the presence of C_8-units is quite as obvious as the C_6-units in starch and cellulose. The simplest orsellinic unit (III) is found to undergo a number of modifications involving ordinary oxidation and reduction (*e.g.*, IV & V) and also nuclear oxidation (VI) and nuclear methylation (II). Another characteristic feature is the lengthening of one of the side chains (6-position; see VII) of the original C_8-unit. The newly entering alkyl group also can have large dimensions, a feature noticed more commonly in mould products.

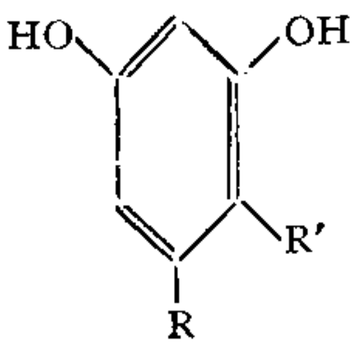
The recent work[2,3] on the mechanism of the biogenesis of citrinin (VIII) using tracer



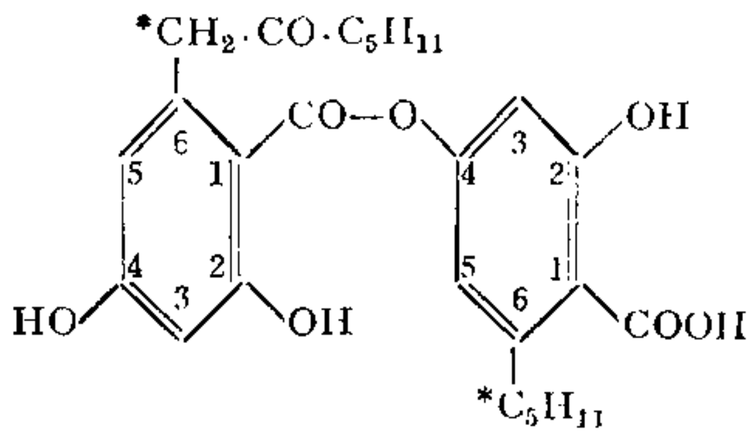
I R = H : Lecanoric acid
VI R = OH : Diploschistesic acid



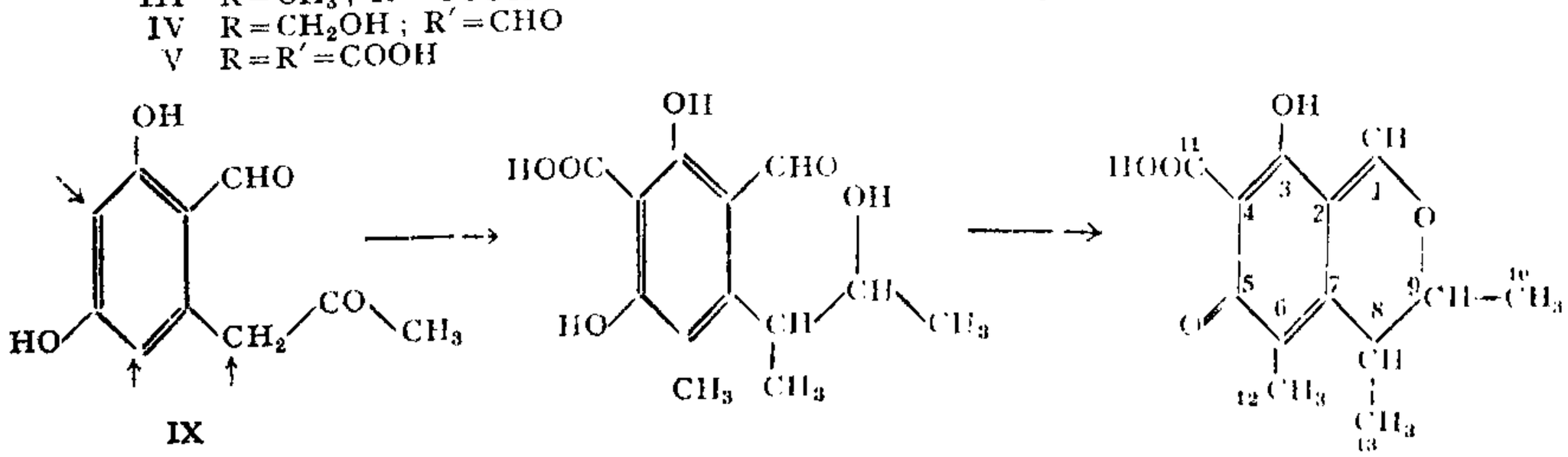
II Protocetraric acid



III R = CH_3 ; R′ = COOH
IV R = CH_2OH ; R′ = CHO
V R = R′ = COOH



VII Physodic acid



IX

VIII

technique fully supports the earlier suggestion[4] based on the C_5-unit according to which the carbon atoms numbered 11, 12 and 13 are the result of entry of single carbon units. The precursor could be visualized as a keto compound (IX) which can undergo C-methylation not only in the benzene nucleus but also in the particular active centre of the side chain.

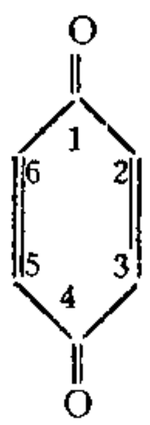
The quinones can be considered under a number of heads based on the complexity of the compounds.

1. Toluquinone Derivatives

In the earlier paper by Aghoramurthy and Seshadri,[4] the similarity between the metabolic products of lichens and moulds was pointed out and the C_5-unit scheme was shown to be applicable to the toluquinones of fungal origin. As typical examples, the biogenesis of methoxytoluquinone, fumigatin, spinulosin and aurantiogliocladin was explained and this was supported by the laboratory synthesis[5] of these compounds starting from C_8-unit systems.

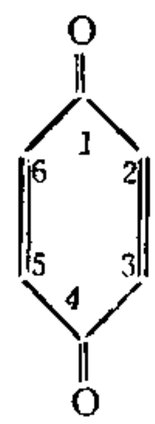
Simple toluquinone and its ω-hydroxy derivative, gentisylquinone, lack the presence of nuclear hydroxyl groups. They could have the same origin as fumigatin except for the incidence of stages of nuclear reduction. The common occurrence of $-CH_2OH$ group as in gentisylquinone has already been pointed out. Two possibilities exist: (*i*) hydroxylation of the active methyl group or (*ii*) hydroxymethyl being the earlier stage undergoing reduction to a methyl group. The co-occurrence of *o*- and *p*-xyloquinones and trimethylbenzoquinone

Table I



	Compound		Position of substituents	Source
1	Toluquinone	..	2-Methyl	Flour beetles
2	Gentisylquinone	..	2-Hydroxymethyl	*Penicillium patulum*, *P. divergens*
3	*o*-Xyloquinone	..	2 : 3-Dimethyl	Arachnids
4	*p*-Xyloquinone	..	2 : 5-Dimethyl	do.
5	Trimethylbenzoquinone	..	2 : 3 : 5-Trimethyl	do.
6	Methoxytoluquinone	..	5-Methoxy-2-methyl	*Coprinus similis*, *Lentinus degener*
7	Fumigatin	..	6-Hydroxy-5-methoxy-2-methyl	*Aspergillus fumigatus*
8	Spinulosin	..	3 : 6-Dihydroxy-5-methoxy-2-methyl	*A. fumigatus*, *Penicillium spinulosum* *P. cinerascens*
9	Aurantiogliocladin	..	5 : 6-Dimethoxy-2 : 3-dimethyl	*Gliocladium* spp.

Table II



	Compound		Position of substituents	Source
1	Embelin	..	3 : 6-Dihydroxy-2-undecyl	*Embelia* spp., *Myrsine* spp., *Rapanea neurophylla*
2	Rapanone	..	3 : 6-Dihydroxy 2-tridecyl	*Rapanea maximowiczii*, *Oxalis purpurata* var. *jacquinii*
3	Mæsaquinone	..	3 : 6-Dihydroxy-5-methyl-2-nonadecyl	*Mæsa japonica*
4	Ubiquinones	..	5 : 6-Dimethoxy-2-methyl-3-$[CH_2-CH=C(CH_3)-CH_2]_{6-10}.H$	Pig's heart, baker's yeast
5	Ethylbenzoquinone	..	2-Ethyl	Flour beetles

would suggest that they have resulted by the further nuclear methylation of toluquinone (by free radical process) or of the corresponding quinol (by ionic reactions or formaldehyde condensation). The importance of these methylbenzoquinones in relation to vitamin E has been discussed by Rao and Seshadri[6] and this will be mentioned again later on.

2. Toluquinones with Lengthened Side Chain

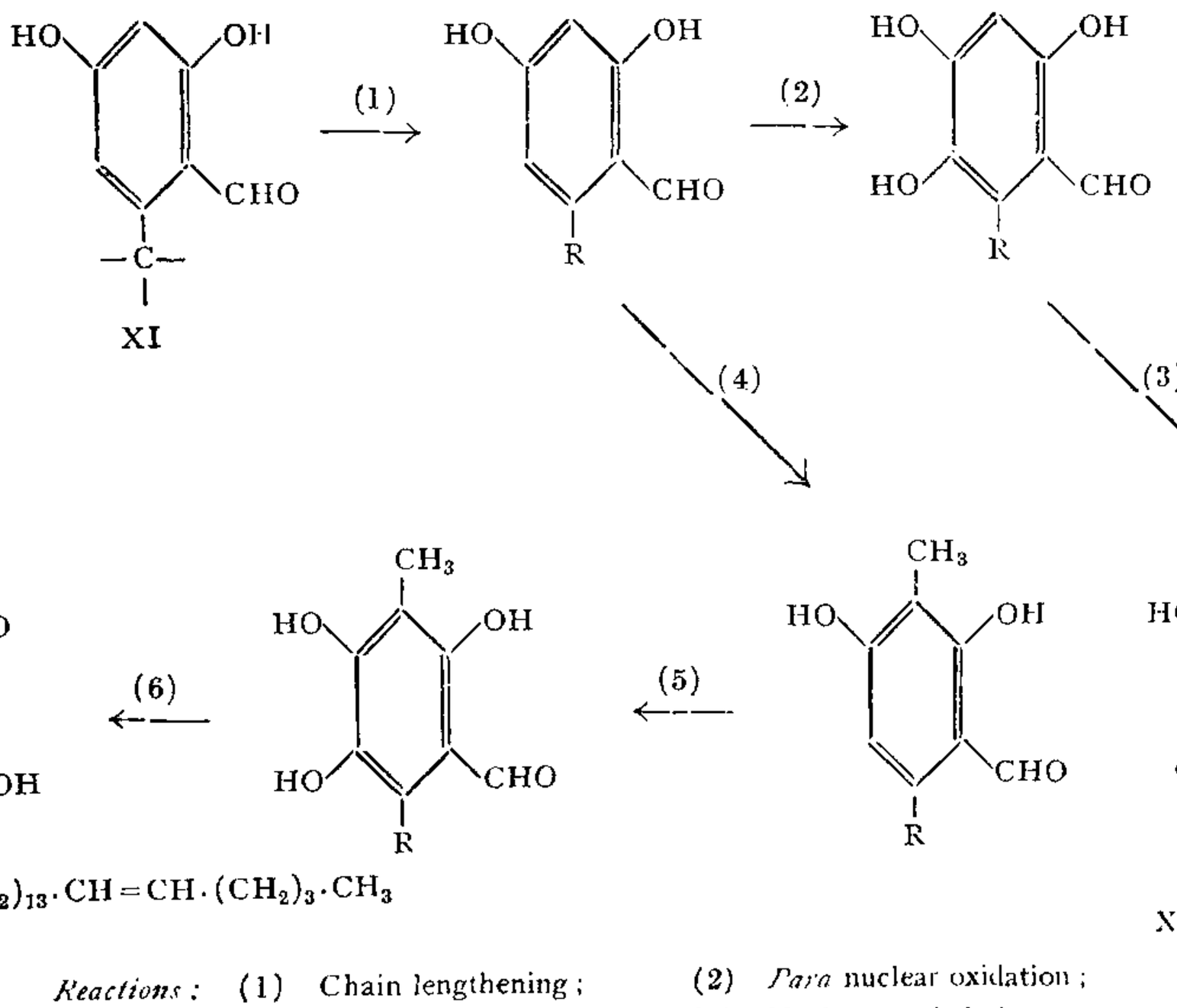
Embelin (X) is a derivative of 3 : 6-dihydroxy-2-methylbenzoquinone and its biogenesis from the appropriate C_8-unit (XI) can be represented as given below. Rapanone (XII) differs only in having a longer side chain and mæsaquinone (XIII) contains an extra methyl group and the position occupied by this is the normal γ-position of the orsellinic (C_8-) unit.

Ubiquinones (XIV) can be more directly derived from 5 : 6-dimethoxy-2-methylbenzoquinone (fumigation methyl ether) (XV) involving substitution in the 3-position by isoprene system. This is analogous to what is found in the case of vitamin K_2.

Ethylbenzoquinone, though a simple molecule, is somewhat exceptional in having an even (two carbon) side chain but it could be included in the toluquinone group if a propionic acid side chain (C_3) could be considered to undergo decarboxylation. This feature is commonly found in the porphyrin series where the propionic acid and ethyl side chains are found.

3. Tocopherols

A number of tocopherols have been isolated from vegetable oils like wheat germ oil and cotton-seed oil and also from leafy vegetables (Table III).



Reactions : (1) Chain lengthening ; (2) *Para* nuclear oxidation ;
(3) *Ortho* nuclear oxidation ; (4) Nuclear methylation ;
(5) *Para* N.O. ; (6) *Ortho* N.O.

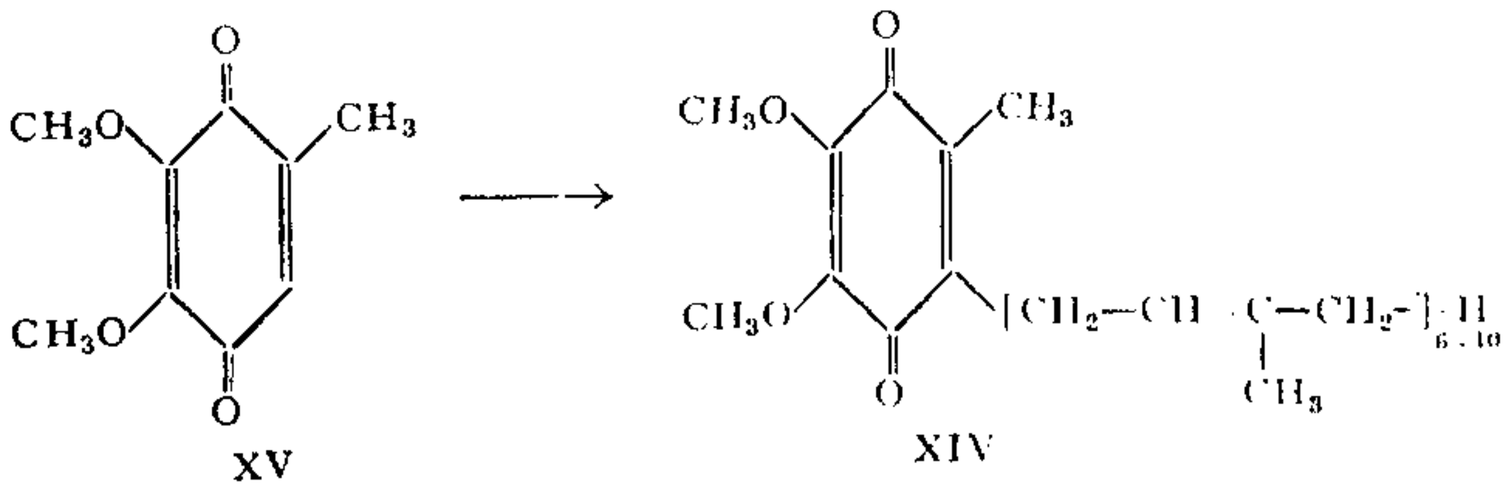
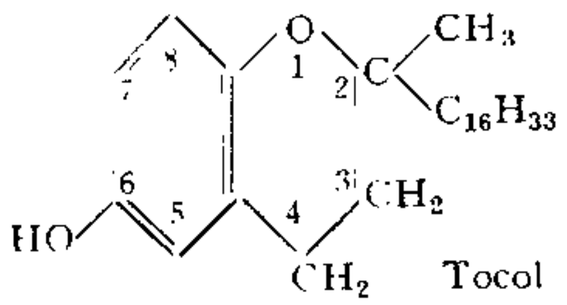


TABLE III



Tocol

	Compound	Position of substituents
1	α-Tocopherol	5 : 7 : 8-Trimethyl
2	β-Tocopherol	5 : 8-Dimethyl
3	γ-Tocopherol	7 : 8-Dimethyl
4	δ-Tocopherol	8-Methyl
5	ε-Tocopherol	5-Methyl
6	η-Tocopherol	7-Methyl
7	ξ-Tocopherol	5 : 7-Dimethyl

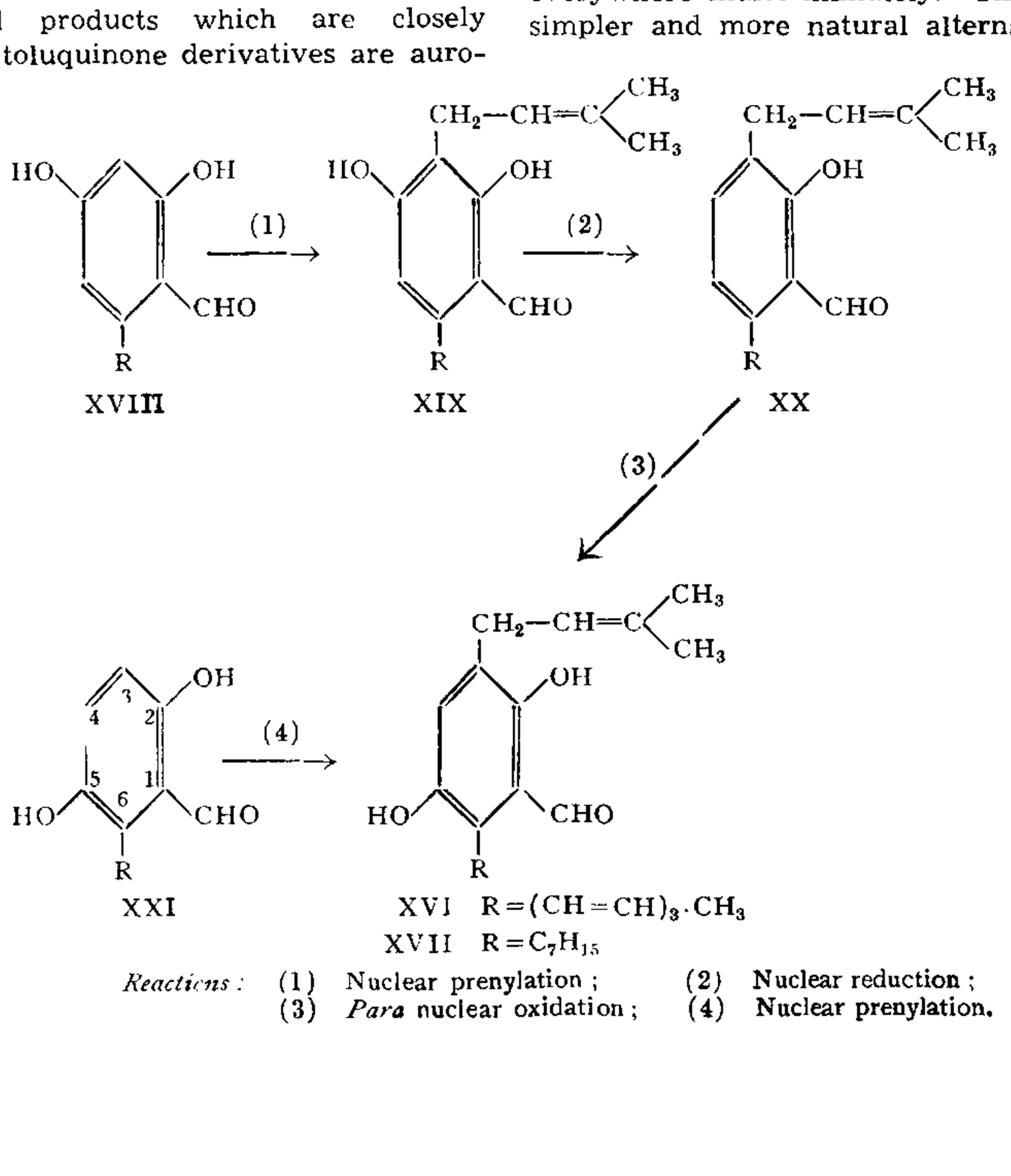
The relationship between the simple methyl substituted benzoquinones (Table I) and the tocopherols (Table III) is quite suggestive. It would appear that the corresponding quinols are the important intermediates. In plants, they undergo condensation with phytol to yield the tocopherols whereas in insects they undergo oxidation giving the corresponding quinones. The occurrence of the related series in the two places is highly significant.

4. Quinol Derivatives

Two mould products which are closely related to the toluquinone derivatives are auroglaucin and flavoglaucin. Their constitutions have recently been revised[7] as (XVI) and (XVII) respectively and the new structures fall into the C_8-unit scheme better. The main steps are chain lengthening (XVIII), nuclear prenylation (XIX) in the 3-position followed by nuclear reduction (XX) and *para* nuclear oxidation (XVI & XVII). In the orsellinic unit, entry of alkyl and other electrophilic groups is facile in the 3-position located between the two hydroxyl groups and hence the above suggestion (reaction 1). However, since reactive groups like the prenyl attack the quinol systems[8] also easily, the alternative prenylation of the alkyl substituted gentisic aldehyde (XXI) cannot be excluded. In this case, the 3-position will get preferentially activated by the *para* alkyl whereas the 4-position will be deactivated by the *para* aldehyde and hence the formation of the compounds (XVI & XVII) can be explained.

Benzoquinones of other origins

Though C_8-units occur widely and there is great validity for the C_8-unit origin of a large number of quinones and their derivatives, the scheme should not be pressed into service everywhere indiscriminately. There seem to be simpler and more natural alternative routes in



XVIII XIX XX

XXI

XVI R = $(CH=CH)_3 \cdot CH_3$

XVII R = C_7H_{15}

Reactions : (1) Nuclear prenylation ; (2) Nuclear reduction ; (3) *Para* nuclear oxidation ; (4) Nuclear prenylation.

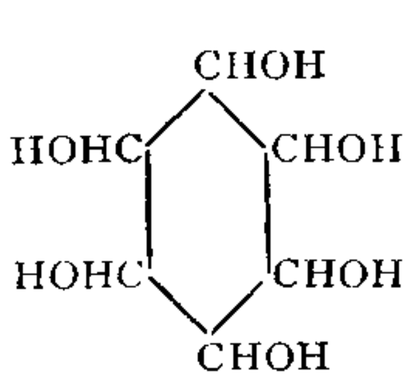
many other cases. Some typical examples are given below.

1. *Simple benzoquinone derivatives*

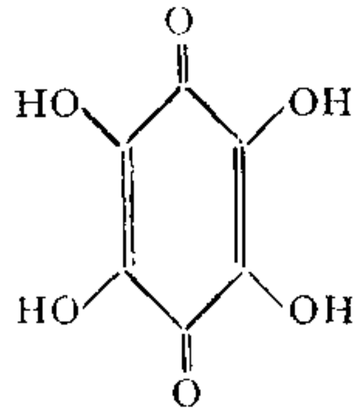
TABLE IV

	Compound			Source
1	Benzoquinone	..	..	Insects
2	Methoxybenzoquinone	..	..	Wheat germ
3	2 : 5-Dimethoxybenzoquinone	..	..	*Polyporus fumosus*
4	2 : 6-Dimethoxybenzoquinone	..	..	Wheat germ, *Adonis vernalis*

These are lacking in C-methyl groups and have methoxyl groups instead. A natural derivation would be from inositol (XXII) which is widely occurring in Nature and which can undergo ready oxidation to inosose and tetrahydroxy-*p*-benzoquinone (XXIII). These oxidations can be carried out fairly readily by means of nitric acid ; further they are known to be effected by micro-organisms also.[9] From the tetrahydroxyquinone (XXIII), graded loss of hydroxyl groups followed by methylation would account for the abovementioned compounds.



XXII



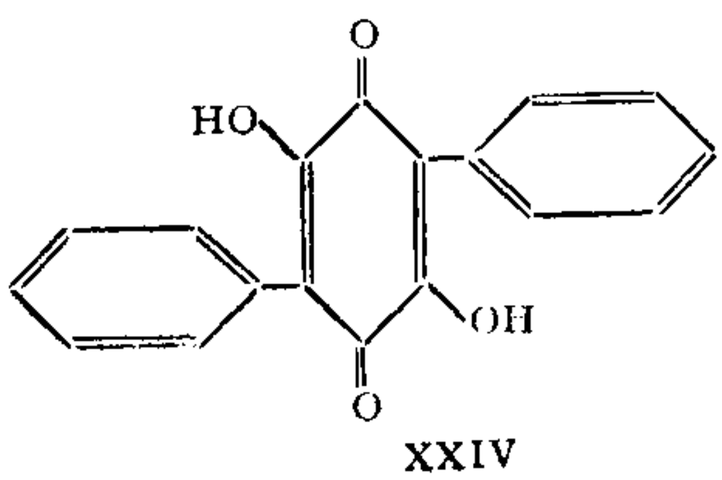
XXIII

2. *Terphenylquinones.*—A number of these compounds are known (Table V) and the more recent members to be recognised under this group are thelephoric acid (XXIV) and volucrisporin (XXV).

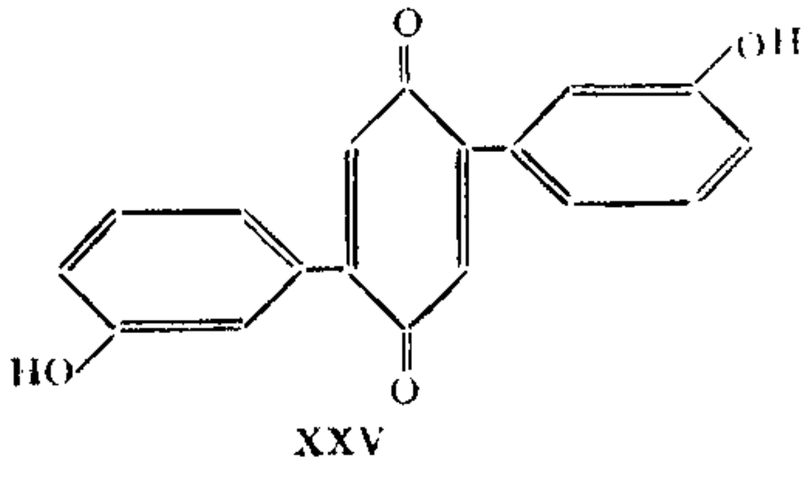
The biogenesis of this group of quinones has been suggested by Seshadri[12] as involving the linking of two C_9-forked units. Thelephoric acid (XXIV) and volucrisporin (XXV) are of special interest. Thelephoric acid was formerly considered to be a phenanthrene-quinone pigment, but recent work has shown that this structure needs change. It probably contains two methylenedioxy groups and belongs to the terphenyl series. Volucrisporin (XXV) has no *para*-

TABLE V

	Compound			Source
1	Polyporic acid	..	..	*Polyporus nidulans*, *P. rutilans*, *Penisphora filamentosa*, *Sticta coranata*, *S. colensoi*
2	Atromentin	..	..	*Paxillus atrotomentosus*
3	Leucomelone	..	..	*Polyporus leucomelas*
4	Muscarufin	..	..	*Amanita muscaria*
5	Thelephoric acid[10]	..	..	*Thelephora palmata*, *Lobaria isidiosa*
6	Volucrisporin[11]	..	..	*Volucrispora aurantiaca*

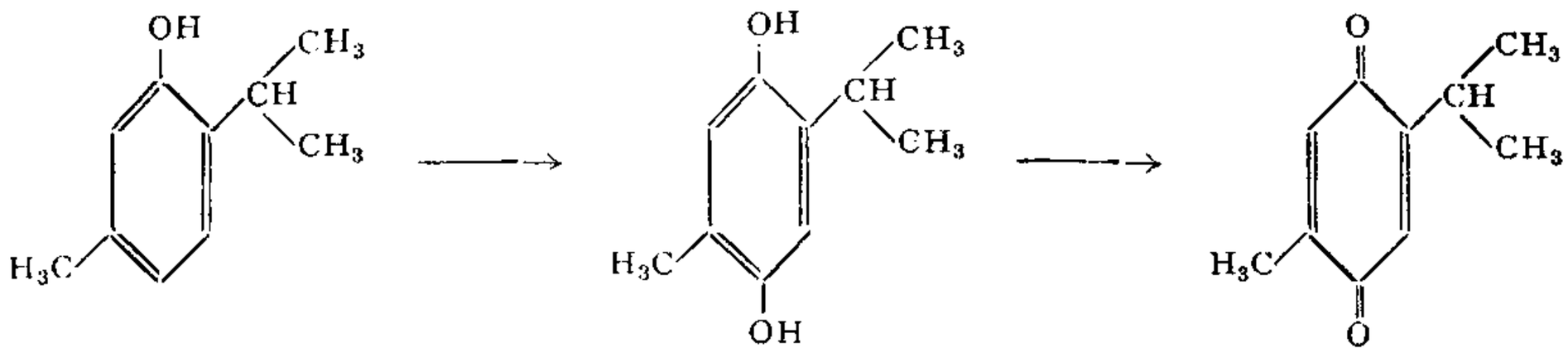


XXIV

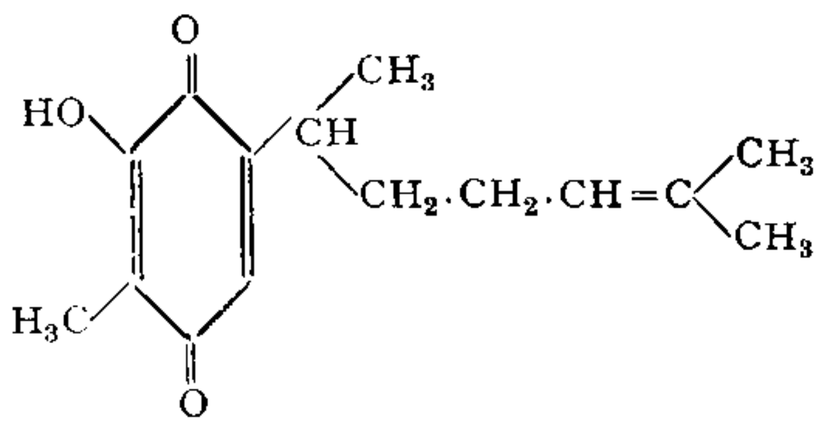


XXV

dihydroxy group and possesses a *meta*-hydroxyphenyl system. It seems to be possible that a catechol system is the real precursor and both the *para* and *meta* hydroxy compounds arise by selective reduction at some stage.



XXVII XXVI



XXVIII

3. *Thymoquinone derivatives.*—Compounds belonging to this group seem to be rather exceptional. Thymoquinone (XXVI) itself occurs in the seeds of *Carum roxburghianum*, heartwood of *Tetraclinis articulata* and in the incense cedar. Hence it is natural to expect that it is derived from thymol (XXVII) by oxidation. Therefore it has a terpene origin. A compound which seems to be closely related to thymoquinone would be perizone (XXVIII). The additional stages involved are chain lengthening of the C_3-system by means of an isoprene unit and introduction of a hydroxyl group.

Summary

The C_8-unit scheme satisfactorily accounts for the biogenesis of (*i*) toluquinone derivatives, (*ii*) extended toluquinones, (*iii*) tocopherols and (*iv*) quinol derivatives. However, simpler benzoquinone derivatives, terphenylquinones and thymoquinone derivatives have other origins, *e.g.*, inositol, C_9-units and terpenoid systems.

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