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UBIQUINONES (COENZYME Q)

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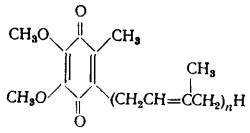
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The studies carried out in recent years demonstrate the outstanding role of substituted quinones, ubiquinones (coenzyme Q) (I), in intracellular electron transport coupled with oxidative phosphorylation [1-8]:



(I)

The data on this new group of coenzymes are collected in the present review and certain hypotheses concerning the participation of quinones in intermediate reactions in oxidative phosphorylation are considered.

I. DISCOVERY AND NATURAL SOURCES OF UBIQUINONES

At the end of 1955 a group of investigators at the University of Liverpool carried out experiments designed to elucidate the mechanism of the effect of vitamin A in growth processes and in cases of xerophthalmia [9]. They isolated from the mucus membrane of the horse intestine a substance, the spectrum of which had characteristic absorption maxima at 272 and 400 nm. [10,11] Somewhat later the same investigators isolated chromatographically from the non-hydrolysable fraction of liver lipids and other mammalian tissues (under normal conditions and under conditions of vitamin A deficiency) other analogous fractions which were denoted by the letters SA, SB, and SC. [12-16] It was further elucidated that the substance in fraction SA is identical with that isolated from the intestine and that it is indeed present in human and animal liver, kidneys, spleen, blood, and pancreas and is localised within the cell [17-22]. It was established that the substance of the fraction SA contains a cyclic group of the quinone type and a side-chain with a definite number of double bonds. The compound was given the name "ubiquinone", which indicates its chemical type and wide distribution in nature [17,18,20].

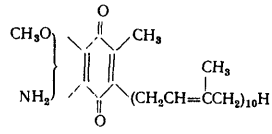
Simultaneously with the investigations in Liverpool, Swiss chemists of the Hofmann-La Roche Company [23,24] isolated two ubiquinones from pig heart and from yeast after processing a large amount of natural material. The first ubiquinone had a side-chain of ten isoprenoid units in position 6 — ubiquinone(50) or UQ_{10} — and the second a side-chain of six isoprenoid units — ubiquinone(30) or UQ_6. Soon the same investigators achieved the synthesis of UQ_6 and UQ_{10} and also of their homologue UQ_9 and showed that these quinones are identical with the natural compounds [24,25].

In 1957 yet another group of investigators, from Wisconsin University, published their work on the isolation from beef heart mitochondria of a substance with properties characteristic of quinones and called coenzyme Q_{275} (quinone with an ultraviolet absorption maximum at 275 nm) [26,27]. Soon, in collaboration with the American chemists of the Merck Company (New Jersey), the investigators from Wisconsin demonstrated the identity of coenzyme Q_{275} with the ubiquinones discovered by the workers of the Liverpool school and in Switzerland [28-30].

At the Fourth International Biochemical Congress in Vienna in 1958 the reports of all the groups of investigators were presented and the identity of the compounds confirmed. In 1961 the Committee on Enzymes of the International Biochemical Union [31] recommended the name "ubiquinone" to unify the terminology for this class of substances, in view of the fact that the nature of this cofactor had already been established.

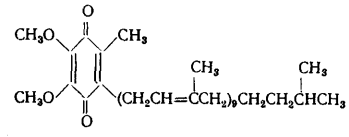
Natural ubiquinones (UQ_6, UQ_7, UQ_8, UQ_9, and UQ_{10}) have been found in various tissues of animals [10-13,15,16,19,24-26,32-38] and plants [39,40] and in micro-organisms [23,28,41-46]. UQ_6, [23,28,45,46] UQ_7, [28,45,47] and UQ_8 [28,45,47] are encountered almost exclusively in micro-organisms, only traces being found in animals [47]. UQ_9 [25,28,37,38,40,45,47] and particularly UQ_{10} [11,14,21,24-26,34-41,44,45,47] are distributed mainly in animals and in higher plants [48], and UQ_9 is found in vegetable oil [30] and in aloe [37]. The heart tissue of rhesus monkeys contains UQ_{10}. These animals are suitable objects for UQ_{10} tests in various diseases. UQ_{10} has been found in the nerve tissue of the frog. This fact can be used in the investigation of the role of UQ_{10} in neurology. UQ_{10} has also been found in tumour tissues in man and in rodents [49]. In man UQ_{10} has been isolated from heart tissue and other organs [38,50]. A comparative estimate of the content of ubiquinone(50) in various organs showed that the organism of the adult man contains 0.5–1 g of UQ_{10}.

Micro-organisms are capable of synthesising all the natural homologues of ubiquinones (UQ_6–UQ_{10}). [24,28,38,45] The cells of *Ochromonas mathamensis* produce UQ_{10} and those of *Polyporous schweinitzii* both UQ_9 and UQ_{10}. [49] An analogue of UQ_{10}, rhodoquinone with one free amino-group (II), [51] has been isolated from a culture of *Rhodospirillum rubrum*:



(II)

Another representative of the group of ubiquinones has been isolated from the cells of *Gibberella fujckuroi* and *Penicillum stipitatum* [52,53]. Identification of this compound, obtained from two types of culture, showed that the tenth isoprenoid residue of the side-chain is saturated. This new compound, called UQ_{10}(H-10), has the structure (III): [53-55]

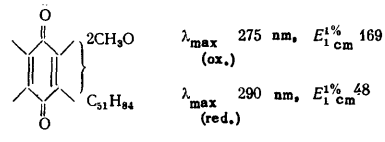


(III)

II. DETERMINATION OF THE STRUCTURE OF UBIQUINONES

1. Ubiquinone(50) (UQ_{10})

The general formula found [29] for UQ_{10} is $C_{59}H_{90}O_4$; the following partial formula (IV) has been put forward on the basis of the displacement of the ultraviolet maximum from 275 to 290 nm after reduction under mild conditions:



(IV)

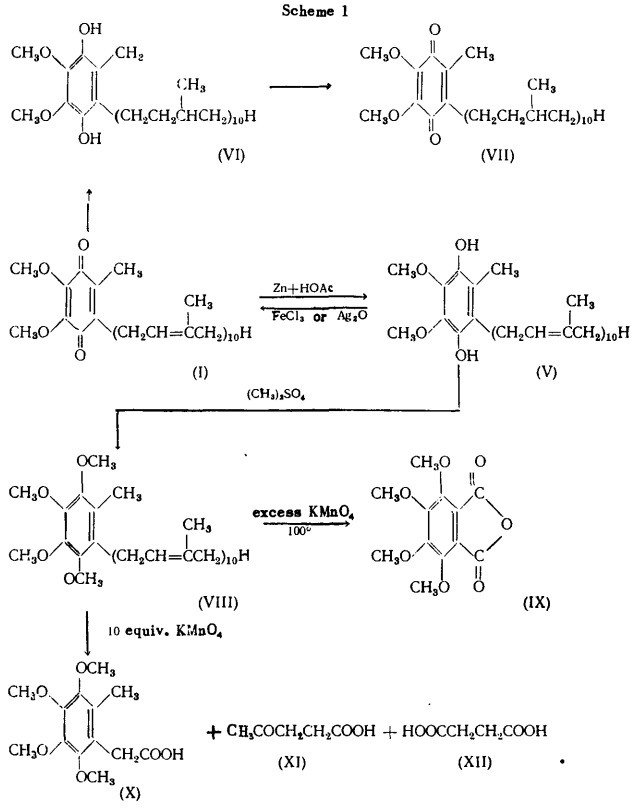
Determination of the O–Alk residues showed the presence of two methoxy-groups. Since it was suggested that the UQ_{10} molecule contains the benzoquinone ring, the two CH_3O groups could occupy three different positions. Comparison of the ultraviolet spectra of UQ_{10} in the quinone and

hydroquinone forms with those of aurantiogliocladin[56] (2,3-dimethoxy-5,6-dimethyl-1,4-benzoquinone) revealed their close similarity. However, on the basis of these data, one cannot finally conclude that UQ_{10} is a derivative of 2,3-dimethoxy-5-methylbenzoquinone, because the ultraviolet spectra of 2,6-dimethoxy-3,5-dimethyl- and 2,5-dimethoxy-3,6-dimethyl-1,4-benzoquinones[57,58] differ only slightly from the ultraviolet spectra of the isomeric aurantiogliocladin.

Chemical conversions (Scheme 1) suggested that one of the substituents in the *p*-quinone ring of UQ_{10} is a polyisoprenoid chain[28,29]: on catalytic reduction of UQ_{10}, 11 moles of hydrogen are absorbed; eicosahydroquinone (VI) is formed and after oxidation is converted into eicosahydro-UO_{10} (VII). Oxidation of UQ_{10} with alkali and potassium permanganate leads to the formation of levulinic, acetic, and succinic acids. The isoprenoid nature of the side-chain of UQ_{10} has been confirmed by nuclear magnetic resonance[59] and a difference between the protons of the methyl groups of the ring and the isoprenoid chain has been demonstrated. Together with other evidence, the NMR data confirm to a large extent (but do not provide the final proof) the positions of the two CH_3O groups, one CH_3 group, and of the isoprenoid chain of ten units.

The positions of all the substituents in the quinone ring of UQ_{10} were finally demonstrated by oxidative degradation. Dimethylhydro-UQ_{10} (VIII) was obtained in a crystalline form by the reduction of UQ_{10} (I) to the hydroquinone (V) and exhaustive methylation. Oxidation of compound (VIII) with potassium permanganate in aqueous alkaline solution at 100° gave, after sublimation, tetramethoxyphthalic anhydride (IX). Oxidation of compound (VIII) with potassium permanganate in acetone gave 2-methyl-3,4,5,6-tetramethoxyphenylacetic (X), levulinic (XI), and succinic (XII) acids.

Scheme 1



Another group of investigators, who studied independently the structure of UQ_{10},[9,24] subjected ubiquinone(50) to reductive acetylation followed by oxidative degradation of diacetylhydro-UQ_{10} and isolated acetone and levulinic aldehyde in the form of 2,4-dinitrophenylhydrazones and also 3,6-diacetoxy-4,5-dimethoxy-2-methylphenylacetic acid, which was characterised via its *p*-toluidide derivative.

Thus chemical conversions and spectroscopic data carried out by different investigators showed that UQ_{10} is 2,3-dimethoxy-5-methyl-6-[3-methyl-2-butenylenakis--(3-methyl-2-butenylene)]-1,4-benzoquinone.

2. Ubiquinones(30), (35), (40), and (45) (UQ_6–UQ_9)

The ultraviolet spectra of various natural ubiquinones[60] are the same, but the extinction coefficient is inversely proportional to the length of the carbon chain (decrease of the mole fraction of the chromophore). Qualitatively the infrared spectra of ubiquinones are also the same[24]. Each of the natural ubiquinones is characterised by a different value of R_f in paper and thin-layer chromatography[61,62] and also by a different redox potential[63,64]. The molecular weight of ubiquinone homologues has been determined by the esterification of the OH group of the corresponding [^{14}C]-ubiquinols with acetic anhydride followed by the measurement of the ^{14}C radioactivity in the acetate derivatives[65]. These results confirm that each quinone differs from the succeeding homologue of the given group by one isoprene unit (I, n = 6–10). Thus the ubiquinones isolated from natural sources have been characterised as UQ_6 (*Saccharomyces cerevisiae*), UQ_7 (*Torulopsis utilis* A), UQ_8 (*Azotobacter vinelandii*), and UQ_9 (*Torulopsis utilis* B).[28]

III. SYNTHESIS OF UBIQUINONES

1. Synthesis of the Polyisoprenoid Side-Chain

Formula (I) shows that ubiquinones contain an unsaturated side-chain with a variable number of isoprenoid units linked to one another "head to tail". The double bonds in the side-chain have the *trans*-configuration. The corresponding unsaturated terpenoid alcohols [of type (XV), see Scheme 2 and Table 1] with the all-*trans*-configuration of the double bonds, necessary for the synthesis of ubiquinones, were obtained by methods developed in recent years in the chemistry of isoprenoids.

Condensation of acetone (XIII, x = 0) with sodium acetylide in liquid ammonia followed by partial hydrogenation of the product (XIV, x = 0) gives methylbutenol (XV, x = 0).

Scheme 2

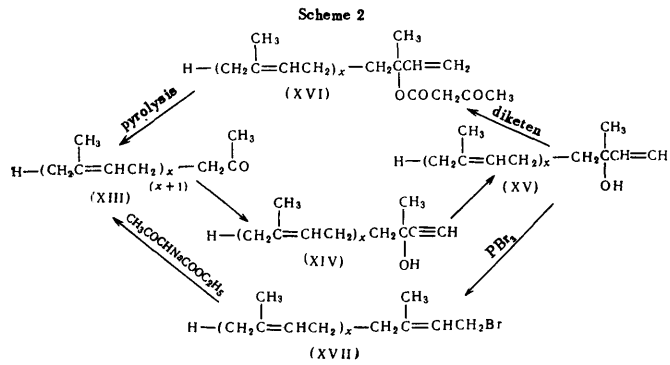


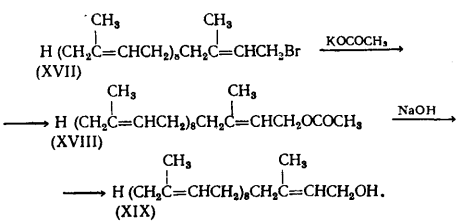
TABLE 1.

x	Ketones	Tertiary alcohols
0	C_5-ketone (A)	C_5-alcohol (methylbutenol)
1	C_8-ketone (methylheptenone)	C_{10}-alcohol (L)
2	C_{13}-ketone (GA)	C_{15}-alcohol (N)
3	C_{18}-ketone (FA)	C_{20}-alcohol (GL)
4	C_{23}-ketone (GGA)	C_{25}-alcohol (FL)
5	C_{28}-ketone (FGA)	C_{30}-alcohol (FN)
6	C_{33}-ketone (FFA)	C_{35}-alcohol (FGL)
7	C_{38}-ketone (FGGA)	C_{40}-alcohol (FFL)
8	C_{43}-ketone (FFGA)	C_{45}-alcohol (FFN) (isosolanesol)
9	C_{48}-ketone (FFFA)	C_{50}-alcohol (FFGL)

A = acetone, G = geranyl, F = farnesyl, L = linalo-ol, N = neralidol.

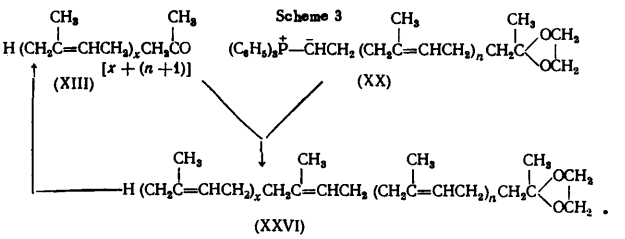
When the latter is condensed with diketen[66] and the resulting acetoacetate (XVI, $x = 0$) is pyrolysed, methylheptenone (XIII, $x = 1$) is obtained. Repetition of similar operations gives geranylacetone (XIII, $x = 2$) via linalo-ol (XV, $x = 1$); the new double bond in geranylacetone has the *trans*-configuration to the extent of two thirds and the *cis*-configuration to the extent of one third. Subsequent increase of chain length by one isoprenoid unit gives rise to farnesylacetone (XIII, $x = 3$).

One of the methods of synthesis of isoprenoid ketones consists in the preparation of primary bromides (XVII) from the corresponding tertiary vinyl carbinols (XV) and subsequent condensation with sodioacetoacetic ester[67]. The isoprenoid ketones (XIII) obtained in this way after ketonic hydrolysis contain 85% of the *trans*- and 15% of the *cis*--forms. Subsequent sixfold increments of the chain length of *trans*-geranylacetone (XIII, $x = 2$) by the C_5-unit [68,69] with separation of the stereoisomers gives the *trans*-C_{43}--ketone (XIII, $x = 8$). The latter is converted in the usual way into the primary C_{45}-bromide (XVII, $x = 8$), which is also obtained from the natural alcohol solanesol (XIX).[69,70] This bromide can be converted, via the C_{48}-ketone (XIII, $x = 9$), into the *trans*-tertiary alcohol (XV, $x = 9$) and the corresponding primary C_{50}-alcohol[69]. Treatment of the C_{45}--bromide (XVII, $x = 8$) with potassium acetate followed by hydrolysis of compound (XVIII) gives the C_{45}-alcohol (XIX) which is identical with the natural solanesol, as shown by the determination of the melting point of a mixed sample and a comparison of the corresponding X-ray diffraction patterns[25,69].

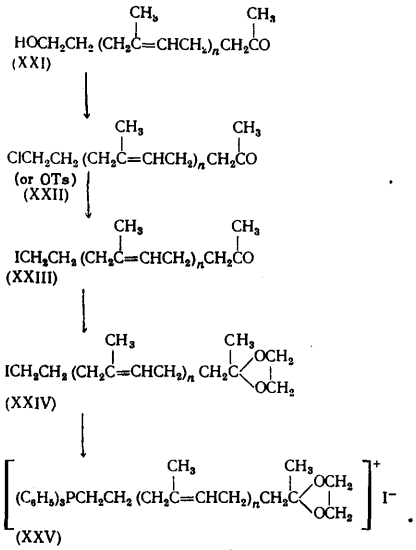


Another method of synthesising polyisoprenoid ketones consists in a gradual increase of the length of the carbon chain by mono-, di-, or tetra-isoprenoid units using difunctional compounds in the Wittig olefin addition reaction[71-73] (Scheme 3).

Isoprenoid ketones of the type of methylheptenone (XIII, $x = 1$), *trans*-geranylacetone (XIII, $x = 2$), and *trans*--farnesylacetone (XIII, $x = 3$) can be made to undergo the olefin addition reaction using the phosphorane (XX).[71-73]



The bifunctional stereoisomeric phosphoranes (XX, $n = 0$ and $n = 1$) are synthesised from acetylpropanol (XXI, $n = 0$) [71] and the di-isoprenoid C_{10}-keto-alcohol (XXI, $n = 1$) respectively[72,73]: the OH group is replaced by iodine [compound (XXIII)], the carbonyl group is protected by the formation of the ethyleneketal (XXIV), the phosphonium salt (XXV) is formed, and the phosphorane is finally produced by further reaction with sodium methoxide in dimethylformamide:



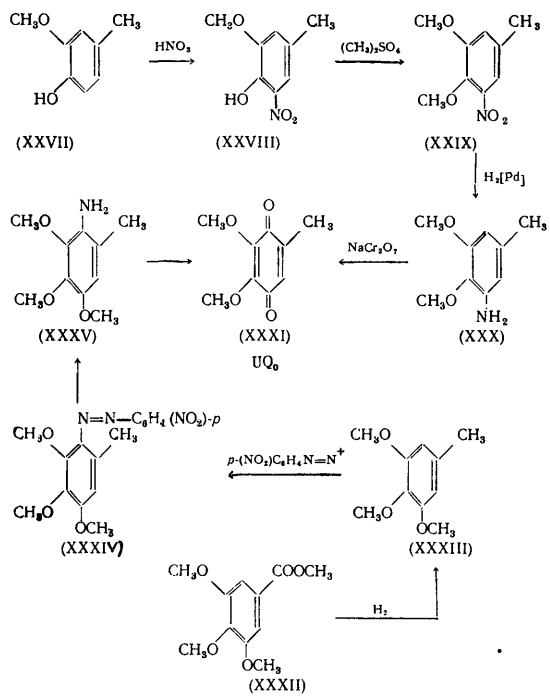
The resulting ethyleneketals (XXVI) with the carbon chain lengthened by five and ten carbon atoms respectively and the isoprenoid ketones (XIII, $x = n + 1$) obtained from them by the hydrolysis of the ketal group are formed as a mixture of *cis*- and *trans*-isomers with respect to the new double bond, in proportions of 60 : 40. Individual *trans*--isomers required for subsequent syntheses are obtained by vacuum fractionation in the case of geranylacetone (XIII, $x = 2$) and farnesylacetone (XIII, $x = 3$). The *trans*-isomers of successive isoprenoid ketone homologues are isolated by crystallisation at low temperatures[65].

2. Synthesis of UQ_0

2,3-Dimethoxy-5-methyl-1,4-benzoquinone (XXXI) — the ubiquinone chromophore — has been called UQ_0 and its position in the series of ubiquinones is analogous to the position of menadione among vitamins K. However, the corresponding biological similarity between UQ_0 and menadione has not been observed[74]. UQ_0 was synthesised long before the discovery of the ubiquinone group[75] (Scheme 4).

Creosol (XXVII), obtained by the reduction of vanillin over $Pd/BaSO_4$ using the Rosenmund method[76], is converted into nitrocreosol (XXVIII),[77] the methylation of which gives 5-nitrohomoveratrol (XXIX). The reduction of the latter to 5-aminohomoveratrol (XXX) and oxidation

Scheme 4



of the amine with sodium dichromate in sulphuric acid yield 2,3-dimethoxy-5-methylbenzoquinone (XXXI).

An alternative synthesis of UQ_0, from the ethyl ester of trimethylgallic acid, was described after the discovery and determination of the structure of ubiquinones[78]. Trimethylgallate (XXXII), obtained by the methylation of gallic acid[79], is reduced over a copper–chromium catalyst to 3,4,5-trimethoxytoluene (XXXVIII). Coupling with *p*-nitrophenyldiazonium salt and subsequent reduction of the diazo-compound (XXXIV) lead to trimethoxytoluidine (XXXV), which is oxidised to 2,3-dimethoxy-5-methylbenzoquinone (XXXI).

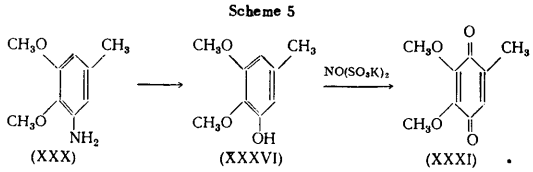
Other syntheses of UQ_0 described in the literature are modifications of the procedures already given above. It has been suggested[80] that 2,3-dimethoxy-5-methylphenol (XXXVI), obtained from aminohomoveratrol (XXX), be oxidised to 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XXXI) with the aid of potassium nitrosodisulphonate (Fremy's salt) (Scheme 5).

In addition UQ_0 (XXXI) can be obtained from nitrovanillin (XXXVII) [8] by the series of conversions shown in Scheme 6.

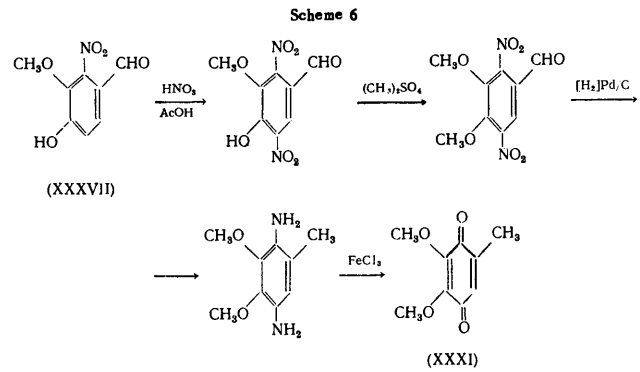
3. Synthesis of UQ_1–UQ_{10}

The ubiquinones UQ_1–UQ_{10} have been synthesised[23,25,67,82–87] by the condensation of 2,3-dimethoxy-5-methylhydroquinone (XXXVIII) with the tertiary (XV) or primary allyl

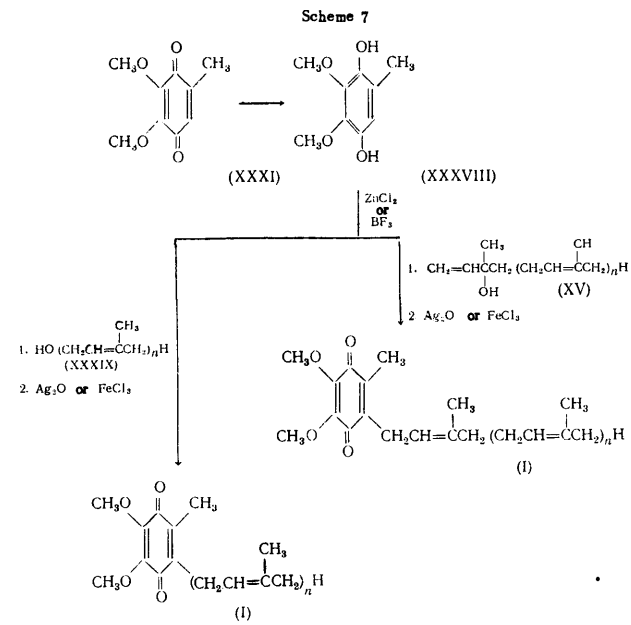
Scheme 5



Scheme 6



Scheme 7



alcohol (XXXIX) to give the corresponding substituted hydroquinones (Scheme 7). Zinc chloride or boron trifluoride-ether or the two together are used as catalysts for this reaction. The hydroquinones are oxidised with silver oxide or ferric chloride to give the ubiquinones (I) (see Table 2).

The identity of the synthetic and natural products has been established by determining the melting points of mixed samples, by ultraviolet and infrared spectroscopy, by paper and thin-layer chromatography, and by X-ray diffraction. The last method proved to be exceptionally accurate for the identification of crystalline isoprenoid homologues[25].

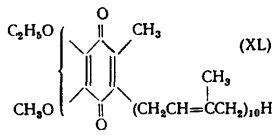
TABLE 2.

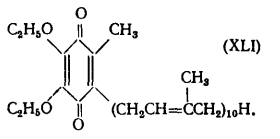
Synthetic quinone	M.p.	λ_{max} = 275 nm in petroleum ether		Synthetic quinone	M.p.	λ_{max} = 275 nm in petroleum ether	
		$E^{1\%}_{1\,cm}$	ϵ			$E^{1\%}_{1\,cm}$	ϵ
UQ_1	oil	590	148×10^3	UQ_6	19–20°	260	153×10^3
UQ_2	oil	455	145×10^3	UQ_7	31–32°	229	151×10^3
UQ_3	oil	390	151×10^3	UQ_8	37–38°	206	150×10^3
UQ_4	oil	326	148×10^3	UQ_9	44–45°	187	149×10^3
UQ_5	oil	292	152×10^3	UQ_{10}	49°	176	152×10^3

IV. CONVERSION PRODUCTS OF UBIQUINONES

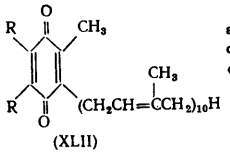
1. Products of the Nucleophilic Replacement of the Methoxy-Groups

The isolation of ubiquinones consists mainly in the hydrolysis of the test substance with hot alcoholic alkali, extraction of the non-hydrolysable lipids, purification of the extracts by column chromatography with the appropriate adsorbent, and crystallisation from polar solvents[32,33]. When ethanol is present in the hydrolytic process, there is a possibility of the nucleophilic replacement of the methoxy--groups, the amounts of the resulting monoethoxy- and diethoxy-derivatives, (XL) and (XLI), depending on the temperature and the duration of hydrolysis[50].


(XL)


(XLI)

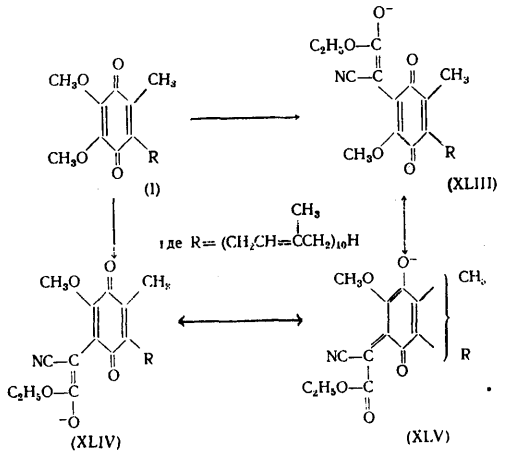
The capacity of the methoxy-groups of the ubiquinones to undergo nucleophilic replacement permits an approach to the synthesis of higher alkoxy-homologues (XLIIa), derivatives containing nitrogen and sulphur [(XLIIb) and (XLIIc) respectively], and the ubiquinone (XLIId) with a radioactive methoxy-group.


(XLII)

a) R=R'O; b) R=R'NH—, R'R"N—;
c) R=R'S—; d) R=$C^{14}H_3O$—;
e) R=$(CH_3)_2CHCH_2CH_2O$—;
f) R=$(CH_3)_2CHO$—.

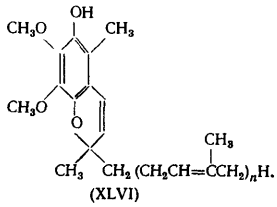
The di-isopentyloxy- and di-isopropoxy-homologues [(XLIIe) and (LXIIf) respectively], which are of definite interest in connection with the determination of the role of UQ_{10} in various enzymic systems, have been synthesised in this way[88].

The determination of UQ_{10} in human urine (a modification of the Craven reaction) is based on this principle[50]. The blue colour produced by the reaction of UQ_{10} with cyanoethyl acetate is due to the conversion of UQ_{10} (I) into compounds (XLIII), XLIV), and (XLV):


(I) (XLIII) (XLIV) (XLV)

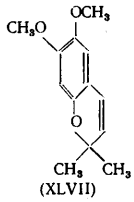
2. Ubichromenols

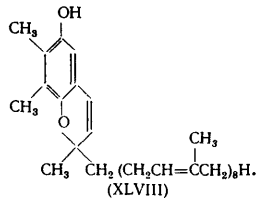
Ubichromenol is the trivial name given to the ubiquinone isomer in which the third carbon atom of the side-chain forms a chromen ring with the quinone oxygen [compound (XLVI)]:


(XLVI)

The nomenclature of ubichromenols is derived from the corresponding ubiquinones. The compound which is the isomer of ubiquinone(50) is called ubichromenol(50) although its side-chain contains only 46 carbon atoms. Ubichromenol(50) (XLVI, n = 9) has been isolated from the kidneys and liver of humans[89] and from the liver of rats suffering from vitamin A deficiency (the substance which was initially denoted by the letters SC [15,34,90-96]).

The structure of ubichromenol(50) was established in a study of its spectroscopic properties[91], by comparing them with those of two known chromens: ageratochromen (XLVII) [97] and solanochromen (XLVIII):[98]


(XLVII)


(XLVIII)

Thus it was shown that ubichromenol(50) (XLVI) is 2,5-dimethyl-7,8-dimethoxy-2-{[3-methyl-2-butenyloctakis--(3-methyl-2-butenylene)]methyl}-3-chromen-6-ol[91].

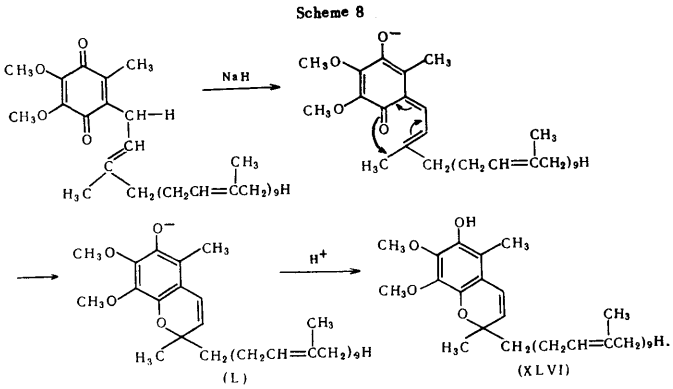
Ubichromenols can be obtained from ubiquinones by passing the latter through an alumina column with subsequent elution using various solvents with[93] and without[94,99] dilute hydrochloric acid. This reaction led to many doubts as to whether ubichromenol as such is a natural component of animal origin or whether it is formed as a result of isomerisation in the organism or during isolation[92,100-103].

Biosynthetic studies using the [2-^{14}C]lactone of mevalonic acid demonstrated convincingly that ubichromenol has a common precursor with ubiquinone and is a product of biosynthesis in the rat organism[104,105]. Furthermore, ubichromenol(50), isolated from human kidneys, is optically active[95,106], while the compound obtained by the cyclisation of UQ_{10} is racemic.

The synthesis of 6-chromenol (XLVI) in high yield has been achieved by the cyclisation of UQ_{10} under the influence of sodium hydride[107] (Scheme 8).

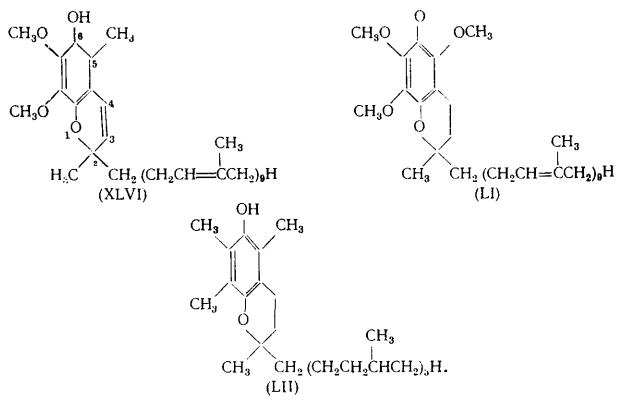
The elimination of a proton from the first carbon atom of the side-chain and the withdrawal of electrons towards the quinone oxygen in position 4 lead in all probability to the intermediate (XLIX) which is stabilised by the electron shift. The formation of the bond between the quinone oxygen in position 1 and the 3-carbon atom in the side-chain yields the 6-hydroxy-anion of 6-chromenol (L). When this intermediate is protonated, ubichromenol(50) (XLVI) is formed.

Scheme 8



Ubichromenols can also be obtained on a preparative scale from ubiquinones in the presence of pyridine [108].

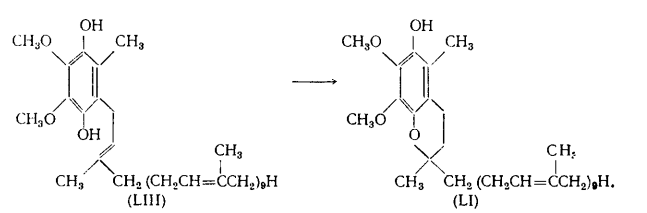
Certain common features in the structure of α-tocopherol (LII) and ubichromenol (XLVI) as well as its analogue saturated with respect to the 3,4-bond [ubichromanol (LI)] led to the investigation of the vitamin activity of these compounds.



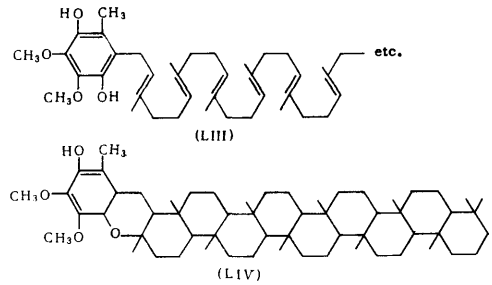
However, it was found [109] that, while ubichromenol exhibits a definite vitamin E activity, ubichromanol (LI), which would appear to be more similar to α-tocopherol (LII), does not. In this connection, ubichromenol may be regarded as a non-specific antioxidant [110,111].

3. Ubichromanols

Interesting observations were made by Folkers in the preparation of the corresponding chromanol (LI) from ubiquinol(50) (LIII): [50]

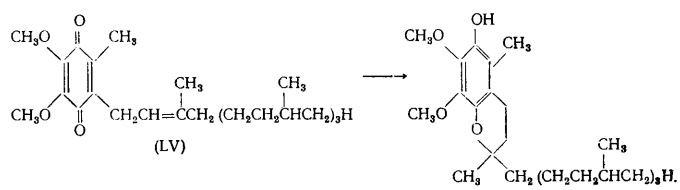


When ubiquinol(50) is treated with potassium bisulphate under conditions which are well known to be suitable for the preparation of 6-chromanols, the corresponding chroman (LI) is formed [112]. However, under the action of stannous chloride [113], instead of the expected product (LI) a mixture of substances was obtained in which, according to NMR spectroscopic data, there are protons characteristic of saturated hydrocarbons instead of the protons characteristic of the isoprenoid chain, and the *p*-hydroxy-group is absent. The authors believe that, as a result of the high reactivity of the isoprenoid side-chain, intramolecular condensation of the isoprenoid residues of compound (LIII) takes place in this case with formation of compound (LIV):



Different degrees of cyclisation of compound (LIII) were responsible for the formation of a mixture of substances.

The formation of the chromanol from hexahydroubiquinone(20) (LV) takes place in the usual way on boiling the quinone in glacial acetic acid in the presence of an excess of stannous chloride:



The double bond of the first, unsaturated isoprenoid unit of the phytol residue of compound (LV) becomes localised on formation of 6-chromanol; there are no other unsaturated centres which would favour the cyclisation of the side-chain of hexahydro-UQ_4. Hexahydroubiquinone(20) is the most convenient member of the ubiquinone group for various biological tests [114].

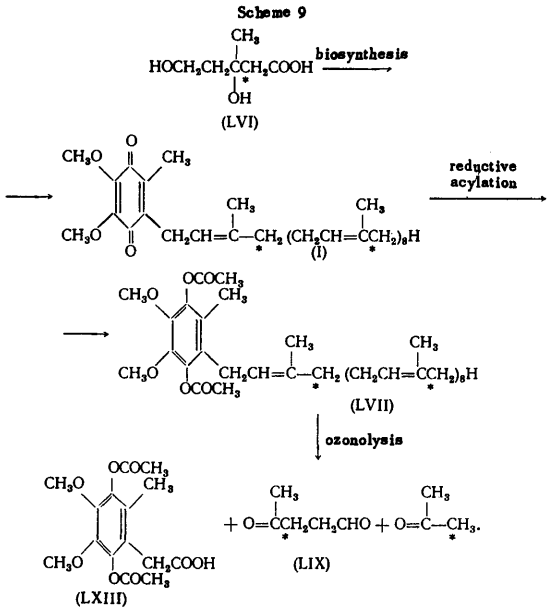
V. BIOSYNTHESIS OF UBIQUINONES

In order to assess the physiological significance of ubiquinones, to which an important function in the oxidative processes in the cell is attributed [115], it is important to know whether the living organism can itself synthesise them or whether they have to be supplied from the outside.

1. Biosynthesis of the Isoprenoid Side-Chain

Experimental studies *in vitro* and *in vivo* showed that [2-^{14}C]mevalonate [104,105,116,117] and [2-^{14}C]acetate [118-121] are incorporated only in the side-chain of the ubiquinone. The limited role of mevalonic acid in the biosynthesis of ubiquinones was confirmed by the oxidative degradation of labelled UQ_9. [122,123] A specimen of [^{14}C]UQ_9, obtained biosynthetically from [2-^{14}C]mevalonic acid (LVI), was acylated reductively to diacetyl[^{14}C]dihydro-UQ_9 (LVII), which was then subjected to selective degradation by ozonolysis. Radioactive levulinic aldehyde (LIX) and acetone were isolated from the reaction mixture as the corresponding dinitrophenylhydrazones (Scheme 9).

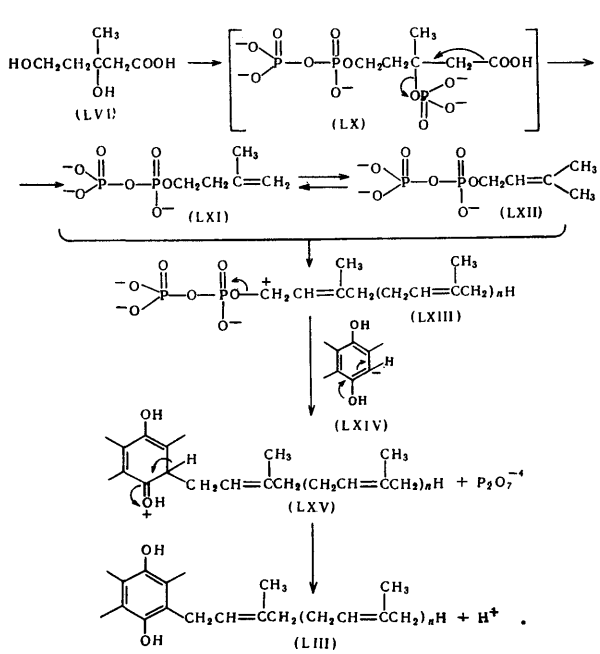
Scheme 9



3,6-Diacetoxy-4,5-dimethoxy-2-methylphenylacetic acid (LVIII), formed from the aromatic ring of the ubiquinone molecule, was isolated in the crystalline form and did not contain the radioactive label.

The above results are consistent with the postulated biosynthesis of terpenoids such as squalene [124] and carotenoids [125], according to which the polyisoprenoid side-chain of ubiquinone can be built up as a result of successive increments by one C_5-unit (Scheme 10). Mevalonic acid (LVI) [126] is converted in three stages into the derivative (LX) with three phosphate residues. As a result of decarboxylation and dephosphorylation, the latter yields isopentenyl pyrophosphate (LXI) [127,128] — "active isoprene" or the "structural C_5 unit" [129]. Δ^3-Isopentenyl pyrophosphate is capable

Scheme 10



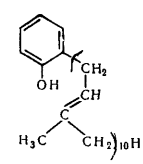
of isomerising to dimethylallyl pyrophosphate (LXII), [128-130] which is the terminal unit in isoprenoid polymers. Successive increments of the chain length of dimethylallyl pyrophosphate by C_5 units leads to isoprenoids with a carbon chain of increasing length, such as geranyl pyrophosphate (LXIII, n = 1), farnesyl pyrophosphate (LXIII, n = 2), etc. Geranylgeranyl pyrophosphate (LXIII, n = 3) [131] and the free alcohol solanesol [132], corresponding to the C_{45}-pyrophosphate (LXIII, n = 8), have been found in animal tissues. These compounds are probably synthesised in the same way as the lower representatives of this group.

Comparatively recently the polymer with twenty isoprenoid residues (C_{100}) has been found in human kidneys and has been given the name dolichol [133,134]. In this connection, one may assume that in the animal organism there are a number of enzymes which are responsible for the formation of polyisoprenoid homologues which are then used for the synthesis of squalene, the side-chains of ubiquinones, vitamins K_2, and other isoprenoids.

2. Biosynthetic Pathways for Ubiquinones

The discovery of allyl pyrophosphate as an alkylating agent in the biosynthesis of polyterpenoids became the basis for the development of a possible mechanism of the addition of the isoprenoid chain to the appropriate hydroquinones [128,129,135,136]. It is suggested that the alkylation of the unknown hydroquinone precursor (LXIV) with allyl pyrophosphate (LXII) involves the formation of an intermediate (LXV), which loses a proton and is converted into ubiquinol (LIII). On the basis of this hypothesis, it is quite likely that in the formation of ubiquinone itself the animal organism can use as donors of aromatic rings certain benzoquinone derivatives supplied with food or synthesised by the intestinal microflora. In this connection, a study has been made of a number of radioactive compounds containing aromatic rings to elucidate their possible participation in the formation of the ubiquinone chromophore. These were aromatic amino-acids [137,138] {[^{14}C]phenylalanine [139-142] and [^{14}C]tyrosin [141]}, vitamin E, [117,143] (labelled with tritium by Wilzbach's method [144]), and also 2,3-dimethoxy-5-methylbenzoquinone, 3-hydroxy-2-methoxy-5-methylbenzoquinone (fumigatin), and 2,3-dihydroxy-5-methylhydroquinone, labelled selectively in position 5. [145] Only [^{14}C]phenylalanine was found to be incorporated into the UQ_9 molecule in rats [146,147].

2-Decaprenylphenol, a biosynthetic precursor of ubiquinone containing simultaneously the aromatic ring and the isoprenoid side-chain, has been isolated recently from the lipid fraction of *Rhodospirillum rubrum* [148], which contradicts the above hypothesis that the incorporation of the isoprenoid side-chain is one of the last stages in the biosynthesis [149].



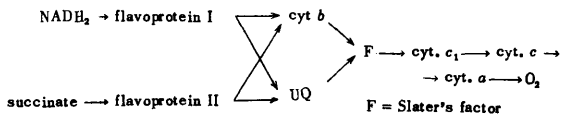
It is believed that this precursor can be obtained by the enzymic decarboxylation of *p*-hydroxybenzoic acid [150,151] after the latter had been first alkylated with decaprenyl pyrophosphate. *p*-Hydroxybenzoic acid is formed biosynthetically from shikimic acid [152].

It has been shown experimentally that, in the biosynthesis of ubiquinone, methionine [149,153] and formate [154] can serve as donors of methyl groups in the *O*-methylation reaction. Furthermore, formate is a source of the methyl group in the benzene ring [154].

VI. ROLE OF UBIQUINONES IN ELECTRON TRANSPORT IN OXIDATIVE PHOSPHORYLATION. HYPOTHESES CONCERNING THE POSSIBLE MECHANISM OF THE PROCESS

Ubiquinones are localised in the mitochondria in animal and higher plant cells at relatively high concentrations (NAD : cyt. $a \simeq$ UQ : cyt. $a \simeq 15$). This suggested that they participate in the electron transport system of the respiratory chain. Experimental data show that, on incubation under anaerobic conditions with substrates such as succinate and $NADH_2$, endogenous ubiquinone in mitochondrial preparations is reduced to ubiquinol while under aerobic conditions the latter is reoxidised to the quinone [155,156] (the redox potential is +0.122 V [157]). Furthermore, the extraction of ubiquinone bound in mitochondria with organic solvents results in loss of enzymic activity, which can be restored by the addition of ubiquinone [158]. In the attempts to determine the function of ubiquinone in electron transport these two findings were the subject of thorough investigations in non-phosphorylating systems [26,158-164]. The results of the determination of the concentration of ubiquinone in mitochondria [165], the kinetics of oxidation–reduction reactions [166-168], and the study of the effect of inhibitors [166] and of the effect of the extraction of ubiquinone on enzymic activity [158,169-174] led to certain hypotheses concerning the role of ubiquinone in the respiratory chain [175].

In the "reconstructed" respiratory chain described by Green [176] in the plenary lecture at the Fifth International Biochemical Congress ubiquinone precedes cytochrome *b*, the entire electron flux passing through ubiquinone. However, later studies in Green's laboratory [177] and Doeg's data [178] showed that ubiquinone and cytochrome *b* provide two alternative pathways for the electron flux [8]:



Comparison of the data on the kinetics of the oxidation–reduction reactions of ubiquinone in mitochondria with the overall rate of electron transport favours the second view [159,166,175,179].

One of the most important achievements of modern biochemistry is the demonstration of the central metabolic role of adenosine triphosphate (ATP) as the universal donor of chemical energy in the cell. The continuous renewal of ATP is an oxidation reaction, in which electron transport is coupled with phosphorylation — with synthesis of ATP. In the animal cell this process is localised in intracellular granules (mitochondria) where all the enzymes required for respiratory phosphorylation and part of the oxidative cell enzymes are to be found. A number of attempts have been made to determine the redox state of ubiquinone in mitochondria as a function of various phosphorylating conditions, in which the effect of inorganic phosphate and ATP was examined [4,168,179-181].

The studies of Todd and coworkers [182] showed that oxidation of quinol phosphates (LXVI) *in vitro* can result in the formation of the "active metaphosphate" (LXVII) which forms pyrophosphate from inorganic phosphate and adenosine diphosphate from adenosine monophosphate (Scheme 11). [183,184]

This scheme constitutes to some extent a model of oxidative phosphorylation. The formation of quinol phosphate from quinone in the presence of inorganic phosphate can be represented by Scheme 12.

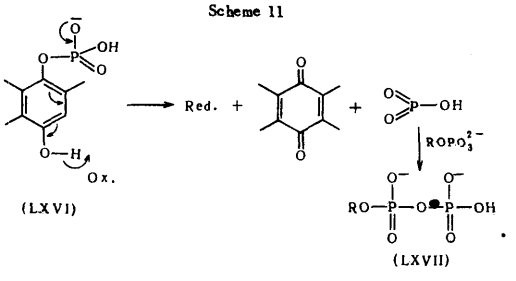
Wieland proposed a simple mechanism for such "reductive phosphorylation" [185] (Scheme 13).

However, many attempts to carry out this reaction with benzo- or naphtho-quinones under various laboratory conditions proved unsuccessful.

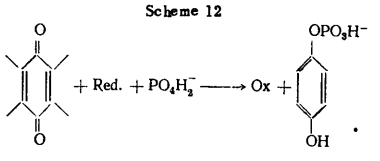
Clark and Todd [186] examined hypothetical ways of obtaining quinol phosphates from quinones in the series of ubiquinones and vitamins K (Scheme 14).

Quinones of type (LXVIII) have a tetrasubstituted quinone ring and a trisubstituted $\beta\gamma$-double bond in the side-chain. The addition of a proton at the β-position leads to a tertiary carbonium ion (LXIX), which is converted into compound (LXX) as a result of nucleophilic attack by the phosphate dianion (HPO_4^{2-}). The reduction of compound

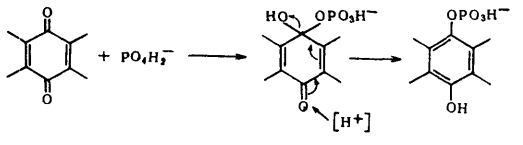
Scheme 11



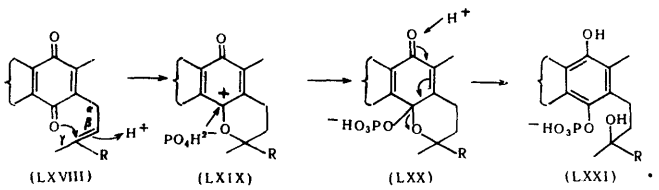
Scheme 12



Scheme 13



Scheme 14



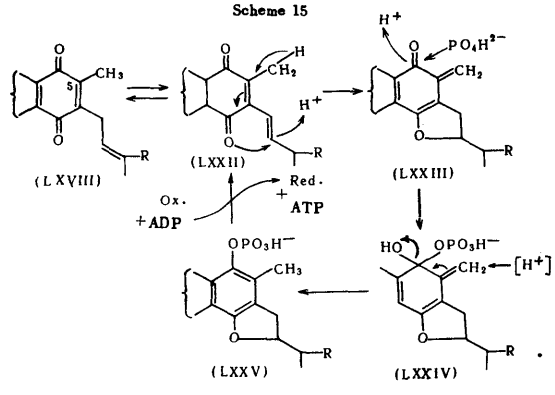
(LXX) and the subsequent opening of the chroman ring result in the formation of the corresponding quinol phosphates (LXXI). It is suggested that compound (LXXI) is then dehydrated and a $\beta\gamma$-double bond forms as in (LXVIII).

The mechanism of the synthesis of quinol phosphates proposed by Todd presupposes the formation of a phosphorus centre in position 4, whereas in biologically active systems this should be located in position 1. The latter was confirmed by a number of workers who demonstrated the phosphorylating role of 6-naphthochromanol phosphate [54,187,188]. Chmielewska [189] noted that ubiquinones and vitamins K with the methyl group in position 5 can occur in an active *ortho*-quinonoid form. The latter exhibits an enhanced capacity for nucleophilic addition reactions. Accordingly, Chmielewska suggested a consecutive series of reactions to account for the participation of quinones in oxidative phosphorylation (Scheme 15).

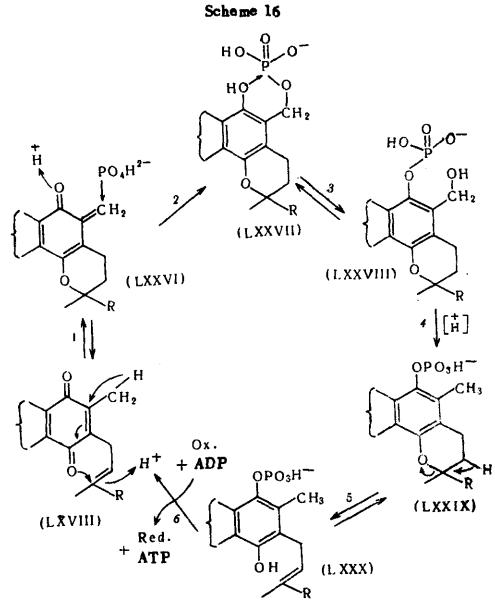
5-Methylquinone (LXVIII) is converted, via the isomerisation product (LXXII), into the *ortho*-quinonoid form (LXXIII), stabilised by the heterocyclic ring. The addition of the phosphate dianion to compound (LXXIII) yields compound (LXXIV), from which the quinol phosphate (LXXV) is then formed. The oxidation of compound (LXXV) is accompanied by the synthesis of ATP and leads to the recovery of the initial quinone, thereby completing the phosphorylation cycle. Chmielewska's hypothesis presupposes the 1,2-addition of the phosphate residue to the quinone oxygen [(LXXIII) → (LXXIV)]. The complexity of the 1,2-addition in such systems renders this mechanism unlikely.

On the basis of purely theoretical considerations, Vilkas and Lederer [190] modified Chmielewska's mechanism and proposed their own version of the mechanism of the addition of inorganic phosphate to methylene quinones (Scheme 16). This scheme presupposes the formation of methylene quinones or quinone methides (LXXVI, reaction 1) with a pyran ring and not a furan ring as suggested by Chmielewska [189], which is confirmed by the existence of chromans in the series of ubiquinones and vitamins K. According to this mechanism the phosphoric acid residue is not fixed at the quinone oxygen but in the 1,4-position of the conjugated quinone methide $O{=}C{-}C{=}CH_2$, with formation of benzyl phosphate (LXXVII, reaction 2). The intramolecular migration of the phosphate residue to the phenolic hydroxyl (LXXVIII, reaction 3) and the reduction of compound (LXXVIII) results in the formation of 6-chromanol phosphate (LXXIX, reaction 4). Ring opening results in the formation of the quinol phosphate (LXXX, reaction 5), which on being oxidised produces ATP and is converted into the initial quinone (LXVIII, reaction 6).

Scheme 15



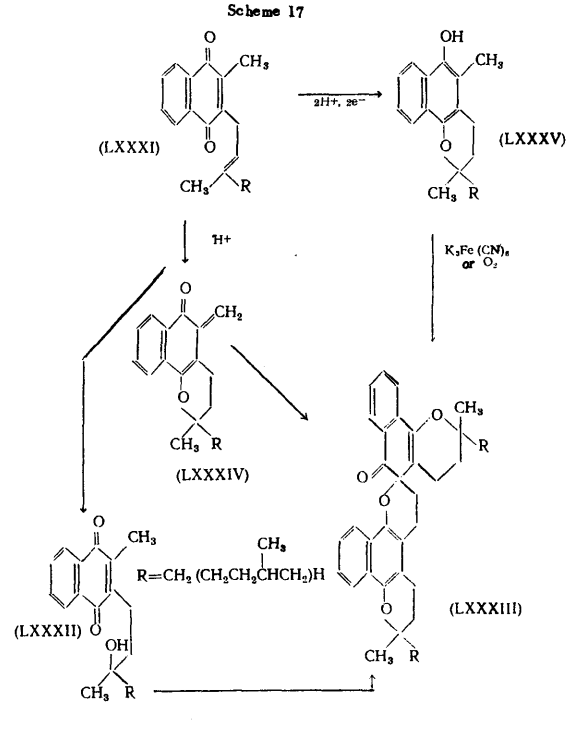
Scheme 16



The key feature of Lederer's theoretical considerations consists in the assumption of the 1,4-addition of the phosphate residue to the quinone methide postulated by Chmielewska. Both authors consider the presence of the methyl group in position 5 of the quinone ring and of the $\beta\gamma$-double bond to be important for the phosphorylation process [191].

In recent years the first two stages of the mechanism, i.e. the formation of quinone methides of chromans (reaction 1) and 1,4-addition to these compounds (reaction 2), have been confirmed experimentally. The studies of Folkers' group [192,193] showed (Scheme 17) that vitamin $K_{1(20)}$ (LXXXI) gives rise to a hydroxyquinone (LXXXII) under the influence of sulphuric acid.

Scheme 17



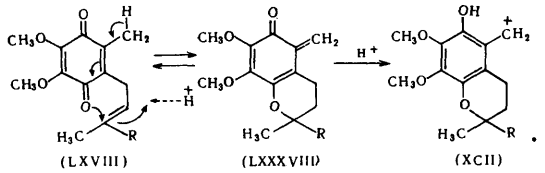
Further reactions in the presence of sulphuric acid gave an oily substance, to which the authors attributed the structure of the dimer (LXXXIII) and showed that the formation of such a compound can be accounted for only by the preliminary formation of the quinone methide (LXXXIV).

Experimental confirmation of the formation of quinone methides was also obtained in Lederer's studies [191,194], in which the dimer (LXXXIII)† was isolated in a crystalline form and its structure was established by mass-spectrometry. It has been shown by means of model reactions that under acid conditions vitamin $K_{1(20)}$ can isomerise to the chromanyl quinone methide (LXXXIV).

Folkers and coworkers [192,193,195,196] obtained 5-phosphomethyl-6-chromanyl acetates (XC, a, b; XCI), the mechanism of the synthesis of which presupposes the intermediate formation of quinone methides and 1,4-addition to the latter (Scheme 18).

When acetyl chloride is allowed to act on γ-hydroxyhexahydro-UQ_4 (LXXXVI), the product is probably the cation (LXXXVII), which is converted via the quinone methide (LXXXVIII) into 5-chloromethyl acetate (LXXXIX). The 1,4-addition is confirmed by the synthesis from compound (LXXXIX) of three new 5-phosphomethyl derivatives (XC, a, b; XCI) [192,196] with the aid of silver dibenzyl phosphate and subsequent selective debenzylation.

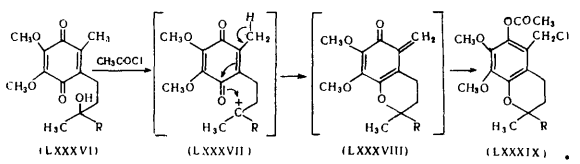
After analysis of the experimental data obtained, Folkers et al. [196] put forward their version of the synthesis of the "active phosphate". The addition of a proton to the double bond of the first isoprenoid unit of the side-chain of compound (LXVIII) results in an electron shift accompanied by cyclisation and the elimination of a proton from the 5-methyl group:



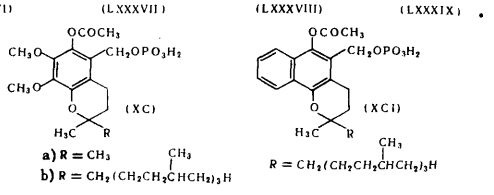
(LXVIII) (LXXXVIII) (XCII)

This is the principal factor in acid catalysed isomerisation. Evidently compounds (LXVIII) and (LXXXVIII) are equivalent in the molecular sense. The addition of a proton to the quinone methide (LXXXVIII) yields the carbonium ion (XCII). The authors believe that this protonated quinone methide (XCII) is a more likely form of quinone methide in chemical reactions in enzymic and non-enzymic processes. The carbonium ion (XCII), which has a deficiency of electrons in the 5-methyl position, is capable of interacting with the phosphate anion. In this connection, the authors suggest the following sequence of reactions, which account for the participation of quinones in oxidative phosphorylation (Scheme 19). Experimental confirmation of this mechanism would render unnecessary the subsequent stages of Lederer's mechanism given above.

Scheme 18



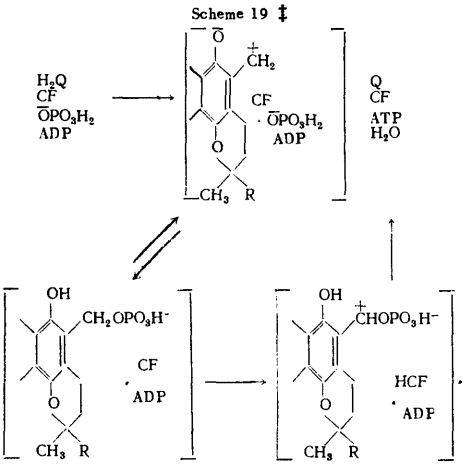
(LXXXVI) (LXXXVII) (LXXXVIII) (LXXXIX)



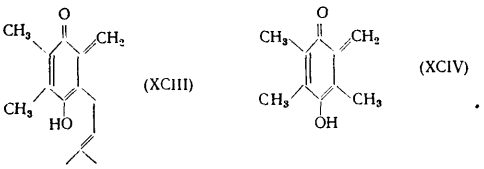
(XC) (XCI)

a) R = CH_3 b) R = $CH_2(CH_2CH_2CHCH_2)_3H$ R = $CH_2(CH_2CH_2CHCH_2)_3H$

Scheme 19 ‡



Scott put forward a number of new postulates concerning the intermediate compounds in oxidative phosphorylation in the quinone series [197]. On the basis of observations of NMR signals from deuteriated methanol, he suggests the formation of quinone methides without a chroman ring, of the type (XCIII) and (XCIV):



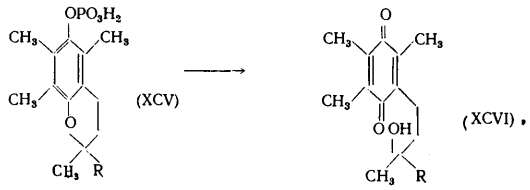
(XCIII) (XCIV)

In Scott's view, such quinone methides are more likely to be in equilibrium with the corresponding quinones than the quinone methides (LXXVI) derived from chromans proposed by Lederer. Furthermore, Scott demonstrated the complexity of the formation of the hydroquinone phosphate (LXXX) from chromanyl phosphate (LXXIX) (Scheme 16) and the reversibility of this reaction, although he does not exclude the probability of a process of this kind in the presence of enzymes. He suggests that direct oxidation of chromanyl phosphate be taken into consideration, and illustrates this using as an example the oxidation of (±)-α-tocopherol phosphate (XCVa) and the phosphate ester

† A dimer of this type can be obtained by oxidising naphthochromanol with potassium hexacyanoferrate(III) [191] or oxygen [233].

‡ CF is the mitochondrial substrate-coupling factor. Scheme 19 is based on the formulae given by R.E.Erickson, A.F.Wagner, and K.Folkers, [J.Amer.Chem.Soc., 85, 1535 (1963)] (Ed. of Translation).

of 2,2,5,7,8-pentamethyl-6-chromanol (XCVb) to the corresponding hydroxyquinones (XCVIa, b) in the presence of cerium sulphate.



(XCV) (XCVI),

where R = $C_{16}H_{33}$ (a) and R = CH_3 (b).

The mechanisms quoted above, i.e. hypotheses which explain the chemical reactions of quinones in oxidative phosphorylation, are to a large extent speculative, since none of them has been adequately confirmed experimentally. So far they are working hypotheses, whose validity will have to withstand the test of time.

VII. CERTAIN BIOLOGICAL AND THERAPEUTIC FUNCTIONS OF UBIQUINONES IN ANIMALS AND IN MAN

The role of ubiquinones in intracellular mitochondrial electron transport was considered above.

UQ_{10} has been identified as a component of the liver aldehyde oxidase [198]. This enzyme — which is a xanthine oxidase found only in the homogenate of the soluble fraction of rabbit liver and probably of cytoplasmic origin — has been isolated recently in a crystalline form [198]. The purified enzyme contains two molecules of flavine-adenine dinucleotide, eight iron atoms, two molybdenum atoms, and two UQ_{10} molecules per mole of protein.

The studies of Leonhäuser et al. [199] showed that UQ_{10} is present in microsomes.

The 6-chromanol derived from hexahydroubiquinone(20) has been most widely used in studies designed to elucidate the therapeutic action of compounds of the ubiquinone group in animals and in man. This chromanol facilitates the breeding of rats [114], enhances the mobility of sperm cells in chickens [200], and has a favourable effect on monkey dystrophy [201]. It has yielded satisfactory clinical results in the therapy of certain forms of anaemia in infants [202].

Therapeutic and prophylactic tests recently established that hexahydroubiquinone(20) in the quinone form is active in rabbit dystrophy [203,204]. Furthermore, the study of α-tocopherol deficiency in rhesus monkeys yielded interesting comparative data for UQ_{10} and vitamin E. It was found that UQ_{10} as such markedly increases the number of reticulocytes and the amount of haemoglobin [205]. These are the first data concerning the activity *in vivo* of members of the ubiquinone group in the quinone form.

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During the preparation of the manuscript for the press interesting papers were published on the chemistry of ubiquinones, menaquinones, and tocopherylquinones [206-211,232,233], and yet another natural member of the ubiquinone group, containing 25 carbon atoms in the side-chain (UQ_5) was isolated [212]. Papers were published on the synthesis of the hydroxy-analogues of ubiquinones [213,214] and a definite view concerning the structure of rhodoquinone was established [215].

The discovery of 2-decaprenylphenol [148], the biosynthetic precursor of ubiquinone, and its next analogue 2-decaprenyl-6-methoxyphenol [216], led to a revision of the biosynthesis of ubiquinones. Further studies of this biosynthetic pathway for the cyclic component showed that the ring in ubiquinone, menaquinone, plastoquinone, and α-tocopherylquinone is synthesised from shikimic acid [217-219].

The participation of ubiquinone in electron transport was examined by a number of workers [220-224], and it has been suggested that ubiquinone can have a function other than that of electron carrier [225].

The role of ubiquinones in oxidative phosphorylation was discussed [226,227] and hypotheses have been put forward concerning the impossibility of the participation of ubiquinone methines as intermediates in oxidative phosphorylation [228,229]. Studies on the biological importance of ubiquinones were published [230,231].

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SPECTRA OF ORGANIC MOLECULES IN THE FAR AND VACUUM ULTRAVIOLET

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