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PHENOL–DIENONE REARRANGEMENT IN THE REACTIONS OF PHENOLS

V. V. Ershov, A. A. Volod'kin,
and G. N. Bogdanov

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1. INTRODUCTION

Study of the chemistry of phenols is of great practical value, apart from its relevance to theoretical aspects of organic chemistry. The use of phenols and their derivatives in the production of various plastics, dyes, effective bactericides, insecticides, herbicides, etc. is well known. Phenols are successfully employed as oxidation inhibitors in motor fuels, oils, and edible fats. Finally, as Emanuel' *et al.* have shown[1-3], phenolic inhibitors can be utilised in experimental oncology and in other types of biological research. However, the literature contains too few general accounts of the chemical properties of phenols. It is only recently that a number of review papers have been published, dealing with individual properties of phenols[4-9].

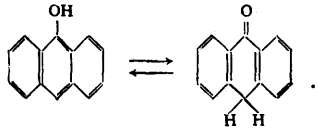
The present paper discusses reactions of phenols involving disruption of the aromatic bond system of the phenol and leading to the formation of cyclohexadienones. The formation of such substances is very often postulated also as an intermediate stage in many reactions of phenols. Cyclohexadienone compounds are in some cases stable, and can be isolated in the free form, whereas in other cases their existence can be assessed only by spectroscopic methods. The conversion of a phenolic structure into a cyclohexadienone structure has been termed a phenol–dienone rearrangement. It must be remembered that such a change does not correspond to the usual concept of a rearrangement in organic chemistry, since it occurs during the reaction of the phenol with some reagent and results in the formation of a compound containing a new substituent in the carbon ring. This rearrangement is essentially a rearrangement of the aromatic bond system of the phenol. The reverse process, the conversion of *gem*-substituted cyclohexadienones into phenols, which is a typical rearrangement and is usually accompanied by a migration of substituents within the ring, is called a dienone–phenol rearrangement. In view of its fundamental difference and intrinsic significance, the latter rearrangement will not be considered here.

Phenols usually undergo the phenol-dienone rearrangement when acted on by reagents of electrophilic or radical type. In this respect the halogenation of phenols has been most fully studied, and to a less extent their nitration, some alkylation reactions, and several radical reactions of phenols. Below we shall examine only those aspects of these well-known reactions that have a direct bearing on the phenol–dienone rearrangement of monohydric monocyclic phenols and that lead to the formation of compounds having a "quinolide" structure. We apply the term "quinolide", in contrast to "quinonoid", to the structure of cyclohexadienones in which a carbon atom *ortho* or *para* to the carbonyl is linked by single bonds (not by a double bond) to two atoms or groups of atoms.

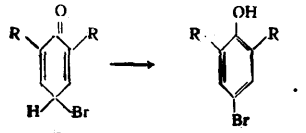
2. EFFECT OF STRUCTURE OF PHENOL ON EASE OF FORMATION OF DIENONE COMPOUNDS

The formation of cyclohexadienone structures might be most simply explained by a tautomeric change in the phenols. However, tautomerism has not been detected in monohydric monocyclic phenols containing no other functional group[10]. In several simple phenols cyclohexadienone structures are formed only at the instant of reaction with electrophilic and radical reagents. If, on the other hand, the existence of tautomerism is postulated in the phenol–dienone system,

and it is remembered that keto–enol tautomerism usually involves migration of a proton, the transition to a dienone system of bonds could be regarded, in the case of phenols, as the simplest example of electrophilic substitution. In this case the question of tautomerism would be reduced to that of the stability of the resulting dienones. If it is assumed that an intermediate compound having a quinolide structure is nevertheless formed as a result of interaction of the phenol with a proton, this compound would be so unstable that its existence could not be detected†. In the naphthol series, and especially with anthrol, however, such compounds are quite stable, and can even be isolated in the free state. In the case of anthrol, a tautomeric form having the carbonyl structure exists, and is called anthrone:



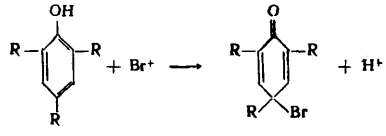
Among monohydric monocyclic phenols, stable quinolide compounds are obtained only when at least one *gem*-substituent in such a compound is not a hydrogen atom. Thus in the bromination of some 2,6-dialkylphenols[12,13], for example, quite stable quinobromide compounds (I) have been isolated, which gradually undergo spontaneous rearrangement to the *p*-bromophenols (II):



(I) (II)

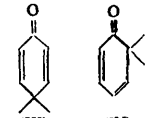
The migration of the hydrogen atom involved in this change is not reversible.

It is generally accepted at the present time[14,15] that, in the action of electrophilic reagents on a phenol, an intermediate compound with a *p*- or an *o*-quinolide structure is formed initially as a transition state. This intermediate subsequently rearranges to the energetically more favourable aromatic system of a phenol. The tenability of this concept is supported by the fact that intermediate compounds of quinolide structure are formed in some cases by the action of electrophilic agents on phenols, depending on the structure of the original phenol and on the reaction conditions. These compounds may be fairly stable, and in several cases have either been detected in dilute solution by spectroscopic methods[13,16] or have been isolated in the free state[12,13]. If the reaction is stopped at the initial stage, stabilisation of the aromatic system does not occur, and a cyclohexadienone is formed solely as a result of the phenol–dienone rearrangement of the initial phenol:



† Some writers postulate that, in the case of the simplest phenols, *p*- and *o*-quinolide structures exist as mesomeric forms[11].

Cyclohexadienones can exist in two isomeric forms (III) and (IV), corresponding to a *p*-quinolide (III) and an *o*-quinolide (IV) structure:



(III) (IV)

The existence of one form or the other will, of course, depend on the nature of the compound. If cyclohexadienones are formed by the action of electrophilic reagents on alkylphenols, for example, the cyclohexa-2,5-dienone system is obtained preferentially, for electrophilic substitutions of phenols have a lower activation energy in the *para*- than in the *ortho*-position, and the *para*-isomers, to which also corresponds the transition state having a *p*-quinolide structure, usually predominate among the reaction products. The fact that electrophilic reagents attack mainly the *para*-position in the phenol molecule has been discussed quite fully in the literature (see, for example, Ref. 17), and is beyond the scope of the present paper. Unfortunately, however, hardly any work has appeared on a quantitative assessment of the factors governing the course of reactions accompanied solely by a phenol–dienone rearrangement.

An analysis of published data which are available at the present time leads to the following general conclusions concerning the phenol–dienone rearrangement.

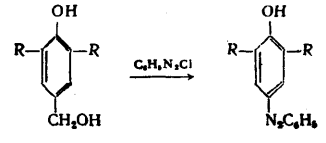
1. Cyclohexadienones are formed most readily by the action of electrophilic reagents on 2,4,6-trisubstituted phenols. They are formed considerably more rarely in the absence of substituents in the *ortho*- or *para*-positions.

2. Reactions accompanied by phenol–dienone rearrangement take place by the action mainly of strong electrophilic reagents on the appropriate phenols (during halogenation, nitration, etc.).

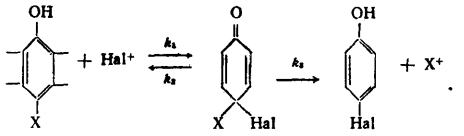
3. The ease of the phenol–dienone rearrangement increases with increasing steric hindrance of the phenolic hydroxyl, *i.e.* with increasing bulk of the substituents in the 2,6-positions of the phenol.

The rules governing phenol–dienone rearrangement are somewhat different for reactions involving radical substitution of phenols (which will be discussed below).

It does not follow from the above generalisations that a phenol in which the *para*- and even both *ortho*-positions are occupied by some kind of substituents must necessarily form a stable dienone compound when acted on by a sufficiently strong electrophilic reagent. Very often the resulting dienone, for which a transition to an aromatic structure with elimination of a proton is impossible, undergoes a similar conversion involving either migration of a substituent in the ring (dienone–phenol rearrangement) or elimination of one of the previous substituents. In the latter case it is customary to speak of the substituting action of the electrophilic reagent, and the most diverse substituents and groups can thus be eliminated, depending on the conditions. Cases are known of halogenation, nitration, and azo-coupling involving replacement of a CH_2OH group[18], for example:

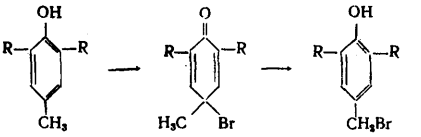


3,5-Dibromobenzoquinoneimine chloride (Gibbs reagent) reacts with phenols containing the substituents OR, CH_2NRR', Cl, COOH in the *para*-position, with the formation of deeply coloured indophenols, which are also obtained from the corresponding phenols containing no substituents in the *para*-position[19]. If the phenol contains a *p*-OR group, the latter is eliminated with formation of the corresponding alcohol, while a CH_2NRR' group results in the formation of formaldehyde and an amine. Among the above reactions of phenols involving substitution, halogenation has been studied in the greatest detail. On the whole this process depends on the stability of the quinolide structure obtained, and comprises two stages, each of which takes place independently. According to Cannell's data[16], the rate of substitutive bromination of several phenols depends ultimately on the rate of decomposition of the quinolide structure (the latter reaction is of first order). Halogenation accompanied by substitution can in general be represented as follows:



Accumulation of the intermediate quinolide compound may occur in this process depending on the relative reaction velocities. Thus, for example, tribromophenol is obtained by the bromination of sodium 3,5-dibromo-4-hydroxybenzenesulphonate in aqueous solution at 25°. Chlorination of this compound takes place similarly. There is no reaction with iodine. Ultra-violet and visible spectra show that the reaction involves the intermediate formation of a 2,6-dibromocyclohexadienone structure, which is sufficiently stable for its spectrum to be obtained in dilute solutions[16]. However, the bromination of sodium 4-hydroxy-3,5-dinitrobenzenesulphonate is considerably more rapid. In this case the presence of a cyclohexadienone structure could not be detected even at 0°, and with excess of bromine one of the nitro-groups was also replaced, with the formation of 2,4-dibromo-6-nitrophenol[20]. From this example, it is clear that the stability of the quinolide structure, which ultimately determines the main mode of the reaction, is substantially influenced by the nuclear substituents. Substitution of nitro-groups for halogen atoms in the 2,6-positions of phenol appreciably increases the rate of the corresponding reaction. On the other hand, an increase in the activation energy of decomposition of the quinolide structure, which determines its stability, would also depend on the nature of the bond between the displaced group and the aromatic ring: *i.e.* in order to make the quinolide structure more stable, the substituent X should be chosen such that the activation energy required to rupture its bond with the carbon atom would be increased. This hypothesis is supported by the fact that the stability of the quinolide structure increases in the sequence $X = H \ll COO^- < SO_3^- < Br < CH_3$.[20] For example, substitutive bromination of 3,5-dibromo-4-hydroxybenzoic acid ($X = COO^-$) in aqueous solution at 0° is complete in 7 sec, but the half-reaction time at 25° of a substance having a cyclohexadienone structure when $X = SO_3^-$ is 126 min. The rate of bromination of phenol, in which X = H, is 200 times as rapid as the rate of substitutive bromination of hydroxybenzoic acid ($X = COO^-$), the initial stage of the reaction showing little or no tendency to reversibility in the first case, whereas in the second case ($X = COO^-$) the reaction is reversible[21].

An alkyl group is firmly bound to the aromatic ring, and is seldom eliminated during halogenation or nitration. The bromination of *p*-cresol, for example, yields the corresponding quinobromide[22]. Compounds of this type are quite stable. They can rearrange[23] to form the aromatic phenol system in a new way, with conversion into the corresponding benzyl bromides (see below):



In some cases the reverse reaction — debromination of the quinobromide — may take place, with a return to the aromatic structure of the original phenol[24,25].

The strength of the bond between the alkyl group and the aromatic ring is appreciably diminished in t-alkylphenols. Phenols containing a *p*-t-butyl group, for example, can be halogenated with substitution, the reaction being accompanied by the evolution of isobutene[26]. This reaction occurs especially readily during bromination; chlorination in these cases, however, often stops at the formation of a substance having a dienone structure.

If the phenol contains a *para*-substituent in which the α-carbon atom is linked to oxygen or nitrogen[19], it is also displaced by the action of some electrophilic agents. For example, the action of chlorine water on phenols containing the groups CH_2OH, CHO, and COOH in the *para*-position yields in all cases 2,4,6-trichlorophenol[27]. Bromination[28] and nitration[29] of these phenols take place in a similar manner.

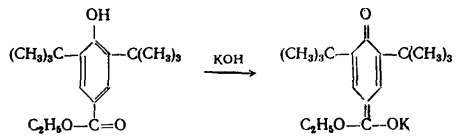
With substitutive nitration of the *p*-substituted phenols as an example, it has been shown[30] that the strength of the bond between the substituent and the ring increases in the sequence $CH_2OH < COOH < CHO \ll CH_3$.

Examples are known in which substitutive bromination, especially with excess of the brominating agent, does not stop at the substitution stage, but continues further to form the correspoinding *gem*-dibromocyclohexadienone[22].

Electrophilic reagents can result in displacement also of *ortho*-substituents in the phenol[30,31]. This usually requires more severe conditions[32,33].

An increase in the bulk of the *ortho*-substituents exerts a substantial influence on the ease of formation of cyclohexadienones from phenols. It is noteworthy that most reactions of phenols involving the phenol–dienone rearrangement have been studied with sterically hindered phenols as examples, which on the whole possess properties rather different from those of ordinary phenols. This is because steric hindrance of the phenolic hydroxyl disturbs the coplanarity between the aromatic ring and the hydroxyl, and also prevents hydrogen-bond formation between the phenol molecules. Spectroscopic methods have shown the complete absence of hydrogen bonds in 2,6-di-t-butylphenol[34]. The molecules of *o*-t-butylphenol have been found to be dimeric, whereas with *o*-s-butylphenol molecules polymeric association is possible[35]. With sterically hindered phenols, the tendency to form dienones is so great that it even results in the ready dissolution in alkalis of 3,5-di-t-butyl-4-hydroxybenzaldehyde, 3,5-di-t-butyl-4-hydroxybenzonitrile, and ethyl 3,5-di-t-butyl-4-hydroxybenzoate[36,37], which involves rearrangement of the phenolic

to a quinolide structure, the appropriate functional group taking part in salt formation.

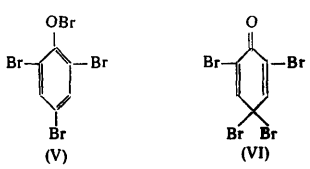


Owing to steric hindrance of the phenolic hydroxyl, 2,6-di-t-butylphenols do not form phenoxides under normal conditions, and do not dissolve in alkalis[38].

3. HALOGENATION OF PHENOL. TRIBROMOPHENOL BROMIDE

Nowadays, synthetic methods enable us to obtain the most diverse halogenated phenols. However, direct halogenation of a phenol in many cases yields immediately trisubstituted phenols, in which a further hydrogen atom can be replaced by halogen under the influence of an excess of the halogenating agent. Such reactions have been most fully studied in the case of the bromination of phenol, which results in a compound containing four bromine atoms. In the literature this compound has been called "tribromophenol bromide". It was first obtained by Benedikt[39] by the action of bromine water on phenol.

The question of the structure of tribromophenol bromide and analogous compounds has been the subject of research and controversy since it was prepared, and has not yet been finally settled. Different writers assign to tribromophenol bromide either the structure of a phenyl ester of hypobromous acid (V) or a *p*-quinolide structure corresponding to 2,4,4,6-tetrabromocyclohexadienone (VI):



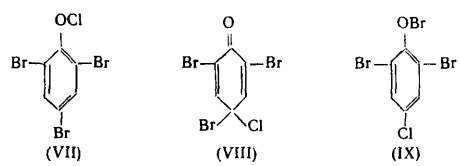
Benedikt regarded tribromophenol bromide, in view of its properties, as a hypobromous ester. It is unstable, readily losing a bromine atom on being heated or on treatment with reducing agents, and reacts with aniline to form tribromophenol and tribromoaniline[40]. Heating tribromophenol bromide with sulphuric acid yields tetrabromophenol‡, which is similar to the compound obtained by Körner[41], together with pentabromophenol, by heating tribromophenol with bromine in a sealed tube at 160°. Pentabromophenol can also be obtained by the action of bromine on tribromophenol in the presence of metallic iron[42]. Further halogenation of polyhalogenated phenols results in the formation of substances resembling tribromophenol bromide in properties and structure. The action of bromine water on tetrabromophenol or pentabromophenol yielded tetrabromophenol bromide and pentabromophenol bromide respectively, which have the general properties of tribromophenol bromide[43]. Chlorination of 2,4,6-trichlorophenol in acetic acid yielded trichlorophenol chloride and pentachlorophenol chloride, both of which contained active chlorine[44,45].

‡ If a quinolide structure is accepted for tribromophenol bromide, these reactions are readily explained as a dienone–phenol rearrangement, which occurs best in acid medium.

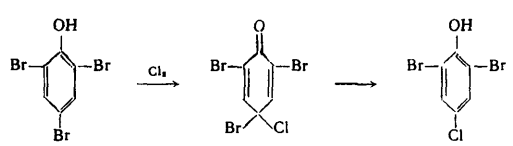
In 1887 Hantzsch[46], and later Zincke[44,47], suggested that tribromophenol bromide has a quinolide structure (VI). In 1900 Thiele[48] showed that, on being heated with lead diacetate in acetic acid, it yields 2,6-dibromobenzoquinone, which in his view provided convincing proof of the quinolide structure of tribromophenol bromide. In 1902 Kastle[49] made an attempt, based on a phenolic structure for the compound, to obtain tribromophenyl benzenesulphonate by the action of sodium benzenesulphonate or tribromophenol bromide. He obtained no such ester, and on this basis attributed a quinolide structure to tribromophenol bromide. Another attempt at a synthetic proof of the structure of the compound, undertaken by Kastle and Loevenhart[50], consisted in treatment with diethylzinc. If the structure were phenolic, an ethyl ether of the phenol would be expected to result, but in fact, a vigorous reaction yielded zinc tribromophenoxide and ethyl bromide.

However, Lauer[51] in 1926, and then Suknevich[52], from a comparison of the products of the chlorination of tribromophenol and of the bromination of 2,6-dibromo-4-chlorophenol, cast doubt on the quinolide structure for tribromophenol bromide, and again suggested a phenolic structure for this and analogous compounds, regarding them as hypobromous (or hypochlorous) esters. Shilov[53] drew attention to the unconvincing character of the rejection of the quinolide structure by Lauer and by Suknevich.

In 1948 Elston *et al.*[54] made an attempt to explain the structure of some polyhalogenophenols on the basis of their chemical properties and their spectra. These workers considered that the spectroscopic data enabled the possibility of a quinolide structure for these compounds only to be supposed, not demonstrated. It was at first assumed that the chlorination of 2,4,6-tribromophenol can yield a compound having structure (VII), tautomeric with (VIII), which is in turn tautomeric with (IX):



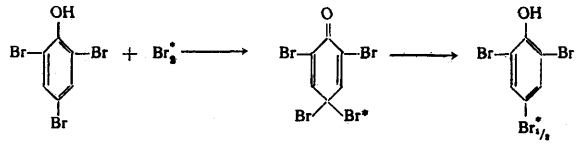
However, they concluded, by analogy with the chlorination of 2,6-dibromo-3,5-dimethylphenol, that a compound probably having the *p*-quinolide structure (VIII) is, nevertheless, formed in the chlorination of tribromophenol. This compound loses a bromine atom on being boiled in alcohol. Hence the overall process can be regarded as chlorination with the replacement of bromine by chlorine:



The reverse reaction, substitution of bromine for chlorine, does not take place. Chlorination with replacement of iodine by chlorine also occurs readily in the case of 2,4,6-triiodophenol[55].

In 1951 a fresh attempt was made to elucidate the structure of tribromophenol bromide and the conditions under which it is formed, using now a tracer method[56]. The compound was obtained by the action of labelled bromine

on tribromophenol. This method of preparation took account of the role of proton-acceptors. Thus in carbon tetrachloride or glacial acetic acid solution, for example, bromine does not react at all with tribromophenol, and does not exchange bromine atoms with it. However, addition of small amounts of pyridine in the first case, or of water in the second, causes the immediate appearance of a precipitate of tribromophenol bromide. Since debromination of labelled tribromophenol bromide roughly halved the original activity, the compound was assigned a quinolide structure (the bromine atoms in position 4 would be equivalent).



If the tribromophenol bromide has a hypobromite structure (V), the product of its decomposition should be inactive. In aqueous suspension tribromophenol bromide exchanges bromine atoms neither with bromine water nor with sodium bromide. A fairly slow exchange occurs when hydrogen bromide acts on the compound, as a result of the reaction

$$C_6H_2Br_3Br^*O+HBr \rightleftarrows C_6H_2Br_3OH+BrBr^*.$$

Tribromophenol bromide and tribromophenol prepared separately exchange bromine with difficulty by themselves in aqueous suspensions, but exchange take place if pyridine, for example, is added to the mixture. The hypothesis that exchange involves the formation of an *o*-quinobromide is not, in the opinion of these workers, inconsistent with the probable *p*-quinolide structure of ordinary tribromophenol bromide, since the equilibrium between the isomers will result in the accumulation in the final product of the most stable *p*-quinolide form.

After publication of the work using labelled bromine, the results of which provided convincing evidence of the quinolide structure of tribromophenol bromide, the existence of this compound as a phenyl hypobromite seemed improbable. In 1958, however, Schulek[57], on the basis of an investigation of a series of its reactions, again ascribed an aromatic structure to it, but now on the assumption that the bromine linked to oxygen bears a partial positive charge.

In 1959 Shilov concluded on the basis of a tracer method that tribromophenol bromide and analogous compounds nevertheless have a quinolide structure[58]. However, Schulek[59] showed, by isotopic exchange of tribromophenol and tribromophenol bromide with $^{82}Br^-$ ions and molecular $^{82}Br_2$, that all the bromine atoms in the latter compound are equivalent, which may be due either to an equilibrium among different structures or to the exchange of all four bromine atoms in the tribromophenol bromide with $^{82}Br^-$ or $^{82}Br_2$. Thus the application of labelled bromine provides no final answer to the structure of tribromophenol bromide; however, most of the published data support a quinolide structure for it.

This is confirmed also by a spectroscopic examination of tribromophenol bromide[60], whose absorption maximum in the infra-red region (5.99 μ) is due to the presence of a conjugated carbonyl group; it has a band in the ultra-violet at 280 mμ, which indicates a *p*-quinolide system of bonds.

The chlorination of phenols follows, in relation to the phenol–dienone rearrangement, somewhat different rules from those for their bromination. This must be borne in mind in attacking the problem of the structure of tribromophenol bromide by the chlorination method. Polyhalogenated, and especially polychlorinated, phenols probably tend initially to form cyclohexa-2,4-dienones, corresponding to an *o*-quinolide structure, on being treated with a chlorinating agent. This has been studied quite thoroughly with t-butyl hypochlorite as example, this chlorinating agent yielding with phenol itself mono- and di-chlorophenols[61]. When, however, this reagent acts on certain 2,6-dihalogenated phenols, substances are obtained which were at first regarded as aryl hypochlorites[62]. Shortly after, however, an *o*-quinolide structure was adopted on the basis of infra-red, ultra-violet, and Raman spectroscopic data and values of the magnetic susceptibility for these substances[63–65]. Such aryl pseudo-hypochlorites prepared by the chlorination of brominated phenols are less stable than those obtained from chlorophenols, and decompose with the evolution of bromine. The process of decomposition obviously involves preliminary isomerisation to a compound having a *p*-quinolide structure, since spectroscopic examination has shown that this is accompanied by disappearance of the band at 350–380 mμ, characteristic of cyclohexa-2,4-dienones, and the appearance of a band at 250–280 mμ, characteristic of cyclohexa-2,5-dienones[64].

Polychlorocyclohexa-2,4-dienones are usually more reactive than, and readily pass into, polychlorocyclohexa--2,5-dienones. For example pentachlorophenyl pseudo--hypochlorite, which has an *o*-quinolide structure, is converted irreversibly into the isomeric compound with the *p*-quinolide structure (slowly on prolonged storage, more rapidly on being heated with 1.5% of $FeCl_3$ or $AlCl_3$ or on intense ultra-violet irradiation[65]). It has also been shown[66] that an *o*-quinolide polychlorophenol chloride reacts considerably more readily with alcohol than does the corresponding compound having a *p*-quinolide structure.

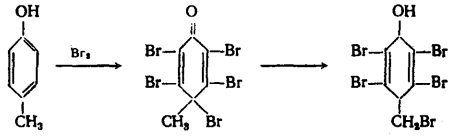
2,3,4,5,6,6-Hexachlorocyclohexa-2,4-dienone (*o*-quinolide structure) contains two reactive chlorine atoms, oxidises an alcohol to an aldehyde, chlorinates phenols and hydrocarbons, condenses with sodium benzenesulphonate with formation of pentachlorophenyl benzenesulphonate, gives an adduct with maleic anhydride, is stable towards hydrogen chloride and sulphur dioxide at 95°, and does not react with metallic sodium at 100°.[63,65]

In 1950 Shorygin also isolated two isomers of pentachlorophenol chloride (m.p. 51° and 106°). The first isomer was readily converted into the second. On the basis of the Raman spectra, however, the isomer melting at 51° was assigned a hypochlorite structure, while that melting at 106° was regarded as 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dienone[67].

4. HALOGENATION OF ALKYLPHENOLS

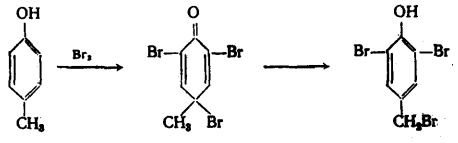
Compared with unsubstituted phenol, alkylphenols show a greater tendency to form cyclohexadienone structures when undergoing halogenation. This tendency becomes more marked with increasing number of alkyl groups in the phenol. The general rules of halogenation accompanied by phenol–dienone rearrangement are maintained with the alkylphenols. In contrast to the halogenation of phenol itself, however, the formation of quinolide structures in these cases has not been, and is not at present, open to serious doubt by investigators working in this field. The halogenation of alkylphenols is more complicated than that

of phenol itself, and is accompanied by side-reactions, since the halogenocyclohexadienones thus formed, which have been termed "quinohalides" are extremely reactive compounds, which readily undergo various changes. Only *m*-cresol is halogenated in a similar manner to phenol[68], treatment with bromine water yielding tribromo-*m*-cresol bromide, which possesses the same properties as tribromophenol bromide. However, exhaustive halogenation of the unsubstituted positions in the phenol occurs even with *o*- and *p*-cresols, followed by halogenation accompanied by phenol–dienone rearrangement. The resulting halogenated cyclohexadienones can readily rearrange to the corresponding benzyl halides. Thus the bromination of *p*-cresol[69] yields the tetrabromoquinobromide (X), which can rearrange to the *p*-hydroxybenzyl bromide (XI).



(X) (XI)

Under milder conditions the exhaustive bromination of *p*-cresol may not occur. The action of bromine water on *p*-cresol, for example[22], produces dibromo-*p*-cresol bromide (XII) together with 3,5-dibromo-4-hydroxylbenzyl bromide (XIII) and 3,5-dibromo-4-hydroxybenzyl alcohol; the last compound is probably formed by hydrolysis of both bromides:

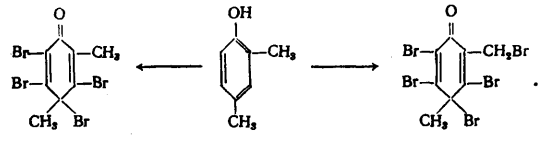


(XII) (XIII)

Dibromo-*p*-cresol bromide (XII) also rearranges to the *p*-hydroxybenzyl bromide (XIII) on being heated to its melting point or on standing in sunlight[70]. On the other hand, bromination of cresols and other alkylphenols with free bromine under more severe conditions (100° and above) at once yields substances in which the bromine is in the benzyl condition[71–77].

The chlorination of *p*-cresol results, just as with phenol, in the formation of polychlorinated compounds having an *o*-quinolide structure. The isomer having a *p*-quinolide system of bonds is also obtained at the same time[69].

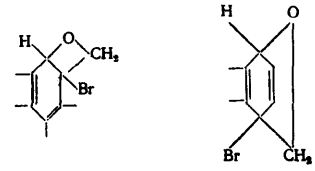
The above generalisations concerning the halogenation of cresols with the formation of cyclohexadienones apply also to the halogenation of polyalkylphenols. For example, the bromination of *m*-xylenol occurs as follows[69,78,79], depending on the conditions:



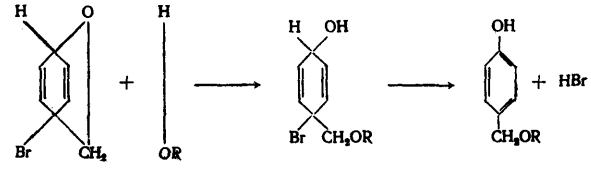
The chlorination of 2,4,6-tribromo-3,5-dimethylphenol, just like that of tribromophenol, involves the replacement of bromine by chlorine, probably *via* a cyclohexadienone structure[54].

The quinohalide compounds obtained from alkylphenols possess all the usual properties characteristic of such compounds: they do not dissolve in alkalis, and they react with alcohols, amines, aqueous acetone, etc. The chemical properties and conditions of formation of these compounds were explored quite thoroughly at the end of the past century[69,79–89]. During 1895–1897 Zincke[69,81] concluded, from an analysis of earlier work and the properties of the compounds obtained by the bromination and chlorination of cresols, xylenols, and 2,4,5-trimethylphenol, that "pseudo-phenols" existed as a separate class of organic compounds, and he suggested that they had a quinolide structure.

Later Auwers came to regard the "pseudo-phenols" as derivatives of β- or γ-oxides[85–89]:

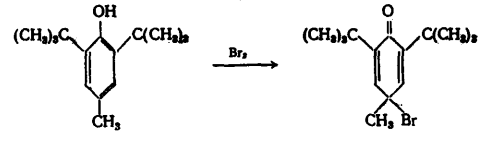


In his view, the first stage in the interaction of a quinobromide with, for example, an alcohol consisted in rupture of the oxide ring with subsequent elimination of a molecule of hydrogen bromide:



However, the oxide form of "pseudo-phenols" was subsequently abandoned, especially in view of the isolation of substances which, according to their properties, would have been methylenequinones[75].

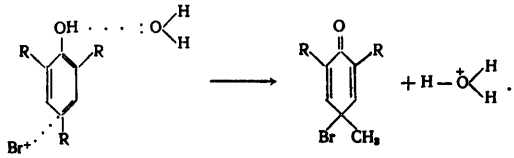
On the basis of the above work, carried out mainly by Auwers and by Zincke, the view arose in the literature that quinobromide compounds can be formed from alkylphenols only after preliminary nuclear bromination of the initial phenol. For a long time quinobromide compounds could not be obtained from 2,4,6-trialkylphenols by the action of one equivalent of bromine. It is only during recent years that it has been possible to obtain such compounds, and only from sterically hindered phenols[33,90–92], 2,4,6-tri-t-butylphenol, and Ionol (4-methyl-2,6-di-t-butylphenol):



The formation in these cases of quinobromide compounds in which only one bromine atom has entered the nucleus was explained by the presence of bulky substituents in the *ortho*-positions of the phenols on the one hand facilitating the formation of a cyclohexadienone structure, and on the other causing steric hindrance to the entry of additional bromine atoms in the *meta*-positions of the phenol.

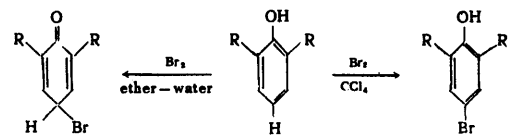
In 1962 Ershov and Volod'kin found[93–95] that, if bromination of the most diverse 2,4,6-trialkylphenols is carried out in the presence of substances possessing proton-acceptor properties (ether, dioxane, pyridine, water, etc.), *p*-quinobromides containing one bromine atom in the molecule are always formed. The effect of proton-acceptors on the formation of quinobromides is linked primarily with their

ability to form a hydrogen bond with the phenolic hydroxyl even in the case of sterically hindered phenols. This has been convincingly demonstrated by means of spectroscopic data in the case of 4-methyl-2,6-di-t-butylphenol[96]. The presence of proton-acceptors facilitates the splitting off of a hydrogen ion from the phenolic hydroxyl by its addition to the lone electron pair of the acceptor, and, furthermore, this is accompanied by an additional increase in electron density in the aromatic nucleus as a whole and in the *para*-position in particular. Electrophilic attack by the bromine is thus directed mainly at the *para*-position, with formation of a quinolide compound:



In the absence of a proton-acceptor, conditions for preferential attack at the *para*-position are not created, and therefore ordinary bromination of the phenol in the unsubstituted *meta*-position takes place. If bulky alkyl groups are present in the *ortho*-positions of the 2,4,6-trialkylphenol, preventing the entry of bromine in the *meta*-position, substitutive bromination in the *ortho*-position, with elimination of the corresponding olefine, can occur in the absence of proton-acceptors.

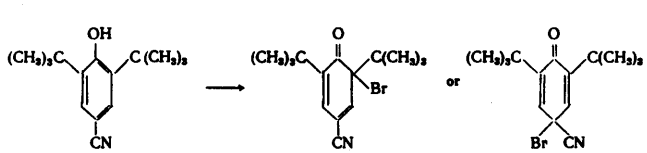
The influence of proton-acceptors is shown very clearly in the reaction of bromine with 2,6-dialkylphenols[12,13]. In this case good yields of quinolide compounds are also obtained in their presence, whereas bromination in non-polar solvents (for example in carbon tetrachloride) at once yields 2,6-dialkyl-4-bromophenols directly:



Since quinohalides are extremely reactive, their preparation from alkylphenols (usually in very good yields) is carried out at low temperatures (between -10° and 0°).

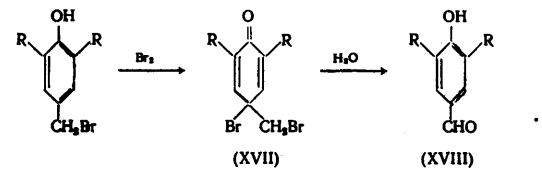
The formation of quinolide compounds has been reported also in the chlorination of some sterically hindered phenols[33,97].

If a 2,4,6-trisubstituted phenol does not contain an alkyl group in the 4-position, quinolide compounds can also be formed in the halogenation of such phenols. However, less work has been done on this question. Quinobromides are probably formed by the action of bromine on 3,5-di-t-butylbiphenyl-4-ol[98] and on 4-hydroxy-3,5-di-t-butylbenzonitrile (XIV)[32], although in the latter case the structure of the product is not proved but is taken to be the *o*-quinolide (XV) on the isomeric *p*-quinolide form (XVI):



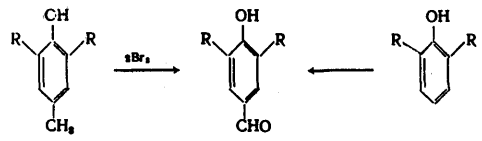
(XIV) (XV) (XVI)

Bromination of various 2,6-dialkylphenols containing a 4-bromomethyl group also yields quinobromide compounds (XVII), which readily form 3,5-dialkyl-4-hydroxybenzaldehydes (XVIII)[99] on hydrolysis:



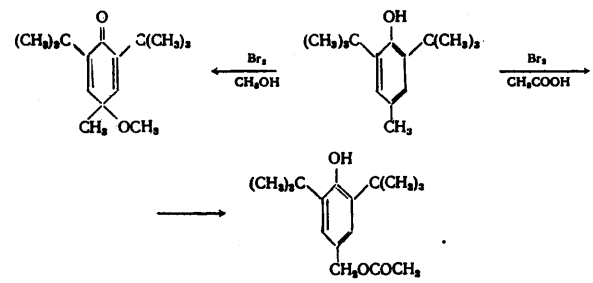
(XVII) (XVIII)

If the corresponding 2,6-dialkyl-*p*-cresols are brominated in the presence of water with two equivalents of bromine in a single operation, the hydroxy-aldehydes (XVIII) are obtained, the formation of which involves an intermediate quinobromide (XVII) stage. Dialkylhydroxy-aldehydes (XVIII) can also be obtained by the direct formylation of 2,6-dialkylphenols by means of hexamethylenetetramine[100].

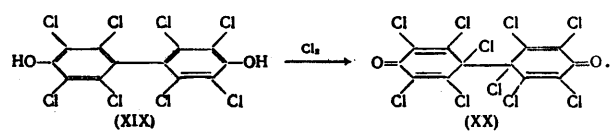


(XVIII)

Other examples are also known of the solvent reacting with the quinobromide which is formed, especially if the bromination of phenols is carried out at elevated temperatures. For example, the action of bromine on Ionol in methyl alcohol yields a quinol§ methyl ether, but in glacial acetic acid 4-hydroxy-3,5-di-t-butylbenzyl acetate is obtained[90].



The halogenation of substituted biphenyl-*pp'*-diols apparently also involves a phenol–dienone rearrangement. Thus chlorination of 2,3,5,6,2',3',5',6'-octachlorobiphenyl-4,4'-diol (XIX) yielded a compound (XX) to which a bis(cyclohexadienyl)dione structure was attributed[101]:



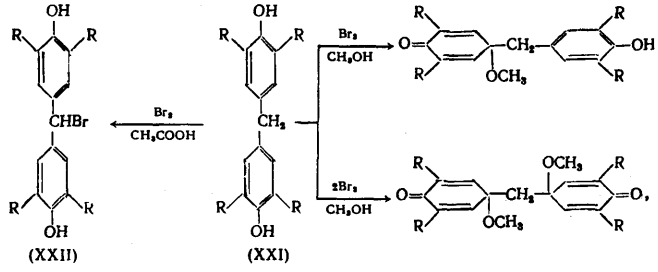
(XIX) (XX)

There is no doubt about the existence of this structure, especially as compounds having an analogous structure have been described several times in the literature[68,102].

The halogenation (bromination) of derivatives of diphenylmethane-*pp'*-diol is an interesting process. It was originally supposed[103,104] that replacement of one hydrogen atom

§ Hydroxy-derivatives of quinohalides (*i.e.* OH for halogen) are here described as "quinols" (Ed. of Translation).

by bromine yields a compound in which one of the rings has a cyclohexadienone structure. However, these hypotheses were not supported by sufficient experimental data. Subsequently, in 1957, it was shown[105] that, in the bromination of 3,5,3′,5′-tetra-t-butyldiphenylmethane-4,4′-diol (XXI), it was possible to isolate only the compound (XXII) in which the bromine was linked to the central carbon atom of the diphenylmethane system. When, however, the above compound was brominated in the presence of alcohol, ethers of the corresponding hydroxy-dienones (quinols) were obtained:



(XXII) (XXI)

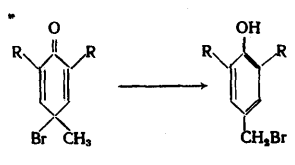
where R = $C(CH_3)_3$.

The formation of quinol ethers can be explained on the one hand as a result of the alcoholysis of quinobromides formed as intermediates, and on the other as a result of the addition of alcohol at the double bond of a methylenequinone, the latter having been produced by dehydrobromination of the bromide (XXII).

5. REACTIVITY OF QUINOHALIDE COMPOUNDS. PROBLEM OF METHYLENEQUINONE

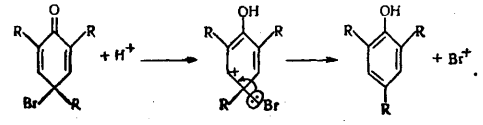
Quinohalide compounds obtained in the halogenation of substituted phenols are very reactive, this being due to the great tendency shown by *gem*-substituted cyclohexadienones to be converted into the aromatic phenol structure. On the other hand, their chemical properties are governed by the extreme lability of the carbon–halogen bond, which, depending on the conditions, can undergo either heterolytic or homolytic fission, and this sharply distinguishes quinohalides from other compounds having a quinolide structure. Almost all the properties of these substances have been studied only with quinobromide compounds. They are insoluble in alkalis, react readily with alcohols, amines, and acids, liberate iodine from potassium iodide in acetic acid solution, etc. Many reactions of these compounds depend on the structure of the initial quinobromide. For example, the reactions of the quinobromide obtained from dibromo-*p*-cresol very often differ markedly from the corresponding reactions of Ionol quinobromide.

The most general property, characteristic of all quinohalide compounds in which the halogen atom is located on a carbon atom linked also to a methyl group, is the "quino–benzylic" rearrangement, accompanied by migration of the halogen to the benzyl position with formation of an aromatic phenyl system. This rearrangement occurs during storage of the quinohalide[23,24,70], and especially readily at elevated temperatures[106]:



The speed of this rearrangement depends appreciably on the nature of the medium. When Ionol quinobromide is heated in different solvents at 59.5° for 2 h, yields of 9%, 44%, and 87% of 4-hydroxy-3,5-di-t-butylbenzyl bromide are obtained in cyclohexane, benzene, and bromobenzene respectively[106]. The velocity of the rearrangement is markedly increased in the presence of catalytic amounts of hydrogen bromide[23,94]. On the other hand, the ease of rearrangement is clearly linked with the bulk of the 2,6-alkyl substituents, and is sharply diminished with increasing steric hindrance at the carbonyl in the quinolide compounds[94]. The mechanism of the rearrangement has not been finally elucidated. Isolated facts indicate that it has a radical mechanism. However, kinetic investigations have shown it to be of first order, so that it most probably has an ionic mechanism[106].

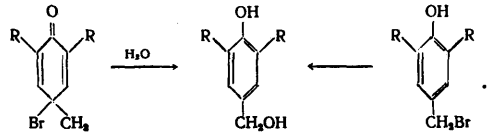
Sometimes, depending on the conditions, for example when Ionol quinobromide is heated in acetone at 60° for 3 h, debromination of the quinobromide takes place instead of the benzyl rearrangement, and the original Ionol is obtained[25]. If there is no possibility of the bromine passing to the benzyl position, the radical type of debromination can occur even when the quinobromide is just heated[91]. However, the most common type of debromination of quinobromide compounds is their behaviour in the presence of large concentrations of acid agents (hydrogen chloride and bromide, sulphuric acid)[107]:



This reaction sharply distinguishes quinobromide compounds from other quinolide derivatives, which under these conditions undergo the dienone–phenol rearrangement.

Very often (but not always) quinobromides and the *p*-hydroxybenzyl bromides formed by the quino–benzylic rearrangement give identical results on treatment with the same reagents. Whether these reactions are preceded by rearrangement of the quinobromide into the benzyl bromide is not considered at all in the literature. Moreover, many authors are inclined to suppose that the initial stage in many reactions of quinohalide compounds is the formation of the corresponding methylenequinone.

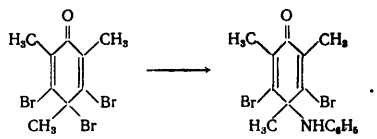
All quinobromide compounds react readily with water to form *p*-hydroxybenzyl alcohols[22,78,80,84,90]. This reaction is usually carried out in aqueous acetone medium. Exactly the same alcohols are obtained also from the corresponding *p*-hydroxybenzyl bromides[72,73,75,106]:



When formation of an alcohol is impossible (with the quinobromide of 3,5-di-t-butylbiphenyl-4-ol), the reaction yields the corresponding quinol[98].

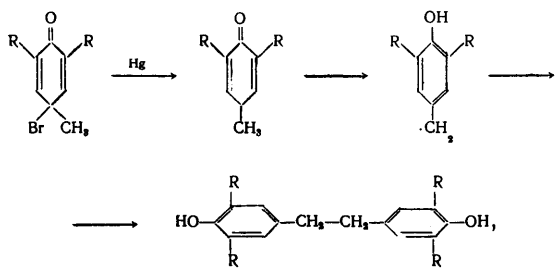
The reaction of quinobromides with alcohols is less clear-cut. Alcohols usually react with quinohalides to form ethers of *p*-hydroxybenzyl alcohol[69,78,80,83,89], which are also obtained by the action of alcohols on the corresponding hydroxybenzylbromides[25,73,108,109]. Quinobromides obtained from sterically hindered phenols, however, react with alcohols to form ethers of quinols, the dienone structure being preserved[33,90].

The reaction of quinobromide compounds with amines is less clear-cut. Early work on the simplest examples showed[78-84] that these compounds react with ammonia, primary and secondary aliphatic amines, and aniline with formation of *p*-aminomethylphenols, which can also be obtained from the corresponding benzyl bromides[23,73,75,77,84,86]. According to Fries[24,70], however, the action of aniline in alcoholic medium containing sodium acetate on the quinobromides of 2,6-dibromo-*p*-cresol and 3,5-dibromomesitol yields quinoamines, substances having a dienone structure which in acid medium can undergo rearrangement to ethers of the phenol:



Ionol quinobromide does not react in ethereal solution with aniline[25] or with tertiary amines (triethylamine, pyridine)[110], but it does react normally with secondary amines to form dialkylaminomethylphenols, which can also be obtained from 2,6-di-t-butylphenol by the Mannich reaction[111].

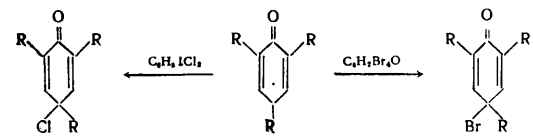
Very little work has been done on the reaction of quinohalides with organic acids and their salts. According to unverified data published in early papers, the action of sodium acetate in acetic acid on quinobromides yields quinol acetates[78,79,82,84,86], from which quinohalides are again formed by reaction with HCl, HBr, and HI.[78,79,82] Reaction of quinohalides with acetic anhydride or acetic acid yields benzyl acetates[82-85]. A similar reaction has been described also in a more recent paper[90]. The interaction of quinohalides with various metals is very interesting. For example, Ionol quinobromide does not react with sodium in ether, but treatment with metallic mercury yields 3,5,3′,5′-tetra-t-butyldiphenylethane-4,4′-diol[106], the reaction having a radical mechanism:



where R = $C(CH_3)_3$.

If it is impossible for the phenoxy-radical which is formed to isomerise into a benzyl radical, a stable phenoxy-radical may result from the reaction. Such a change takes place when mercury, copper, zinc, or especially silver acts on the quinobromide of 2,4,6-tri-t-butylphenol in the absence of oxygen[37,97,106].

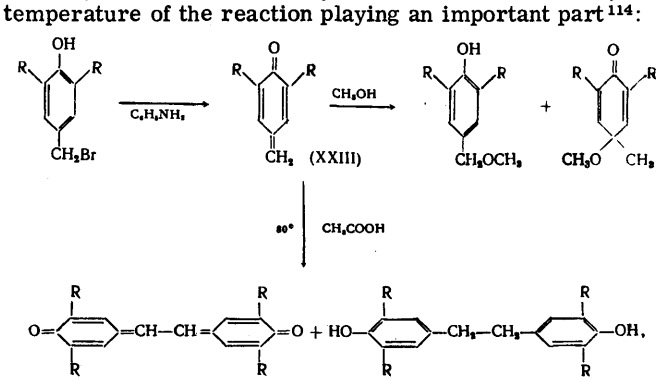
The action of a sodium–potassium alloy on the same quinobromide produces the 2,4,6-tri-t-butylphenoxide[33]. If, however, the quinobromide (quinochloride) of 2,4,6-tri-t-butylphenol is treated in alkaline alcoholic medium with 2,4,6-tri-t-butylphenol or even directly with its phenoxide, a quantitative yield of the 2,4,6-tri-t-butylphenoxy-radical is obtained[112], from which the quinochloride is again formed by the action of iodosobenzene dichloride[97], and the quinobromide is obtained by the action of tribromophenol bromide[113]:



where R = $C(CH_3)_3$.

It has been repeatedly emphasised above that many reactions of quinohalides and of the corresponding *p*-hydroxybenzyl halides give identical results. This is explained[90,114] by the possibility of methylenequinones being formed as intermediates, which can also occur with other compounds of analogous structure. Different workers have made many attempts to isolate a methylenequinone from the reaction mixture. Thus as early as 1898 Auwers supposed that he had obtained a methylenequinone by dehydrating the quinol of 2,4,5-tribromo-3,6-dimethylphenol[115]. Later Zincke[116] heated the quinonitrol¶ of 2,3,5,6-tetrachloro-*p*-cresol with methyl alcohol and obtained an alkali-insoluble substance, which reacted[116,117] with hydrogen bromide to form a nuclear-substituted *p*-hydroxybenzyl bromide, and on being boiled with methyl and ethyl alcohols and with acetic acid it formed the corresponding ethers and ester of benzyl alcohol. Reduction of this substance yielded a substituted *p*-cresol.

In 1905 Zincke[75] obtained, by the action of sodium acetate in absolute benzene on 2,3,5,6-tetrabromo-4-hydroxybenzyl bromide, an amorphous powder, which behaved in all the above reactions as a methylenequinone. Attempts were also made to prepare *o*-methylenequinone starting from *o*-quinonitrol[118,119] and from *o*-hydroxybenzylbromide[120,121]. However, subsequent work showed that the methylenequinone monomer had not been obtained in these cases, but instead dimeric and trimeric derivatives[24,120-122] possessing the properties of methylenequinone had been formed. A cyclic structure was adopted for the dimer of methylenequinone[123,124]. The trimer was obtained by the action of 2 *N* sodium carbonate solution on *p*-hydroxybenzyl bromide in ether[24]. Heating *p*-hydroxybenzyl bromides with caustic soda solution yields polymeric products[125] and stilbenequinones[25]. It was not until 1957 that it was finally reported[25,114] that one of the products of the action of an ethereal solution of aniline on 3,5-di-t-butyl-4-hydroxybenzyl bromide is monomeric 2,6-di-t-butylmethylenequinone (XXIII), obtained in the form of an amorphous powder, which reacts readily with several substances, the temperature of the reaction playing an important part[114]:

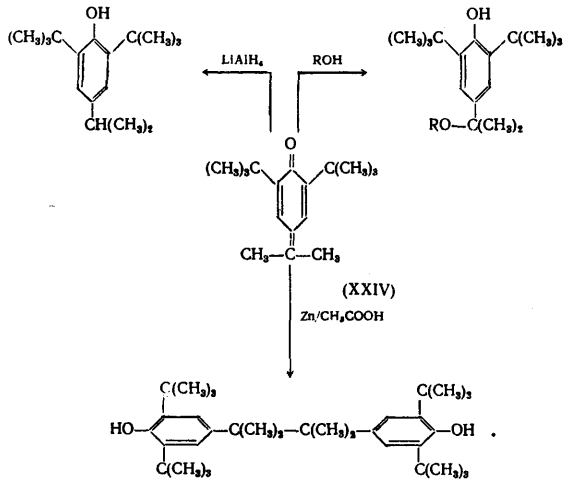


where R = $C(CH_3)_3$.

¶ Nitro-analogues of quinohalides (*i.e.* NO_2 for halogen) are here described as "quinonitrols" (Ed. of Translation).

In later work, however, it proved impossible[126] to isolate this methylenequinone (XXIII) in the free monomeric state. It was then shown that the methylenequinone (XXIII) is stable at a concentration 10^{-2} M in an inert solvent at 20°, 2% of the dimer being formed only after 72 h; whereas the corresponding methylenequinone in which methyl groups have replaced the t-butyl groups in both *ortho*-positions is less stable, and at the same concentration forms 60% of the dimer after only 140 min.

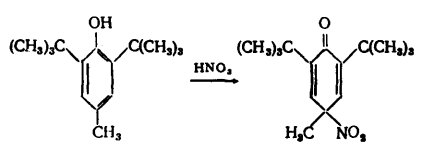
Homologues of methylenequinone are more stable[103,105,109,118,127-130], especially isopropylidenequinone (XXIV)[129], prepared by the oxidation of 2,6-di-t-butyl-4-isopropylphenol with lead dioxide in an atmosphere of nitrogen. The action of hydrogen bromide on this isopropylidenequinone yields a white substance which decomposes rapidly in air. With alcohols in acid medium, addition at the double bond takes place normally. Reduction with lithium aluminium hydride yields 2,6-di-t-butyl-4-isopropylphenol, but on reduction with zinc in acetic acid the corresponding substituted diphenylethane-*pp'*-diol (XXV) is obtained:



(XXV)

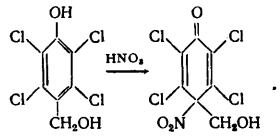
6. NITRATION OF PHENOLS

The nitration of phenols accompanied by phenol–dienone rearrangement has been less thoroughly studied than their halogenation. This is mainly because the nitration is a more complicated process, and is accompanied by several side-reactions, the chief of which is oxidation of the original phenols to the corresponding benzoquinones and biphenoquinones[26,131-136]. Furthermore, the nitration of phenols often involves replacement of a group in the phenol nucleus by a nitro-group[29-31,137]. However, there are grounds for assuming that in most of these cases both substitutive nitration[29] and many oxidation reactions[132,138] of phenols with nitric acid involve the intermediate formation of a cyclohexadienone structure. Nitration of substituted *p*-alkylphenols alone results in the formation of quinonitrols having a structure analogous to that of *p*-quinohalide compounds:



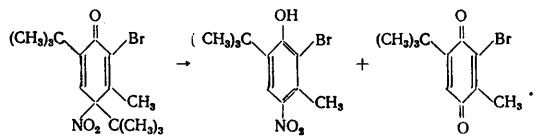
There are indications in the literature[139] also of cases of *o*-quinonitrol formation.

Nitration with the formation of quinonitrols is usually observed in the case of sterically hindered and polyhalogenated *p*-alkylphenols, *i.e.* in fact with those phenols whose structure to an appreciable extent favours the phenol–dienone rearrangement. Quinonitrols have been obtained chiefly from halogenated *p*-cresols[116,117,140,141], xylenols, mesitol[115,132], and *p*-hydroxybenzyl alcohol and its methyl ether[73].



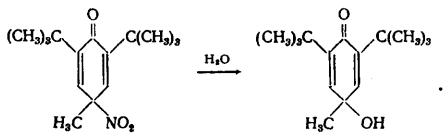
Quantitative yields of quinonitrols are obtained from Ionol[142] and from 2,4,6-tri-t-butylphenol[143]. In order to obtain quinonitrols, the nitration of phenols is usually carried out at a low temperature (0°) with concentrated nitric acid or with a mixture of nitric and acetic acids. At higher temperatures the phenols are oxidised. If, for example, nitration of 2,4,6-tri-t-butylphenol is attempted at 100°, 2,6-di-t-butyl-1,4-benzoquinone is formed instead of the quinonitrol[143].

A distinctive feature of the quinonitrols is their great instability. They are rapidly decomposed by acetic and sulphuric acids[144]:

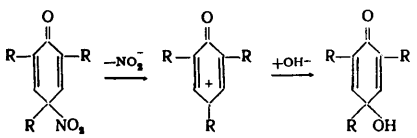


Thermal decomposition (at 90°) is accompanied by the evolution of nitrogen dioxide[91].

Another characteristic of quinonitrols is their ready conversion into quinols:



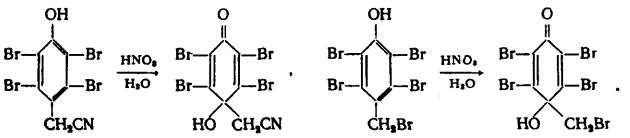
This reaction occurs readily on treatment of quinonitrols with hot water[142], aqueous acetone in the presence of caustic potash or acetic acid[134], sodium acetate in acetic-acid solution[144], etc. It was previously supposed that the formation of a quinol from a quinonitrol is accompanied by the elimination of a molecule of nitrous acid *via* a stage involving formation of a methylenequinone, followed by addition to it of a molecule of water[69,115,116,145,146]. Later, however, it was shown[91,143] that the corresponding quinol is also obtained even when the formation of a methylenequinone is impossible. The quinonitrol prepared from 2,4,6-tri-t-butylphenol, for example, is readily converted into a quinol, which can be explained by an ionic mechanism[143]:



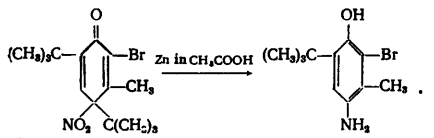
where R = $C(CH_3)_3$.

In this case *p*- and *o*-benzoquinones are formed as side-products.

The ease of formation of quinols is so great that the nitration of substituted *p*-alkylphenols very often does not stop at the quinonitrol stage, but yields the corresponding quinol immediately. Thus in the nitration of 3,5-di-t--butyl-4-hydroxybiphenyl (under conditions analogous to the preparation of the quinonitrol from Ionol) the quinol is formed at once. Direct formation of quinols takes place also during the nitration of substituted *p*-ethylphenols[147], *p*-hydroxybenzyl bromides[72,73,148,149] or chlorides[75], and 2,3,5,6-tetrabromo-4-hydroxyphenylacetonitrile[75]:



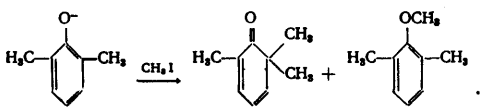
For a long time the structure of the quinonitrols remained a matter of dispute. Many writers were inclined to regard these compounds as nitrous esters. However, a direct bond between nitrogen and carbon in the quinonitrols is convincingly indicated by the formation of substituted *p*-aminophenols when several of them are reduced with zinc in acetic acid[144]. The reaction involves elimination of the alkyl group:



It seems that reduction may be preceded by decomposition of the quinonitrol, which, as mentioned above, takes place in acid medium with elimination of an alkyl group. A case is also known[117] in which reduction of a quinonitrol is accompanied by loss of the nitro-group, the corresponding substituted *p*-cresol being isolated as a product of the reaction.

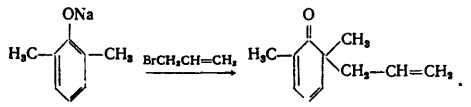
7. ALKYLATION OF PHENOLS

The alkylation of phenols and especially of the corresponding phenoxides also can lead to the formation of cyclic dienones. In contrast to the examples considered earlier, the cyclodienones obtained in this case contain only alkyl groups as *gem*-substituents. The formation of a new carbon–carbon bond affects also the characteristics of the accompanying phenol–dienone rearrangement. In the alkylation of phenoxides with alkyl halides, for example, formation of phenyl ethers is in several cases accompanied by that of cyclodienones having an *o*-quinolide structure. Such dienones are formed even in the alkylation of phenols containing no *p*-substituent[150]:

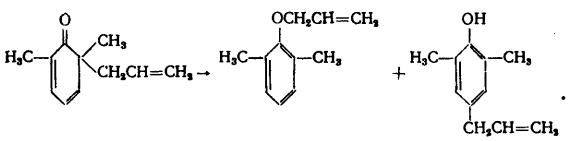


In the alkylation of phenoxides with alkyl halides dienones are usually formed in low yields, the main reaction products being the phenyl ethers. However, the proportions of cyclic dienone and phenyl ether among the reaction products may be varied considerably. The formation of a dienone structure is favoured in these cases[150] by the following factors: decrease in acidity of the initial phenol (for example in the sequence 4-bromo-2,6-dimethylphenol, 2,6-dimethylphenol, mesitol), presence of moisture, decrease in polarity of the solvent, and increase in concentration of the phenoxide during the reaction. If phenoxides of different metals are used, the total yield of reaction products increases in the sequence Li, Na, K. The yield also increases on passing from alkyl chlorides to alkyl bromides and iodides.

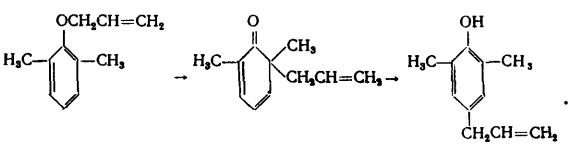
The ease of formation of cyclodienones in the alkylation of phenoxides is most affected by the nature of the alkyl halide. Dienones are formed to a considerably smaller extent when methyl iodide and propyl iodide are used than with benzyl bromide and allyl bromide[150,151]. In 1956 Curtin[152] was able to isolate a cyclohexadienone in 60% yield by the alkylation of sodium 2,6-dimethylphenoxide with allyl bromide at 15°:



The structure of the dienone was proved by the infra--red and ultra-violet spectra, and also by the formation of an adduct with maleic anhydride. On standing, the dimer of the dienone is formed (by a diene synthesis mechanism), and on being heated gives a 64% yield of 4-allyl-2,6-dimethylphenol. Heating the monomeric dienone above 70° yields a mixture containing 27% of allyl 2,6-dimethylphenyl ether and 73% of 4-allyl-2,6-dimethylphenol[153]:



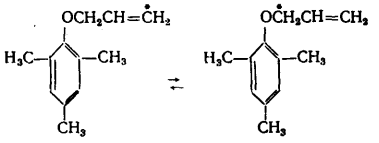
The alkylation of phenoxides with an allyl halide differs from the rearrangement of allyl phenyl ethers (the Claisen rearrangement), although the same final results may be obtained in the two cases. According to modern data[154,155], the Claisen rearrangement is a typical intramolecular rearrangement, which does not occur by an ionic mechanism. It is interesting that, when both *ortho*-positions of the phenol are already substituted, this rearrangement (the Claisen *para*-rearrangement), too, involves the intermediate formation of a quinolide structure. This was shown[156] in 1953 in the case of allyl 2,6-dimethylphenyl ether (the condensation product of maleic anhydride with the corresponding dienone was isolated).



Later this mechanism for the Claisen *para*-rearrangement was confirmed with other examples[157,158].

Allyl mesityl ether (in which the *para*- and both *ortho*--positions of the aromatic nucleus are substituted) gives under the conditions of the rearrangement a good yield of an adduct with maleic anhydride, which suggests that a dienone structure is formed, although it could not be detected by spectroscopic methods[158]. Later work[159] on

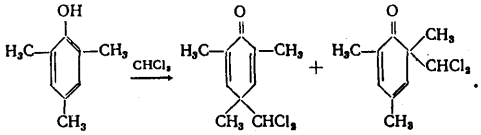
[3-^{14}C]allyl mesityl ether showed that in this case the reaction results in the establishment of equilibrium between two labelled allyl ethers:



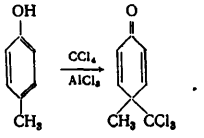
It was assumed that the process involves the intermediate formation of an *o*- or *p*-quinolide structure.

Another interesting example of a phenol–dienone rearrangement occurring in the alkylation of phenols is provided by the anomalous cases of the Reimer–Tiemann reaction†. As long ago as the end of the past century it was noted that *o*- and *p*-substituted phenols form cyclic ketones together with the expected phenolic aldehydes under the conditions of the Reimer–Tiemann reaction (the action of chloroform on a phenoxide). These compounds have a cyclohexadienone structure, and undergo reactions characteristic of ketones[160–164].

In the cast of mesitol, with which the formation of an aldehyde is impossible owing to the absence of vacant *ortho*- or *para*-positions in the phenol, this side-reaction becomes the principal reaction, and a good yield of a cyclic ketone is obtained[165]:

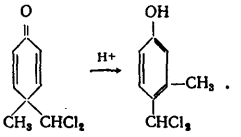


Zincke showed[166] that a ketone of analogous structure is obtained also by the action of carbon tetrachloride on *p*-cresol in the presence of aluminium chloride. This ketone readily forms an oxime and a phenylhydrazone, and sulphuric acid breaks it down into *p*-cresol and carbonyl chloride:

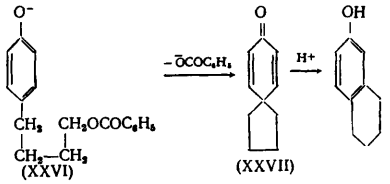


This reaction, occurring in the presence of aluminium chloride, was subsequently termed the Zincke reaction. In 1954 Newman[167] made a detailed investigation of this reaction in the case of *p*-cresol, and showed that it goes smoothly (yield 60%) only with carbon tetrachloride. Attempts to use $CHCl_3$, C_2Cl_6, $CH_2{=}CHCl$, CH_3Cl, or CH_3I in this reaction were unsuccessful. When, however, it was carried out with 1,1,1-trichloroethane, a substance having a dienone structure could be isolated as the 2,4-dinitrophenylhydrazone.

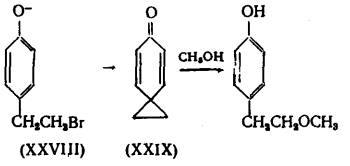
The 4-di(and tri)chloromethyl-4-methylcyclohexan-2,5-dienones resulting from these reactions behave normally in organomagnesium synthesis and the Reformatsky reaction, and in carbon tetrachloride solution are chlorinated (brominated) in the ring with preservation of the dienone structure; in the light halogen adds on at the multiple bonds[168,169]. Depending on the conditions, reduction of such dienones results either in the formation of *p*-cresol derivatives[170] or in reduction of the dichloromethyl group to methyl with preservation of the dienone structure[165,171]. In acid medium 4-dichloromethyl-4-methylcyclohexa-2,5-dienone undergoes dienone–phenol rearrangement[169]:



The alkylation of phenols leading to the formation of spirocyclohexadienones is a very interesting process. Thus 4-*p*-hydroxyphenylbutyl benzoate (XXVI)[172] in alkaline medium gives a 50% yield of a compound having a dienone structure, as has been confirmed by elemental and spectroscopic analyses. This compound can subsequently undergo dienone–phenol rearrangement with the formation of a tetrahydronaphthol:



Intramolecular alkylation occurs similarly also with *p*-2-bromo(or iodo)ethylphenol (XXVIII), which in alkaline medium splits off a molecule of hydrogen halide with closure of a cyclopropane ring and simultaneous phenol–dienone rearrangement[172]. Initially the structure of the resulting spirodienone (XXIX) was proved only by means of spectroscopic data, since it was not possible to isolate the pure material from the reaction products because of its rapid reaction with the methyl or ethyl alcohol used as solvent:



Later the dienone (XXIX) was obtained pure[173] by passing an ethereal solution of *p*-2-bromoethylphenol (XXVIII) through a column containing basic aluminium oxide. This spirodienone is extremely unstable. Even in minute concentrations it reacts with various substances at various pH values with ring-opening. The ring is opened especially rapidly, in acid medium, the period of half-decomposition of the substance in 10^{-5} M solution at 25° being in this case 10 sec. In ethereal solution the dienone can exist at a concentration 5×10^{-3} M for a week; in the solid form it is stable for not more than 20–30 min, after which it is converted into a polymeric ether.

Oxygen analogues of this spirodienone, in which the three-membered ring contains an oxygen atom instead of a methylene group, are more stable. These compounds are readily obtained by the action of alkaline reagents on *p*-bromomethylquinols[73,132,148].

† A fairly detailed survey has recently been published of the Reimer–Tiemann reaction[8].

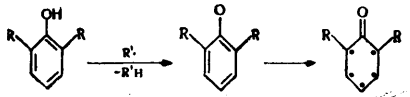
8. FORMATION OF DIENONES IN RADICAL REACTIONS OF PHENOLS

The conversion of phenols into cyclohexadienones in radical reactions must be considered in the light of the general laws of radical processes involving phenols, since those resulting in the formation solely of dienone compounds cannot be isolated as a separate group. It must be remembered firstly that the radical reactions of phenols are somewhat different in character from those of other aromatic compounds, and secondly that their mechanism has not yet been completely elucidated. A great amount of work has been published in this field during recent years, especially in connection with the use of phenols as inhibitors of free-radical oxidation processes in fats, oils, fuels, etc. A good review of the properties of various phenols in radical oxidations will be found in the recently published book by Emanuel' and Lyaskovskaya[174].

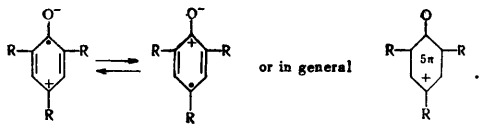
A distinguishing feature of radical reactions of phenols is the initial formation of phenoxy-radicals, which, depending on the structure of the original phenol, may be more or less stable, and may even exist for a long time in the free state. The initial formation of phenoxy-radicals is due to the considerably lower energy of rupture of the O–H bond in the phenolic hydroxyl than of a C–H bond in the aromatic nucleus, so that the rate of a radical reaction in which atomic hydrogen is split off from the hydroxyl will many times exceed the rate of loss of atomic hydrogen from the aromatic ring. From this it follows that, when any radical interacts with a phenol, formation of a phenoxy-radical (by the loss of atomic hydrogen from the hydroxyl) is practically the only process which occurs. Steric factors which impede radical attack on the phenolic hydroxyl should tend to prevent such a reaction. Increasing the bulk of the substituents in both *ortho*-positions of the phenol, for example, diminishes the rate of formation of the phenoxy-radical in the reactions of phenols with diphenylpicrylhydrazyl[175]. According to other workers[176], however, the rate of reaction of $RO_2^{\cdot}$ radicals is about the same with 2,6-dimethylphenol and with 2,6-di-t-butylphenol, since the two bulky *o*-substituents in the latter compound greatly disturb the coplanarity of the hydroxyl with the benzene ring, which in turn appreciably favours the formation of the phenoxy-radical, as this eliminates the non-coplanarity effect.

The existence of phenoxy-radicals has been demonstrated by various methods[174]. The formation of radicals from phenols by the loss of the hydrogen atom from the hydroxyl is indicated also by spectroscopic examination of some stable phenoxy-radicals, the infra-red spectra of which did not reveal absorption bands corresponding to the hydroxyl[33,97,113,184].

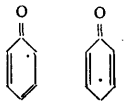
Phenoxy-radicals, which have an unpaired electron on the oxygen atom, usually have a very short life, and rapidly isomerise. This involves redistribution of the bonds with the formal creation of a cyclodienone structure, the unpaired electron being delocalised over the whole aromatic nucleus. With such a structure the phenoxy-radical preserves the π-electron sextet of the aromatic ring with coplanarity of the molecule as a whole. The presence of large, bulky substituents in the 2,6-positions of phenol substantially increases the stability of the resulting radicals:



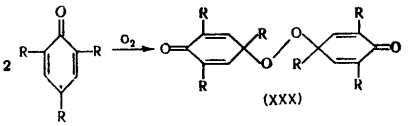
Since the infra-red spectra of several free phenoxy-radicals, especially in the solid state, are very similar to those of quinolide structures, Müller[177] suggested a dipolar ion quinolide radical structure for such radicals, for example:

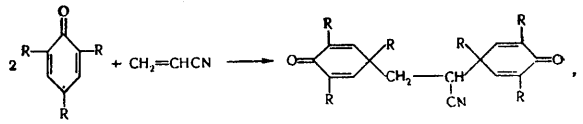


In the present paper we are unable to discuss the finer features of the structure and properties of such free radicals, which are known in the literature under the name of phenoxyls or aroxyls‡. The main peculiarity of phenoxy-radicals is that, depending on the structure of the original phenol, they can subsequently react in two different forms (α- or γ-ketomethyl), corresponding to the *o*- or *p*-quinolide structure:



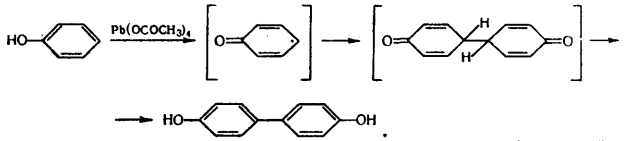
Thus, for example, the action of atmospheric oxygen on the 2,4,6-tri-t-butylphenoxy-radical yields the corresponding quinolide peroxide (XXX)[91], but in the presence of a diene or of acrylonitrile the phenoxy-radical can react at the double bond in these compounds[179]:





where R = $C(CH_3)_3$.

If the phenoxy-radical which is formed is unstable, and cannot be stabilised by addition of another radical at the free valence, recombination of the phenoxy-radicals takes place with the formation of bisphenols. Dimerisation of a phenoxy-radical usually occurs *via* the *p*-quinolide form. Thus the action of an equivalent amount of lead tetraacetate in benzene solution on phenol itself involves the formation of 4,4′-dihydroxybiphenyl[180]:



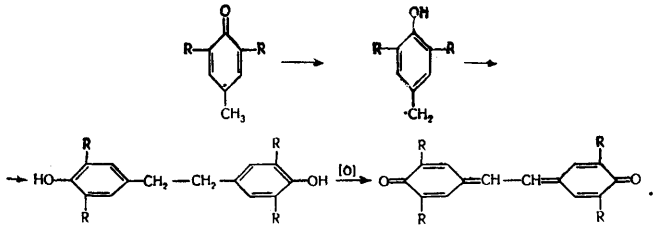
An intermediate compound having a biquinolide structure has been isolated in the oxidation of 2,6-di-t-butylphenol with potassium ferricyanide[142].

‡ The chemical properties of stable phenoxy-radicals (aroxyls) are being intensively studied at the present time by Müller[178].

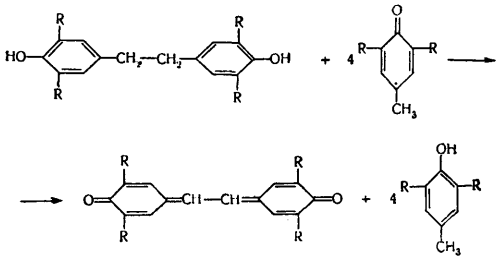
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If the *para*-position in a phenol is substituted, but a vacant *ortho*-position is available, dimerisation of the phenoxy-radicals takes place *via* an *o*-quinolide form[181]. Very often, especially in the presence of oxidising agents, the resulting bisphenols are oxidised to the corresponding biphenoquinones, which are usually isolated as the main products of the recombination of phenoxy-radicals[137,181,182].

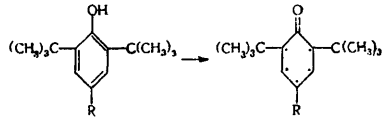
The recombination of 2,4,6-trisubstituted phenoxy--radicals is very interesting. In this case the radicals cannot be linked through unsubstituted *ortho*- or *para*--positions, and if active hydrogen atoms are present in the α-position of the alkyl substituent in the initial phenols, the phenoxy-radicals (probably their *p*-quinolide forms) are converted into benzyl radicals, which combine with the formation of 1,2-di(*p*-hydroxyphenyl)ethanes. These then usually oxidise to stilbenequinones[181-184]:



Stilbenequinones can be formed in radical processes[106] even in the absence of oxidising agents, by the reaction:

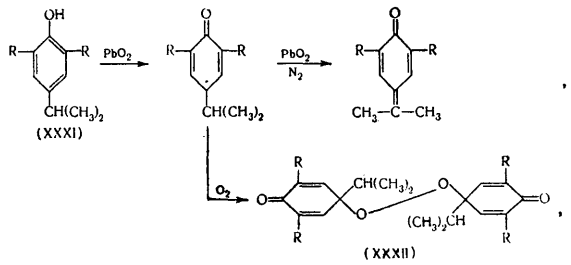


If a phenol contains a *p*-t-butyl group, as for example in 2-methyl-4,6-di-t-butylphenol, the corresponding phenoxy--radical is able to isomerise to a benzyl radical with subsequent recombination involving the hydrogen of the *o*-methyl group[181]. When isomerisation of the phenoxyl to a benzyl radical is made impossible by the absence of hydrogen atoms in the benzyl positions, the free phenoxy--radicals may be long-lived:



where R = $C(CH_3)_3$, OCH_3, $OC(CH_3)_3$, CN, C_6H_5, etc.

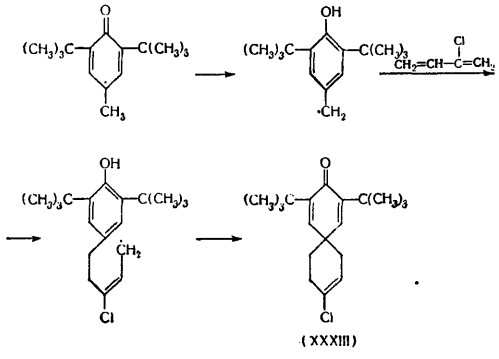
In some cases of the oxidation of phenols with lead dioxide or silver oxide stabilisation of the phenoxy-radical may involve formation of the corresponding methylene-quinone. This reaction is accomplished most smoothly by the action of lead dioxide on 4-isopropyl-2,6-di-t-butyl-phenol (XXXI) in an atmosphere of nitrogen[129]. In the presence of oxygen, however, the initially formed phenoxy--radical reacts with it to form a peroxide (XXXII):



where R = $C(CH_3)_3$.

This reaction has been extended[126] to other examples (mesitol, Ionol, 4-allyl-2,6-dimethylphenol, etc.), and at the present time is employed for the preparation of various methylenequinones.

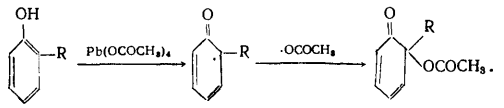
The action of the same oxidants (for example PbO_2) on Ionol and 4-isopropyl-2,6-di-t-butylphenol (XXXI) in the presence of chloroprene may involve reaction of the phenoxy-radical (probably in the isomeric benzyl form, in contrast to the other cases) with the diene to form a compound (yield 75%), which is assigned[185] a spirocyclodienone structure (XXXIII). The mechanism of this reaction has not been finally elucidated.



This reaction is accompanied by the formation of considerable quantities of the corresponding stilbenequinone, which can be assumed to result from dimerisation of the benzyl forms of the radicals.

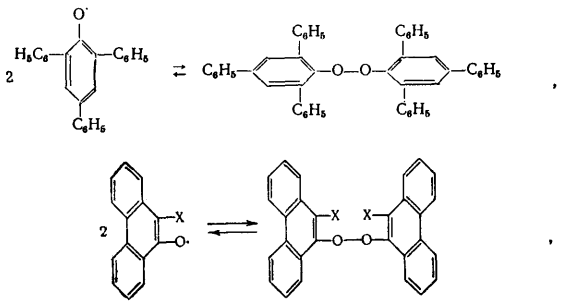
If other radicals are present in excess in the system at the instant of formation of the phenoxy-radical, dimerisation of the latter (itself or as its benzyl isomer) may not occur. The phenoxy-radicals are then stabilised by combination with other radicals present in the system (for example $RO_2^{\cdot}$ in the formation of peroxides, ROCO$^{\cdot}$ in the preparation of acyloxy-derivatives, etc.). A high concentration of such radicals in the system does not completely prevent dimerisation of the phenoxy- (or benzyl) radicals, These are usually competing processes, the main mode of the reaction depending both on the nature of the reactant radical ($RO_2^{\cdot}$, ROCO$^{\cdot}$, etc.) and on the relative stability of the phenoxy-radicals. The rate of recombination of phenoxy- (or benzyl) radicals usually falls with rise in their stability, and the latter increases appreciably with increasing size of *o*-substituents in the phenol.

Cyclodienones are formed in radical reactions of phenols if the phenol molecule already contains a substituent whose orientation (*ortho* or *para*) coincides with the form (*ortho* or *para*) of the phenoxy-radical which is reactive under the given conditions. In contrast to most electrophilic reactions, the *para*-position of the phenol may be unsubstituted[180] in this case:



Dienones are most readily obtained from 2,4,6-trialkylphenols. Even in these cases, however, recombination products of the phenoxy-radicals are very often formed as well.

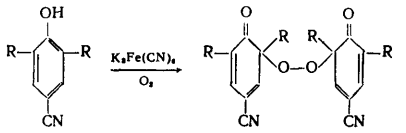
The most characteristic example of the conversion of phenols into dienone compounds in radical processes is the formation of quinolide peroxides by the action of oxygen on free phenoxy-radicals. As already noted, this usually involves formation of *p*-quinolide peroxides[91,129,134,184]. Only the radical obtained from 2,4,6-triphenylphenol is insensitive to oxygen, and this can dimerise *via* the oxygen atom to form a purely aromatic peroxide[186]. Similar properties are shown by the radicals from substituted phenanthren-10-ols[187,188]:



where X = Cl, OC_2H_5.

Such properties of these radicals probably indicate that their unpaired electron is localised on the oxygen atom, which is not usually observed in the monocyclic, non-polyphenylated phenols.

Quinolide peroxides can be obtained directly from the corresponding phenols by oxidation with alkaline potassium ferricyanide solution in the presence of oxygen[98,129,134,189]. Free phenoxyl is formed initially as a result of oxidation by the ferricyanide, and this then reacts with the oxygen to give the peroxide. Under these conditions *p*-quinolide peroxides are usually obtained, and it is probably only the oxidation of 4-hydroxy-3,5-di-t-butylbenzonitrile which results in the corresponding *o*-quinolide compound[32]:

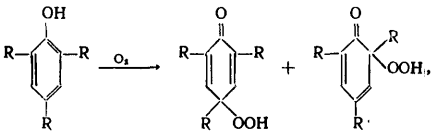


where R = $C(CH_3)_3$.

Silver oxide has been successfully employed[190] instead of potassium ferricyanide to obtain quinolide peroxides under the same conditions.

Quinolide peroxides are solids which darken in the light, are decomposed by sulphuric acid, and liberate iodine from a solution of potassium iodide in acetic acid. Reduction with lithium aluminium hydride yields the original phenol[97]. Thermal decomposition of the peroxide from 2,4,6-tri-t-butylphenol led to the isolation of 2,6-di-t-butylbenzoquinone, the reaction being accompanied by elimination of isobutene[133]. The peroxide obtained from 2,4,6-tri-t-pentylphenol behaves similarly, giving a quantitative yield of 2,6-di-t-pentylhydroquinone on being heated to 226°.[189]

Oxidation of sterically hindered 2,4,6-trialkylphenols in alkaline medium with oxygen alone (in the absence of potassium ferricyanide or silver oxide) gives quinolide hydroperoxides (phenol hydroperoxides)[142,191,192] instead of quinolide peroxides. Ionol, for example, yields Ionol hydroperoxide, which has a *p*-quinolide structure, and the oxidation of 2,4,6-tri-t-butylphenol leads to the formation of two isomeric hydroperoxides having a *p*- and an *o*-quinolide structure[191]:



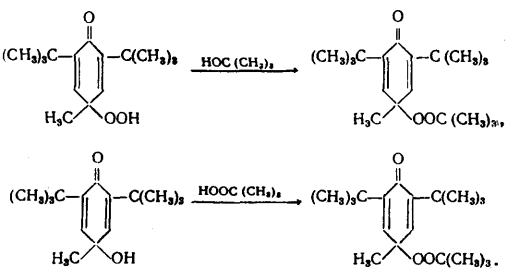
where R = $C(CH_3)_3$.

In alkaline medium *p*-quinolide hydroperoxides can break down to the corresponding quinol or the original phenols, or else may rearrange into the *o*-quinolide hydroperoxides[192].

The literature contains interesting indications[191] that the autoxidation of sterically hindered phenols in alkaline medium may not occur by a free-radical mechanism.

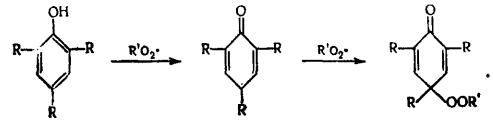
Quinolide hydroperoxides are also obtained by the oxidation of sterically hindered phenols with hydrogen peroxide in t-butyl alcohol in the presence of the ions Co^{2+}, Fe^{2+}, Fe^{3+}, Cu^{+}, and Cu^{2+}. The presence of oxygen does not interfere with this reaction. Reduction of the hydroperoxides with hydriodic acid[191] or with hydrogen in the presence of platinum[193] yields quinols. However, the *o*-hydroperoxide of 2,4,6-tri-t-butylphenol does not give the corresponding quinol on reduction[191].

Ionol hydroperoxide reacts with t-butyl alcohol to form the corresponding alkyl quinolide peroxide (phenol peroxide), which is also obtained by the oxidation of the quinol of Ionol with t-butyl hydroperoxide:



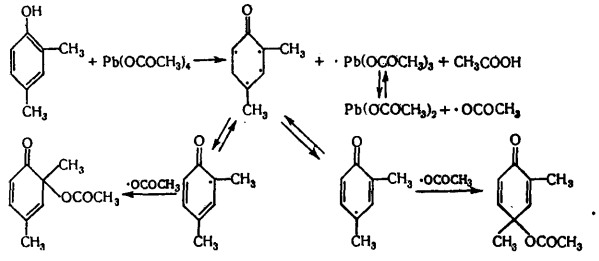
Analogous compounds are obtained also by the interaction of t-butyl hydroperoxide with the corresponding

phenols at the decomposition temperature of the hydroperoxide[194]. The formation of such peroxides of phenols, having a quinolide structure, usually occurs at the same time as the formation of recombination products of phenoxy-radicals in the inhibition by phenols of free-radical oxidation processes[174,195]:

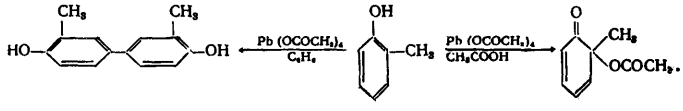


Both isomeric (*o*- and *p*-) quinolide peroxides of the phenols were isolated[183] in the oxidation of 2,6-dimethyl-4-t-butylphenol and 2-methyl-4,6-di-t-butylphenol with alkyl hydroperoxides. Reduction of Ionol t-butyl peroxide gives the theoretical yield of the quinol, but only a very low yield of the corresponding quinol is obtained[183] in the reduction of t-butyl 2,4,6-tri-t-butylphenol peroxide. 3,5-Di-t-butyl-4-hydroxybenzaldehyde is formed in the bromination of Ionol t-butyl peroxide with bromine in acetic acid[194].

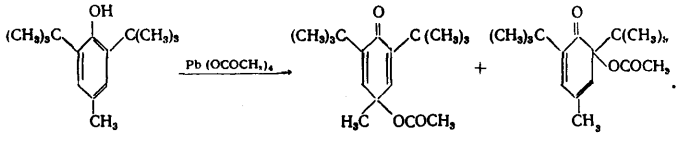
Another example of the formation of dienone compounds in radical reactions of phenols, which has been studied in some detail, is the formation of various acyloxy-derivatives of cyclohexadienones by the action of lead tetraacetate and acyl peroxides on phenols. The most thorough work in this field has been done by Wessely[196-203], who summarised his own results in a short review of quinol acetates[204].



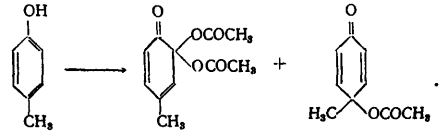
The nature of the substances obtained by the oxidation of phenols with lead tetraacetate depends to a considerable extent on the structure of the original phenol and on the solvent employed. When the reaction is carried out in benzene[180], for example, products of the dimerisation of phenoxy-radicals are usually formed, whereas in acetic acid[196,197] the reaction involves the formation of the isomeric *o*- and *p*-quinol acetates, the main product being the *o*-quinolide isomers:



The tendency of *o*-quinol acetates to be formed in this reaction is maintained with a wide variety of phenols: *o*-cresol, different xylenols, 2,4,6-trialkylphenols, etc. If, however, the phenoxy-radical obtained during oxidation of a trialkylphenol (Ionol, 2,4,6-tri-t-butylphenol) is sufficiently stable, both *ortho*- and *para*-isomers are formed[205]:

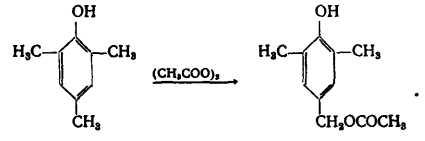


If both *ortho*-positions of the phenol are vacant, while the *para*-position is substituted, an *o*-(*OO'*-diacetyl)-quinone (6,6-diacetoxycyclohexa-2,4-dienone) can be formed in this case too, with a small amount of the *p*-quinol acetate as impurity[180,198]:



The action of lead tetraacetate on mesitol in propionic acid medium yields the quinol propionate[180] instead of the quinol acetate.

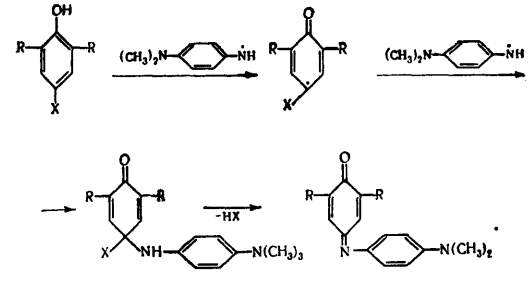
Completely different reaction products are obtained by the action on phenols of acetyl peroxide in acetic acid solution. Thus, for example, mesitol under these conditions gives an 80% yield of the acetate of the corresponding substituted benzyl alcohol[200]:



Mesityl methyl ether does not react with acetyl peroxide in acetic acid, which further confirms the formation of a phenoxy-radical in the course of the above reaction.

The reaction of benzoyl peroxide with phenols has its own peculiarities. It differs from those using lead tetraacetate and acetyl peroxide firstly in that *p*-quinol benzoates are obtained, and secondly in that it is usually accompanied by the formation of large quantities of dimers of the phenoxy-radicals (and of the benzyl radicals in the case of 2,4,6-trialkylphenols). Sometimes one of these reactions may predominate. In the oxidation of mesitol with benzoyl peroxide, for example, a 90% yield of the *p*-quinol benzoate is obtained together with the *p*-stilbenequinone[182]. In the oxidation of Ionol with benzoyl peroxide, a *p*-stilbenequinone derivative was isolated as the sole product of the reaction. 2,4,6-Tri-t-butylphenol reacts with benzoyl peroxide forming the phenoxyl[206].

In 1955 Hünig and Daum[207] published some very interesting work on the formation of quinoamines by the interaction of phenols with radicals obtained by the oxidation of *NN*-dimethylphenylenediamine with potassium ferricyanide. Formation of quinoamines occurs only when the original phenols contains a *p*-alkyl group. In the presence of other groups this radical reaction leads to their replacement by a *p*-dimethylaminoanilino-group. The process occurs as follows:



If X = H, Cl, Br, or even CH_2OH, these groups are eliminated. From mesitol (X = R = CH_3), a 30% yield of the quinoamine is obtained as a salt of perchloric acid. Its structure has been confirmed by elemental analysis and the infra-red and ultra-violet spectra. Reduction of this quinoamine yields mesitol. The quinoamine rearranges readily into 4-aminomethyl-2,6-dimethylphenol. Ionol [X = CH_3, R = $C(CH_3)_3$] and 2,4,6-tri-t-butylphenol [X = R = = $C(CH_3)_3$] form more stable quinoamines than does mesitol.

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The above examples of the formation of cyclohexadienones in electrophilic and radical reactions of phenols may prove useful for an understanding of many of the changes undergone by phenols and their derivatives.

Sterically hindered phenols exhibit an especially marked tendency to form cyclohexadienones. Such phenols display a very specific behaviour also in other reactions, a discussion of which may be of definite interest too.

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USE OF REAGENTS OF THE ARSENAZO–THORON GROUP IN ANALYTICAL CHEMISTRY

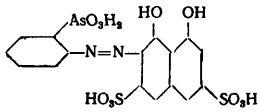
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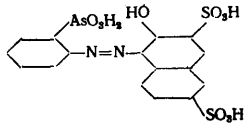
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1. GENERAL REVIEW OF APPLICATIONS

The reagents Arsenazo I [1] and Thoron I [1,2] synthesised by Kuznetsov in 1941 were the first of the general class of reagents of the arsenazo–thoron group:



Arsenazo I



Thoron I

The main use of these reagents is in inorganic spectrophotometric analysis, but they are also used in complexometry, extraction, and coprecipitation methods. More than 40 elements can be detected by reagents of the arsenazo group, and quantitative methods have been developed for the determination of 20 of these in various materials.

Organic reagents containing the arsono-group AsO_3H_2 had previously been used widely in inorganic analysis, the best known being phenylarsonic acid. The presence of the arsono-group causes the formation of particularly stable complexes with several elements, such as zirconium, niobium, and thorium. The reaction products with phenylarsonic acid and many of its derivatives are colourless; the reagents are mainly used for the gravimetric determination of elements or for the removal of interfering elements.

The reagents of the arsenazo group are characterised by the presence of the arsono-group and also an azo-group in the *ortho*-position to it; almost always there is a