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NUCLEOPHILIC REACTIONS OF QUINONES

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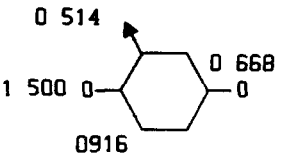
1. INTRODUCTION

Quinones are widely distributed in Nature and are produced by the chemical industry. The principle aspect of the application of quinones is their utilization as organic dyes. Quinonoid compounds are used as dyes, luminophors in colour photography, electrophotography, lasers, photochromic materials, liquid crystal materials, and scintillators.[1–5] The importance of quinones is not however, restricted to the chemistry of dyes. The investigation of the biological activity of quinones is in progress. This is associated not only with the discovery of K-group vitamins but with medicines, herbicides, fungicides and growth-regulating agents as well.[6–16] Quinones are used as analytical reagents, polymer modifiers and reaction catalysts.[17–21] Halogeno- and cyano-quinones are employed in organic synthesis as dehydrogenating agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[22] From the molecular orbital diagram of 1,4-benzoquinone calculated by means of

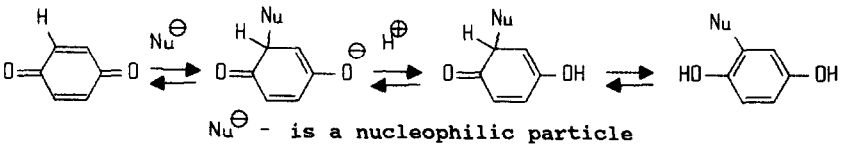


a simple LCAO–MO method, it can be seen that the quinone molecule is very heterogeneous in π-electron density distribution.[23] A wide range of electron density values determines a wide spectrum of chemical reactivity of quinones. Quinones have an important place among homolytic and heterolytic reactions. In this Report one of the most interesting types of the heterolytic reactions will be discussed, namely nucleophilic processes, which exemplify the rich synthetic chemistry of quinones. Electrophilic reactions are restricted, as a rule, to interaction of quinones with hydrogen- and metal-containing reducing agents which transform quinones into hydroquinones or semiquinone complexes.[24–37]

In reviews of quinones, there is practically no information about their nucleophilic and electrophilic reactions.[38–43] This Report discusses the reactions of quinones with nucleophilic agents and gives a summary of the data available from the viewpoint of modern mechanistic ideas.

2. NUCLEOPHILIC ADDITION REACTIONS OF QUINONES

The general scheme of the reaction of 1,4-quinones with nucleophilic compounds is given below. 1,2-Quinones react in a similar way. The final stage results in the formation of a stable aromatic



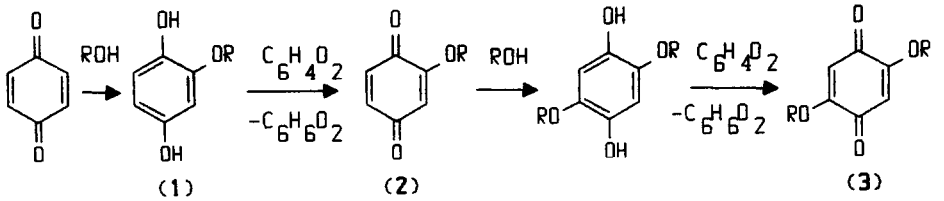
system. In some cases the counter-ion of a nucleophilic particle is not a proton but another electrophile.

By means of the SCF method in STO-3G basis, the coefficients of the highest occupied molecular orbital and the lowest unoccupied molecular orbital (LUMO) of substituted 1,4-benzoquinones and 1,4-naphthoquinones have been calculated. Thus the regularities of the orientating effect of substituents on the nucleophilic addition have been deduced. According to the calculated data for 2-substituted 1,4-benzoquinone, the position actively corresponds to the $5 > 2 > 6$ series in case of donor substituents, and to the $3 > 6 > 5$ series in case of acceptor or unsaturated substituents. The 2- position of 1,4-naphthoquinone is activated by donor substituents at C2 and C6 and by acceptor and unsaturated substituents at C5. The 3-position is activated by donor substituents at C5. *anti*-5-OH Acts as a donor, and *syn*-5-OH as an acceptor.[44] The results of MO calculations are in general agreement with the resonance theory. As will be shown later, they are supported by experimental data, with the exception of the nucleophilic addition to the carbon atom having a donor substituent.

2.1. *Reactions with O-nucleophiles*

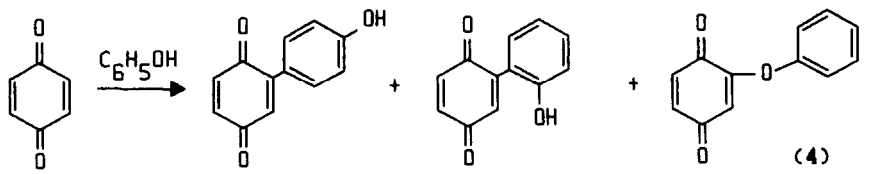
Direct addition of water to quinones resulting in the formation of an adduct is not observed with the exception of a single case of no preparative importance.[45] Primary alcohols react with quinones only in the presence of catalysts, such as zinc, cadmium, calcium and magnesium salts. The reaction with a highly reactive 2-acetyl-1,4-benzoquinone proceeds in the absence of catalysts. The general reaction includes the initial nucleophilic addition of an alcohol to quinone, with the formation of alkoxyhydroquinone (**1**) followed by its subsequent oxidation by the initial quinone

to yield the alkoxyquinone (**2**). Then, one more alcohol molecule is added leading to the formation of 2,5-dialkoxy-1,4-benzoquinone (**3**). Secondary alcohols react with quinones in exceptional cases.



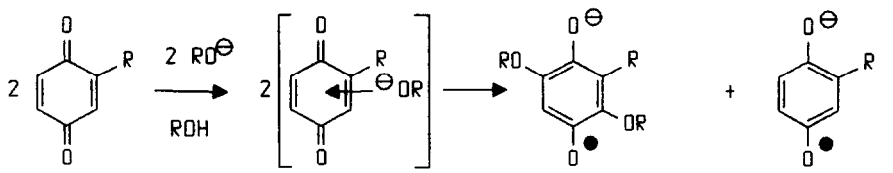
(1) (2) (3)

The tertiary alcohols do not react. In the course of the reactions of phenols with quinones, mostly C-arylated quinones are formed. The yield of aryloxylation products (**4**) is not more than 5%.[45]



(4)

Kinetic studies of the reactions of 1,4-quinones and alcoholate in alcohol showed the initial formation of a charge-transfer complex (**5**) between 1,4-quinone and alcoholate with its subsequent transformation into semiquinone radicals.[46] In the absence of a catalyst, 1,4-benzoquinone does not react



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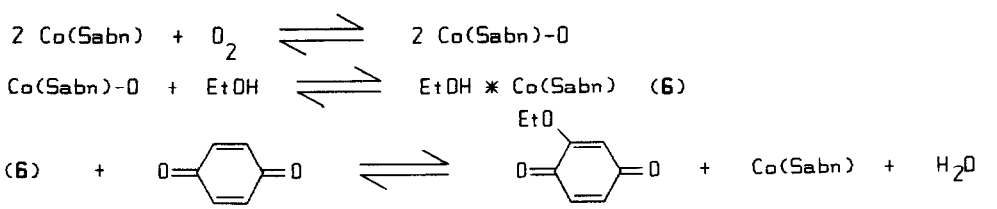
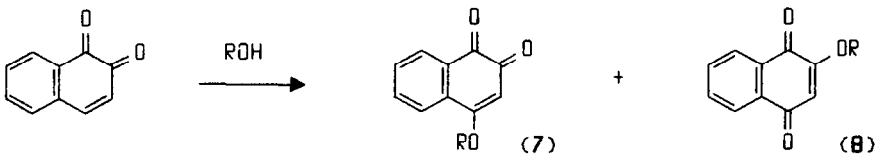
with ethyl alcohol. In the presence of cobalt bis-(N,N-salicylidenethylenediaminate) [Co(Sabn)] and oxygen, the reaction proceeds easily. The process is thought to be carried out in three stages. The



rate of the reaction is determined by the last step. The Co(Sabn) complex with O_2 (2 : 1), in both a solid state and in alcoholic solutions is considered to be a dimer having a Co—O—O—Co bond. To break the O—O bond with the formation of the complex (**6**), then attack by the alcohol on the Co atom is necessary. This attack is impeded by the production of an alkoxyl radical, and by steric hindrance. The reaction of Co(Sabn) with alcohols along with the reversible formation of a complex, has been proven by NMR spectroscopy. The addition of chloroform or benzene, producing a stable adduct with Co(Sabn), which is also capable of bonding with Co(Sabn), results in the substitution of oxygen from the active complex and retardation of the reaction.[47] Boron trifluoride is used for the catalysis of reactions of quinones with alcohols. With the $BF_3 \cdot MeOH$ complex, the introduction of a methoxyl group onto substituted 1,4-benzoquinones can be successfully performed.[48]

1,4-Naphthoquinones having donor substituents in 5- and 8-positions, react with alcohols with the formation of 2-alkoxy-substituted 1,4-naphthoquinones. Sulfuric acid with an iron sulfate additive is used as a catalyst.[49]

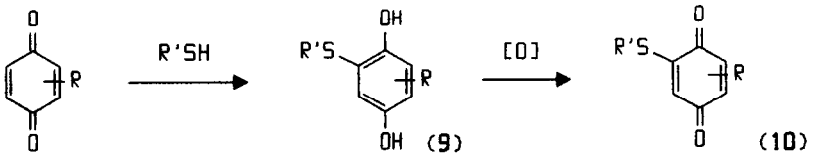
1,2-Quinones and 1,4-quinones react with alcohols in the presence of catalysts. The authors[50] studied the influence of mixtures of sodium iodate and metal salts such as $CoCl_2$, $CoCl_26H_2O$, $CuCl_2$, $CuCl_22H_2O$, $LaCl_27H_2O$, $CeCl_27H_2O$ on the reaction of 1,2-naphthoquinone with alcohols. The yields of 4-alkoxy-1,2-naphthoquinone (**7**) increases from left to right: for the catalysts $CoCl_2$and $CeCl_27H_2O$, the yields are 3% and 79% respectively. In the absence of catalysts, the quinone (**7**) is not formed. With increase of the time and temperature of the reaction, then 2-alkoxy-1,4-naphthoquinone (**8**) is formed with quinone (**7**).



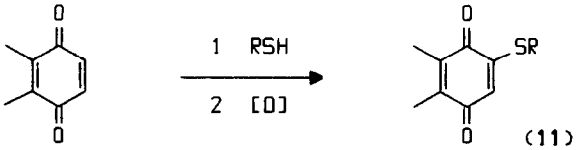
Acenaphthenequinone and *o*-pleiadienequinone and alcohols yield the corresponding quinone acetals.[51]

2.2. *Reactions with* S-*nucleophiles*

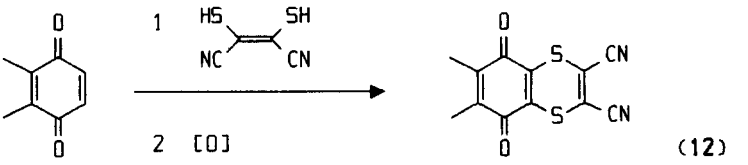
2.2.1. *With thiols.* Thiols and thiophenols react with 1,4-quinones forming the products (**9**) which are then oxidised by air or by the initial quinones giving the corresponding alkylthio- and arylthio-quinones (**10**). If a thiol is used in excess then the products containing thiol groups in various



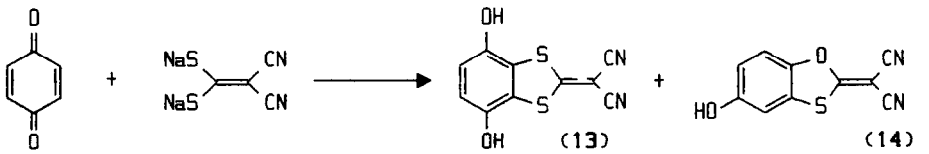
positions are formed. The following features are observed. Quinones with donor substituents produce mainly 2,5-isomers. Quinones with acceptor substituents produce 2,3-isomers. In both cases 2,6-isomers are also formed. 1,4-Quinones having side-chain alkylthio- and arylthio-groups attract the attention of microbiologists and medicinal chemists because these compounds have a high biological activity. The reaction products of 2,3-dimethyl-1,4-benzoquinone with thiophenols have an inhibiting effect on succinoxidase and NADH-oxidase enzymes: the best result was displayed by compounds (**11**, R = 2-naphthyl).[52]



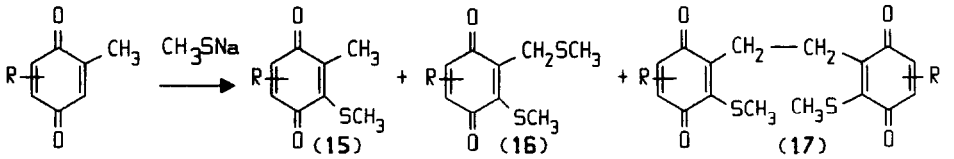
Substituted naphthoquinones were found to have an antibacterial activity.[53,54] The reactions of thiols with quinones consist of two stages, addition and oxidation. Reactions of dithiols include 4 stages (i) addition of the mercapto group to quinone (ii) oxidation of the intermediate (iii) a addition of another mercapto group (iv) oxidation giving the final product. The dinitrile of 2,3-dimercaptomaleic acid reacts with 2,3-dimethyl-1,4-benzoquinone forming a derivative of 1,4-dithia-5,8-dioxo-tetrahydronaphthalene (**12**).[55] Metal dithiolates show more complex reactions with quin-



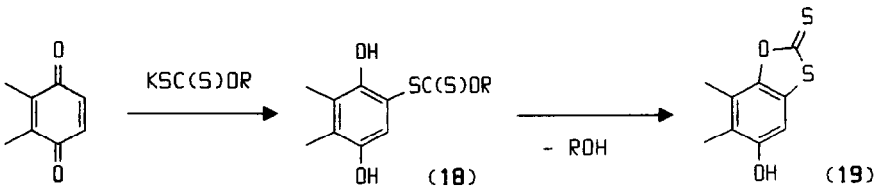
ones. The reaction products are heterocyclic compounds (**13**, **14**) obtained in yields of 40% and 20%, respectively.[56] Metal thiolates are very reactive nucleophilic agents so their reactions with



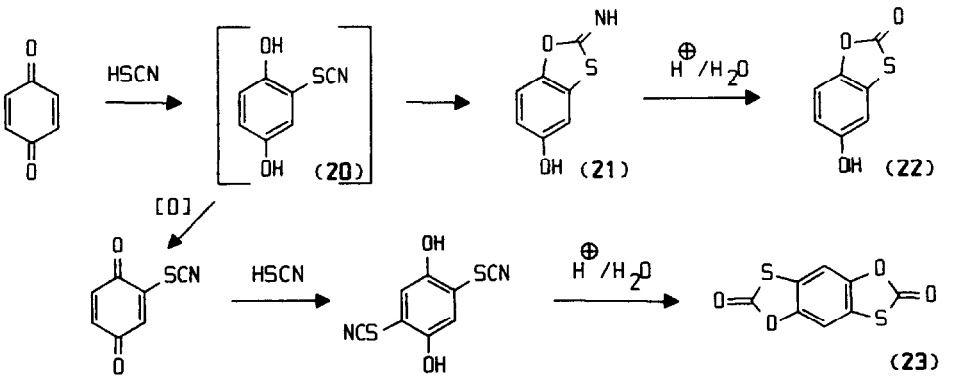
quinones are far less selective than those of thiols. The main reaction products of sodium methanethiolate with methyl-substituted quinones are those of addition-oxidation (**15–17**) and side-chain substitution (**16**, **17**).[57,58] Sulfides, are relatively inert towards quinones. However, the activation of the latter with a 70% sulfuric acid results in the formation of (sulfonio)hydroquinone.[45,59]



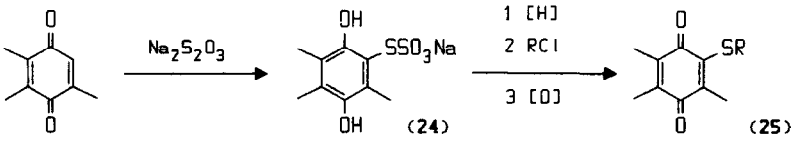
2.2.2. *With thiol acids.* 1,4–Quinones react with dithiocarbonic acids and their salts. Reaction with potassium O-alkyl dithiocarbonate yields the product (**19**), the precursor of which is 1,4-adduct (**18**).[45]



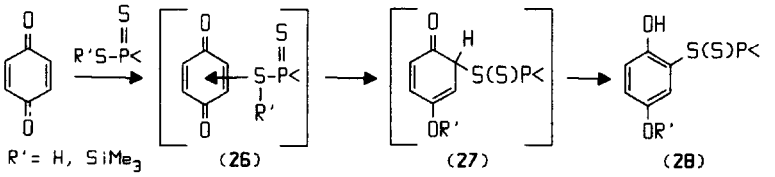
The reaction of thiocyanic acid with 1,4-benzoquinone yields benzo-1,3-oxathioles (**22**, **23**). Depending upon the reaction conditions, then products (**21**), (**22**) or (**23**) are obtained.[60]



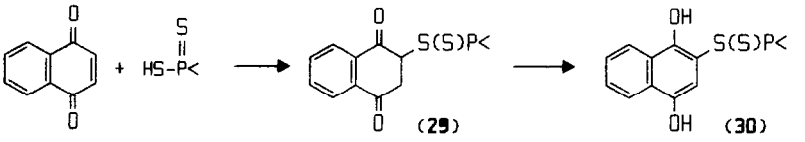
Thiol sulfur is the nucelophilic center of a thiosulfate, thus reaction of sodium thiosulfate with quinones yields sulfothiohydroquinone (**24**) which in some cases can be used for the synthesis of alkylthio-1,4-benzoquinones (**25**).[45]



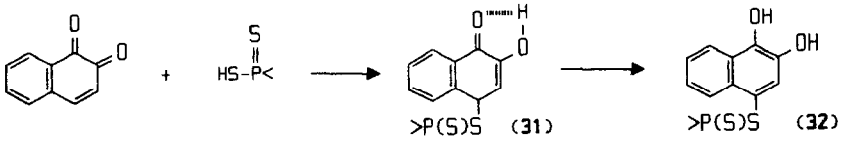
The reaction of dithiophosphoric acids and their trimethylsilyl esters with quinones is of interest. Study of the reaction by kinetic and spectrophotometric methods showed that at first the formation of a n–π type complex (**24**) takes place. Complex (**24**) is then transformed into an intermediate (**27**) and subsequently into a final adduct having 1,4-structure (**28**). The reaction with 1,4-naphthoquinone



proceeds similarly. At first the product of addition to the C=C bond of the quinone (**29**) is formed.

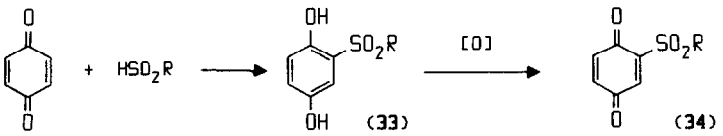


Quinone (**29**) is subsequently transformed into a thiophosphorylated dihydroxynaphthalene (**30**). Reaction of phosphorus dithioacids with 1,2-naphthoquinone have a rather peculiar character. Recorded by IR spectroscopy method, the intermediate (**31**) in the course of time isomerizes giving a final product of 1,4-addition (**32**). The stability of the enol form of the intermediate compound



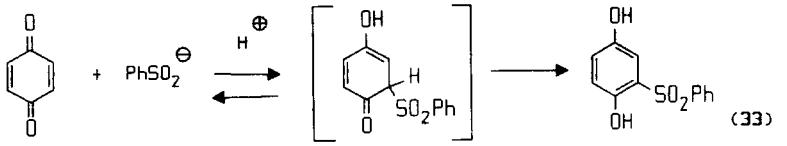
(**31**) causes a gain in the systems energy at the expense of formation of a stable intermolecular H-complex.[61-63]

2.2.3. *With sulfinic acids and sulfites.* The nucleophilic addition of sulfinic acids to 1,4-benzoquinone proceeds easily in the absence of catalysts yielding 2,5-dihydroxyl-1-alkyl(aryl)-sulfonylbenzenes (**33**) which can then be transformed into corresponding sulfonylquinones (**34**). Using



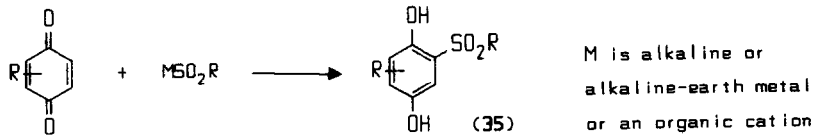
kinetic-isotope investigations, the mechanism of the reaction of a phenylsulfinic acid with 1,4-

benzoquinone in an aqueous medium has been established. At first, the reversible addition of a sulfinate anion of the acid to the quinone takes place giving an unstable adduct which is then isomerized giving the final sulfonylhydroquinone (**33**). The kinetics of the reaction is described by



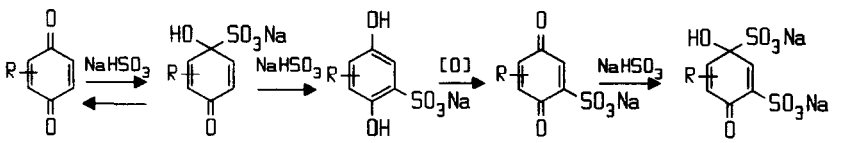
(33)

a second order equation, while each agent is described by a first order equation. Depending on the pH value of the medium, the rate-determining step of the reaction changes. At a pH below 3.1, it is that of addition. At a pH higher than 4.0, it is that of isomerization.[64] The sulfinic acid salts are stronger nucleophiles than the acids themselves. They react with quinones forming sulfonylhydroquinones (**35**).[65]



(35)

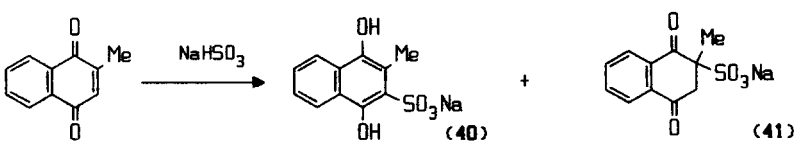
Chloromethanesulfinic acid, hydroxymethanesulfinic acid and other sulfinic compounds react with 1,4-benzoquinone producing unstable adducts which then undergo intra- and inter-molecular condensation reactions yielding the corresponding sulfones.[45] The mechanism of the reaction of sodium bisulfite with 1,4-benzoquinones includes rapid reversible formation of the adduct (**36**) and the subsequent addition of a bisulfite anion to the latter, resulting in the production of final sulfohydroquinone (**37**).[66,67]



(36) (37) (38) (39)

The investigation of the reaction in buffer solutions at pH 5–10 shows that the compound (**39**) which has a high reducing power is formed in the reaction mixture. Because its redox potential is more negative than that of hydroquinone, the compound (**39**) plays an important role in the function of a hydroquinone developer. The compound (**39**) is thought to be produced by oxidation of sulfohydroquinone (**37**) and subsequent addition of sodium bisulfite to the carbonyl group of the quinone (**38**).[68]

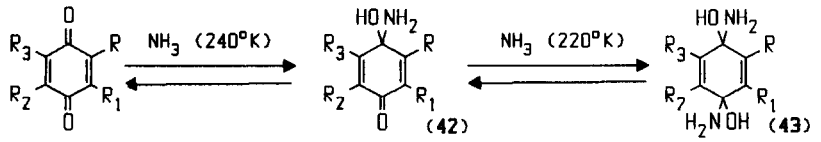
In the reaction of sodium bisulfite with 2-methyl-1,4-naphthoquinone, the product of normal 1,4-addition (**40**) and the 1,2-adduct (**41**) are formed. 1,2-Adduct (**41**) is formed as a result of rare nucleophilic addition to the substituted carbon–carbon double bond of quinone.[68]



(40) (41)

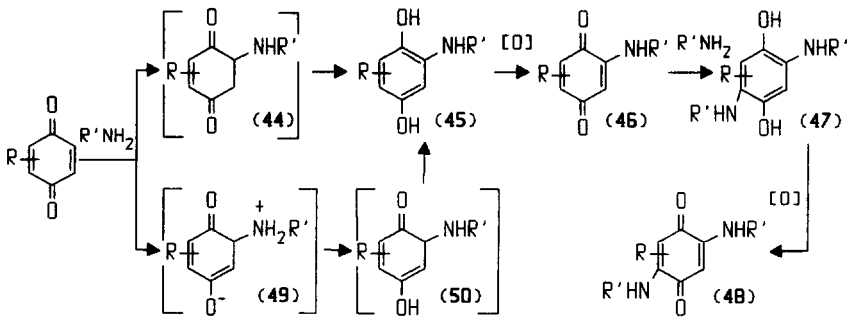
2.3. *Reactions with* N-*nucleophiles*

Ammonia gas reacts with unsubstituted quinones producing amorphous products of unknown structure. Liquid ammonia reacts with substituted 1,4-benzoquinones at 240°K and produces adducts of 1 : 1 composition (**42**). When the temperature of the reaction mixture is 220°K, the di-adduct (**43**) is formed. This reaction is reversible: the introduction of methylene chloride and subsequent evacuation of ammonia yields the initial 1,4-benzoquinone.[69]



Nucleophilic addition of a hydrogen azide to 1,4-quinones is the principle method of production of azidoquinones which can then be employed for the synthesis of aminoquinones.[45,64]

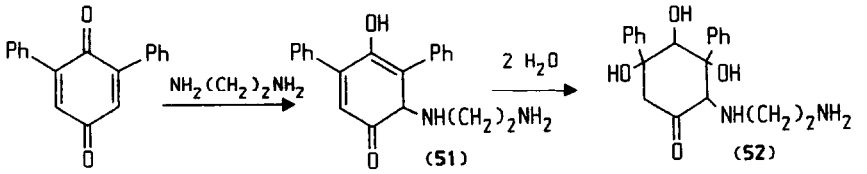
2.3.1. *With primary amines.* 1,4-Benzoquinones react with primary aliphatic amines forming 2,5-diamino-1,4-benzoquinones (**48**) which are produced by oxidation of intermediate 2,5-diamino-hydroquinones (**47**). It is not possible to obtain the initially formed products of mono-amination (**45**, **46**)[70] and 2-amino-1,4-benzoquinone is still unknown.

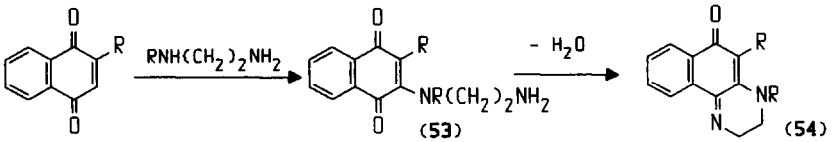


The reaction mechanism includes initial addition of an amine to a carbon–carbon double bond with the formation of the intermediate (**44**). This is then isomerized giving the aminohydroquinone (**45**) which is subsequently oxidized to the monoaminoquinone (**46**). The addition of the second amine molecule produces the diaminoquinone (**48**).[45] In our opinion, the initial stage of the reaction comprises the formation of a dipolar product (**49**), which is then isomerized to the hexadienone (**50**) and then to the aminohydroquinone (**45**). This kind of reaction scheme conforms to the generally accepted view of the mechanism of nucleophilic addition to unsaturated carbonyl compounds.[71]

The reaction of 1,4-naphthoquinones with aliphatic amines results in the formation of 2-amino-1,4-naphthoquinones. If hydroxyl substituents are present in 1,4-naphthoquinone, then addition-oxidation along with substitution takes place. 5,8-Dihydroxy-1,4-naphthoquinone reacts with butyl-amine in the presence of copper(II) chloride giving the main product [2 (or 3), 8-bis(butylamino)]-5-hydroxy-1,4-naphthoquinone.[72]

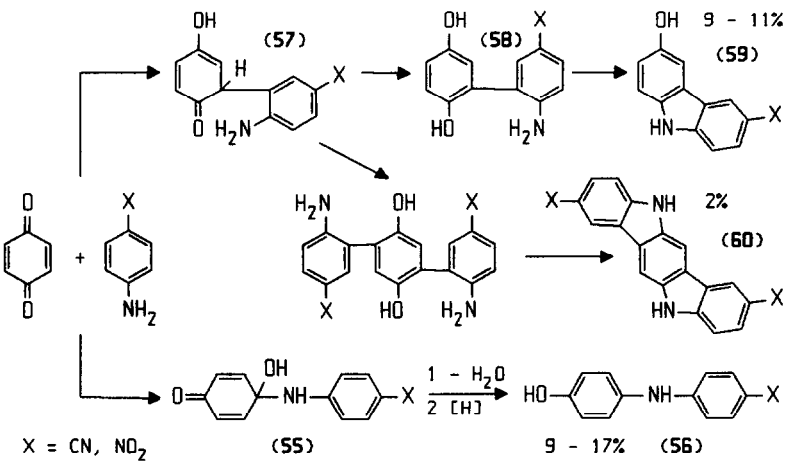
The reactions of 1,4-quinones with aliphatic diamines result in the formation of products having conventional structures. During the reaction of 2,6-diphenyl-1,4-benzoquinone with 1,2-diaminoethane, the intermediate cyclohexadienone (**51**) is formed. The addition of two water molecules finally gives the cyclohexanone (**52**). Similar products are obtained in the case of 1,6-diaminohexane and piperazine.[73] 1,4-Naphthoquinone and diamines at first produces the product of 1,4-addition (**53**). Compound (**53**) is transformed into a cyclic quinone–imine (**54**).[74]



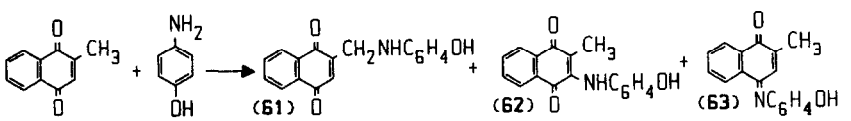


For nucleophilic addition to quinones, aromatic amines are less active than aliphatic amines. Due to a relatively inert nature of aniline, it is possible to obtain 2,5-dianilino-1,4-benzoquinone.[45]

Studying the reaction of substituted anilines with quinones (Nenitzescu reaction), the authors encountered the formation of several compounds.[75] The following scheme is proposed for the formation of the final products (**56**, **59**, **60**).



During the reaction of 2-methyl-1,4-naphthoquinone and *p*-aminophenol, several products (**61**), (**62**) and (**63**)[76,77] are formed.

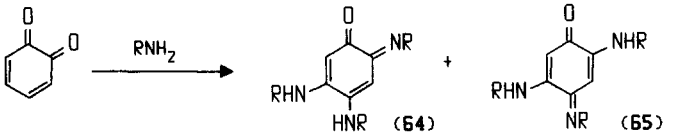


2,6-Disubstituted 1,4-benzoquinones, where the addition to 1,4-position due to steric or electron hindrances is not possible, react with primary aromatic amines by a condensation reaction.[45,78]

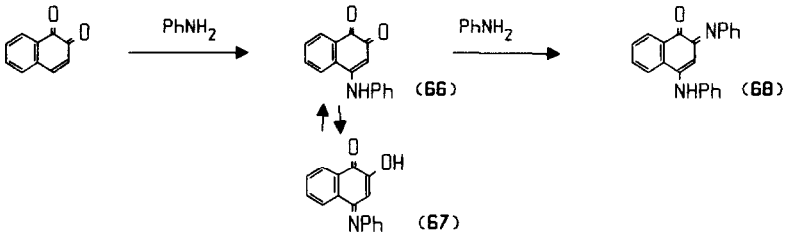
1,2-Quinones, as well as 1,4-quinones, vigorously react with aliphatic and aromatic amines. However, there exists a reaction that can be used to distinguish between 1,2-quinones and 1,4-quinones. Reacting with *o*-phenylenediamine, substituted 1,2-quinones form phenazine condensation products. For 1,4-quinones, such a process is impossible. In the case of unsubstituted

1,2-benzoquinone, condensation is not carried out. Instead, a chain of addition–oxidation reactions occurs with the subsequent formation of a cycloadduct.[45,64]

The reaction of 1,4-addition of amines is generally for unsubstituted 1,2-quinones. The reaction proceeds satisfactorily in the case of aromatic amines but it is complicated by a competing condensation process in case of aliphatic amines. For instance, 1,2-benzoquinone with methyl-, ethyl-, propyl- and butyl-amines forms two types of products (**64**) and (**65**).[79] 1,2-Naphthoquinone and its



substituted derivatives react with primary aliphatic amines producing a number of compounds, the most important of which are derived from substitution and condensation reactions.[80] Aniline is added to 1,4-position of 1,2-naphthoquinone, which upon subsequent air oxidation produces 4-anilino-1,2-naphthoquinone (**66**) which is the only final product of the reaction. If the reaction is

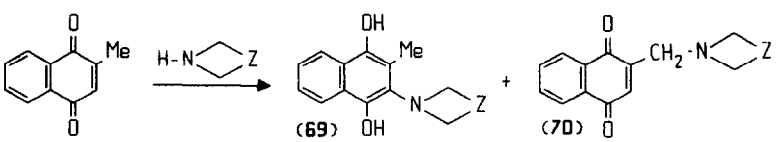


carried out under certain conditions, then one more aniline equivalent can be added yielding the quinone imine (**68**). It has been proved that substituted 1,2-quinone (**66**) in the solid state and in alcohol solution is in the quinonoid form. However in trifluoroacetic acid solution it is in the 1,4-quinone-imine form (**67**).[81] The reactions of 1,2-quinones with amines have been successfully used for the synthesis of compounds having complex structures. Condensation of equimolar amounts of *o*-aminothiophenol with substituted 1,2-benzoquinone in the presence of ferric chloride results in the formation of phenothiazines.[82]

Quinone imines with various substituents have been obtained according to the reaction of 4-substituted 1,2-naphthoquinones with ethylenediamine.[83]

4,4′-Di(1,2-naphthoquinone) react with aromatic amines as well as other 4-substituted 1,4-naphthoquinones, forming condensation products on the carbonyl group in position-2.[84,85]

2.3.2. *With secondary amines.* In general, secondary amines (C_1–C_4) produce monoamino-substituted 1,4-benzoquinones. During the reaction of 1,4-benzoquinone with heterocyclic amines, 2-substituted hydroquinones are formed. These hydroquinones are then air oxidized yielding the corresponding quinones.[86] 2-Methyl-1,4-naphthoquinone combined with pyrrolidine, piperidine, heptamethylene imine producing stable 1,4-adducts (**69**) and products of methyl group hydrogen substitution (**70**).[87] The investigation of the reaction of quinones with secondary amines has pro-



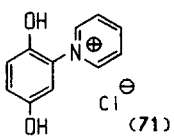
duced the impetus for the study of the chemistry of biologically active quinones. The reactions of 1,4-

benzoquinone, 2-methyl-1,4-benzoquinone, 2-methyl-1,4-naphthoquinone and other 1,4-quinones with amines having psychopharmacological activity such as desipramine, nortriptyline, protriptyline and benzoctamine have been examined and biologically active aminoquinones have been obtained.[88-91]

1,2-Quinones add secondary amines causing the formation of 1,4-adducts. These adducts are then air oxidized yielding 4-amino-1,2-benzo(naphtho)quinones.[45]

2.3.3. *With tertiary amines and pyridine.* Tertiary amines, in contrast with the reactions of primary and secondary amines with quinones do not form products of nucleophilic addition. Nevertheless, they do react with quinones and produce 1 : 1 or 1 : 2 with charge-transfer complexes. In certain cases, the complexes were obtained and characterized.[92] More often, however, they were studied by spectral methods. Spectral bands of the complexes refer to n–π transition from the highest occupied molecular orbital (HOMO) of a donor (amine) to the lowest unoccupied molecular orbital (LUMO) of an acceptor (quinone). The stability of these complexes greatly depends on the donor–acceptor properties of the quinone–amine pair.[93]

Our interest has also been drawn to the reaction of quinones with pyridine which yields products having a dipolar structure. In the presence of hydrochloric acid, 2-pyridino-hydroquinone chloride (**71**) is formed. Similar adducts are formed by the reaction between quinones and quinoline. Quinaldine, and *p*-benzoquinone yields (**72**).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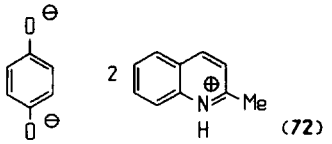
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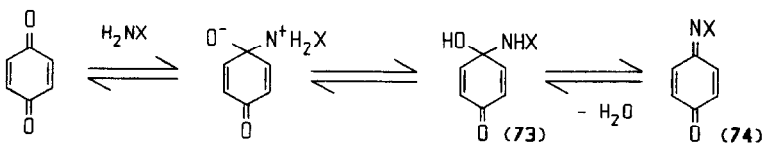
Charge-transfer complexes are obtained not only in the reactions with tertiary amines, but in the reactions with other amines such as aniline, toluidine, ethylamine, diethylamine, piperidine and polyvinylpyridine.[94-96]

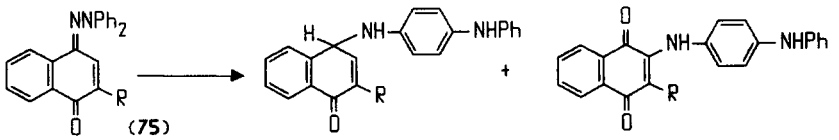
The general reaction scheme of nucleophilic addition of amines to quinones, considered in Section 2.3.1, can be supplemented with a charge-transfer complexing stage. It should, however, be emphasized that complexing has not been identified in all the reactions of amines with quinones.

2.3.4. *With cyanamide, hydroxylamine, hydrazines and hydrazides.* In this section, N-nucleophiles of the general formula H_2NX, where X is CN, OH, NRR, NHC(O)R and $NHP(O)R_2$, are discussed. In reactions with quinones, they are not added to the conjugated system, —C=C—C=O, but to the carbonyl group. The reaction scheme includes a number of reversible stages. The key stages are the nucleophilic addition of a nitrogen atom to a carbon of the carbonyl group, which results in the formation of the quinol (**73**) and the quinone imine (**74**).

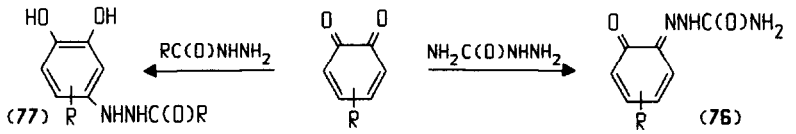

(73) (74)

Quinones do not react with cyanamide, but with silicone derivatives.[97] Hydroxylamine transforms quinones into quinone mono- and di-oximes, which are of interest in that they can be used for the synthesis of aromatic dinitroso compounds.[98] The reactions of hydrazine derivatives with 1,4-quinones yield mono- and di-hydrazones of the quinones.[99] In certain cases, particularly during the reactions with phenylhydrazine, redox processes are observed.[100-103] Of special interest is the

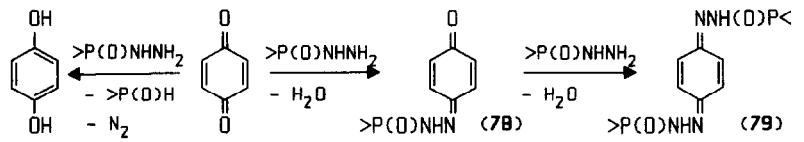
reaction of 1,4-naphthoquinones with diphenylhydrazine when the condensation products (**75**) undergo semidine and prototropic rearrangements.[104,105]



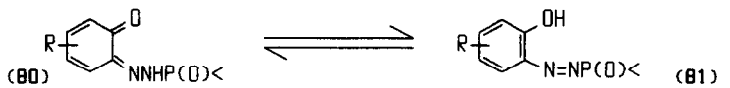
The structure of the reaction products of hydrazine derivatives with 1,2-quinones is determined by reagent structure. 1,2-Quinones are reduced to pyrocatechols. Acyl hydrazines transform 1,2-quinones into 1,2-dihydroxy-3-acylhydrazino-benzenes (**76**). Reaction with semicarbazides and thiosemicarbazides, yields semicarbazones (**76**).[45]



Reactions of quinones with phosphorylated hydrazines are peculiar. When the reaction is carried out under mild conditions, condensation with the formation of phosphorylated hydrazones of quinones (**78**, **79**) takes place. At temperatures above 20°C in polar solvents, a redox reaction occurs



resulting in the formation of hydroquinone, phosphorous acids and nitrogen.[106–108] In the case of 1,2-quinones, products of monohydrazone structure (**80**) are formed. Probably due to steric hindrance, it



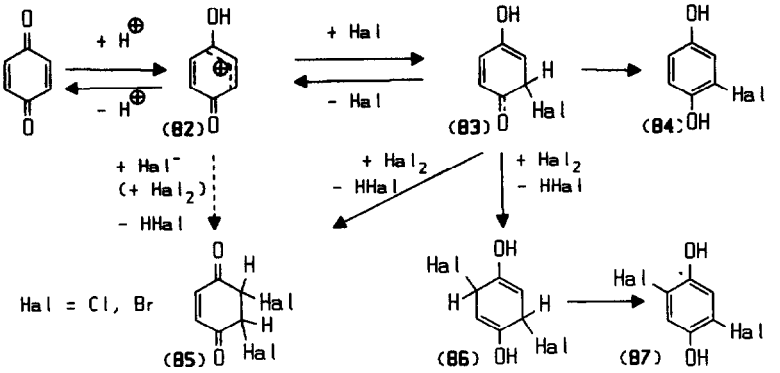
is not possible to obtain dihydrazones. It has been established that the decisive factors affecting the quinone hydrazone–azophenol equilibrium state (**80** ⇋ **81**) are the nucleophilic properties of the medium and the nature of substituents in the quinonoid residue.[109]

An intensive study of bioactive compounds is being carried out in the hydrazone series of quinones. Of particular interest is the synthesis of 4-aryl(aroyl)-hydrazones of 1,4-naphthoquinones which have antibacterial and perhaps antitubercular activity.[110]

2.4. *Reactions with halogeno-nucleophiles*

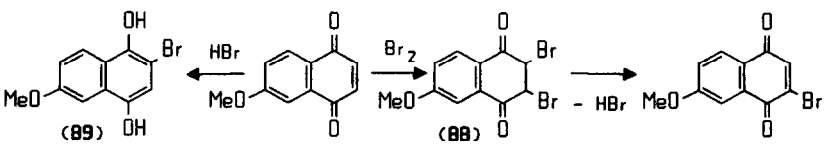
Hydrogen iodide is not added to quinones. It reduces the quinones to hydroquinones. Other hydrogen halides react with quinones according to the scheme of 1,4-addition forming halogeno-hydroquinones (**84**).[111]

At the beginning of the reaction, protonation of quinone and formation of a cation (**82**), which is attacked by a halide anion and transformed into an 1,4-adduct (**83**) take place, the subsequent isomerization of which finally produces halogen substituted hydroquinone (**84**). If a halogen molecule

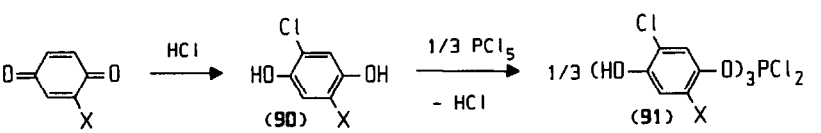


is present in the reaction mixture, the adduct (**83**) is capable of adding one more halogen atom, with the subsequent formation of dihalogeno-quinone (**85**) or the cyclohexadiene (**86**). They are finally stabilized in the form of the dihalogeno-hydroquinone (**87**). It is noted that the preferred sequence (**82**) → (**83**) → (**84**) compared to the sequence (**82**) → (**83**) → (**86**) → (**87**) is associated with less steric hindrance.[111]

In this section, it is important to dwell on reactions of quinones in which the key stage of the processes, in spite of the participation of electrophilic reagents, is that of nucleophilic addition. For instance, during the reaction of 6-methoxy-1,4-naphthoquinone with bromine, the adduct (**88**) and the nucleophilic addition product (**89**) are both formed. (**89**) Is obtained from the initial quinone and hydrogen bromide.[112] A similar phenomenon is observed upon the reaction of phosphorus



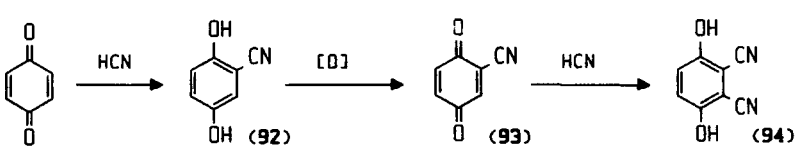
pentachloride with 1,4-benzoquinones. The reaction involves an autocatalytic chain process with an initial stage consisting of the addition of a hydrogen chloride to the quinone. Chlorohydroquinone (**90**) is formed and this subsequently condenses with phosphorus pentachloride, producing the



dichlorophosphorane (**91**) and hydrogen chloride. Hydrogen chloride is then added to the initial quinone starting a new chain of transformations.[113,114]

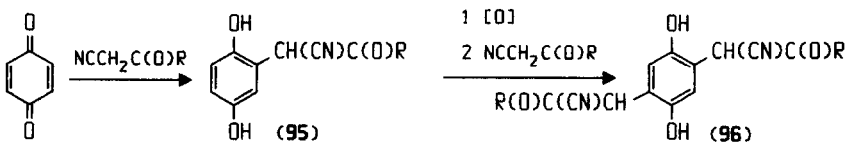
2.5. *Reactions with* C-*nucleophiles*

2.5.1. *With* C–H *acids*. Hydrogen cyanide adds to 1,4-benzoquinone, forming the adduct (**92**). It may subsequently be oxidized to the cyano-quinone (**93**). The reaction of the second molecule of

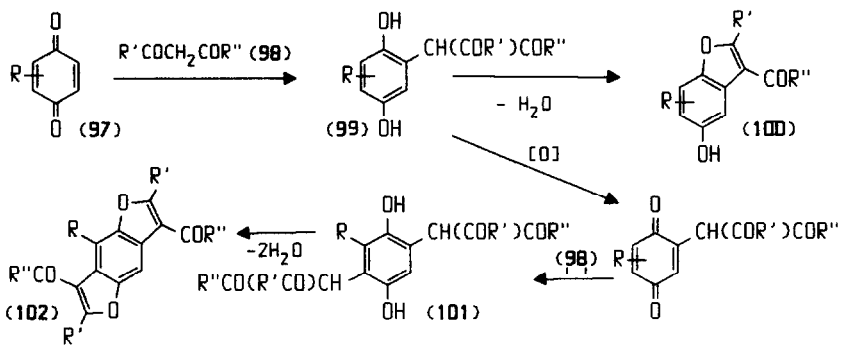


the hydrogen cyanide with the cyano-quinone (**93**) proceeds in an unusual manner. Usually, all of the reactions of monosubstituted 1,4-quinones are accompanied by nucleophilic addition to the 5-position (*para*-position in respect to the substituent). In this reaction, the cyano group enters the 3-position of cyano-quinone (**93**) yielding quinone (**94**). Literature does not give any conclusive explanation for the unusual regioselectivity of the reaction. This reaction is nevertheless very valuable as it provides for the production of the dicyano-quinones, including organic oxidizing agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[115]

The most studied types of C—H acids involved in the reactions with quinones are compounds with an activated methylene group. Carbonyl and nitrile substituents are frequently employed as activators. The reaction involves 1,4-addition of acylcyanomethane to quinone and isomerisation

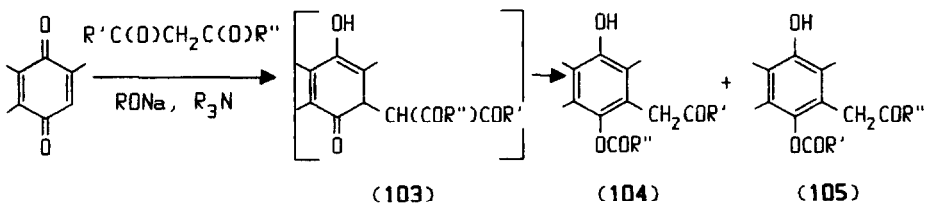


of the adduct. This initial product (**95**), as a result of oxidation and subsequent addition of the second nucleophilic molecule, can then be transformed into the 2,5-dialkyl-hydroquinone (**96**).[116,117] Some reaction products undergo intramolecular cyclization forming indoles and furans.[117,118] A similar scheme takes place in the reactions of quinones (**97**) with 1,3-dicarbonyl compounds (**98**) and their derivatives. At first, the 1,4-adduct (**99**) is formed, whose further transformations are associated with dehydration and cyclization processes [furan (**100**)] or, with oxidation–addition [adduct (**101**)], and subsequent dehydration and cyclization [difuran (**102**)].[119,120]

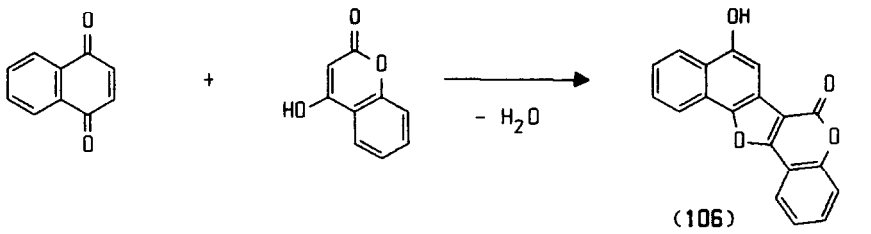


Other processes are also observed. During the reaction of 1,4-benzoquinone with acetylacetone imine, an indole, having a methoxyl substituent on the benzene ring, is unexpectedly obtained.[121]

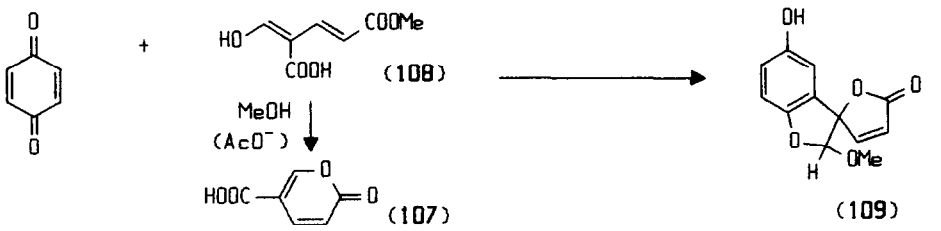
In the presence of strong bases, the reaction of substituted 1,4-benzoquinones with 1,3-diketones proceeds not with the formation of the adduct (**99**), but yields the substituted phenols (**104, 105**). This phenomenon could be attributed to acyltropic transformation of the intermediate (**103**).[122–125]



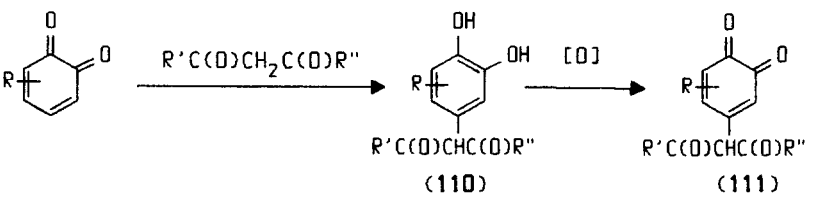
Of unusual interest is the reaction of 4-hydroxy-coumarin, with 1,4-naphthoquinone yielding



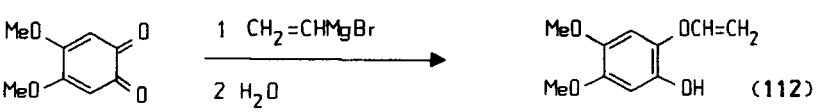
the furan (**106**).[126] 1,4-Benzoquinone and coumalic acid (**107**) with methanol, sodium acetate and acetic acid yields the spirobutenolide (**109**).[127]



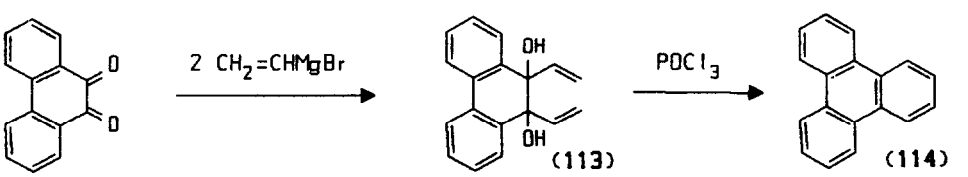
1,2-Quinones, like 1,4-quinones, react with C–H acids and form adducts (**110**). Unlike 1,4-quinone adducts (**99**) which are capable of various transformations, these products (**110**) are oxidized to the corresponding 1,2-quinones (**111**).[128–130]



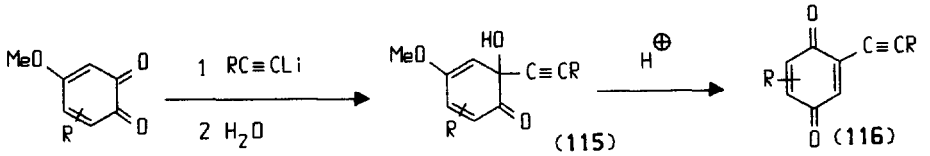
2.5.2. *With organometallic compounds.* Grignard reagents react with quinones according to the nucelophilic addition scheme. The addition of organometallic compounds to quinones leads specifically to attacks on one or on both carbonyl groups of the quinone. During the reaction of vinyl magnesium bromide with 4,5-dimethoxy-1,2-benzoquinone, an adduct is formed which by hydrolysis yields pyrocatechol vinyl ether (**112**).[131] Reaction of vinyl magnesium bromide with



phenanthrenequinone, yields the di-vinyldiol (**113**). Diol (**113**) is subsequently transformed into triphenylene (**114**) by heating with phosphorus oxychloride. It is possible to employ the above reaction for the synthesis of polycyclic hydrocarbons.[132]



Lithium acetylide yields the cyclohexadienones (**115**). Upon acid hydrolysis the compounds (**115**) are transformed into alkynylquinones (**116**).[133,134]



Thus organometallic compounds, add to quinonoid carbonyl groups giving isolable intermediates.

2.6. *Reactions with* P-*nucleophiles*

Practically all the derivatives of 2-, 3- and 4-coordinated phosphorous acid with the phosphorus atom being a reaction center, react with quinones according to the scheme of nucleophilic addition. The structures of adducts are quite diverse and depend upon a number of factors including the nature of substituents in reagents. The most complete and detailed information on the reactions of organo-phosphorus compounds with quinones can be found in reviews.[135]

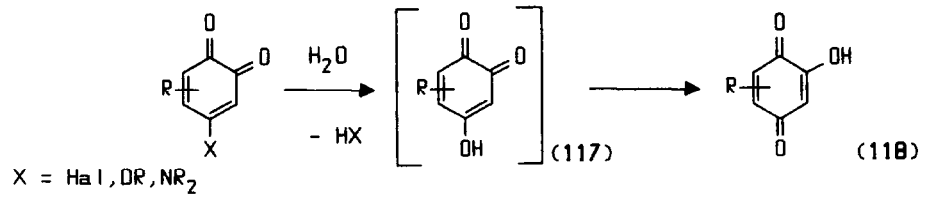
3. NUCLEOPHILIC SUBSTITUTION REACTIONS OF QUINONES

The reactivity of quinones in the reactions with nucleophilic reagents is determined mostly by the π-acceptability of quinones. π-Acceptive properties of molecules are greatly dependent on the energy and symmetry of the LUMO. Energy characteristics of LUMO are determined by its electron affinity. One of the methods of increasing electron affinity is through the complexing process.[136–149] For instance, in gallium dichloride and aluminium chloride complexes of 1,4-benzoquinone, the LUMO structure does not change. The LUMO energy decreases from 0.15 eV to -1.7 eV,[145] resulting in the increase of the reactivity of quinone during nucleophilic reactions. In chemical practice, quinone complexes with a proton, Lewis acids[137,141,142] and metal ions[139,140,147] are employed. However, this method has not yet been developed. Another way of increasing electron affinity involves the introduction of suitable substituents. It is known that the value of electron affinity of unsubstituted 1,4-benzoquinone is comparatively small (1.9 eV).[146] Alkyl substituents decrease electron affinity (e.g. duroquinone 1.59 eV), whereas halogens and especially the cyano group distinctly increase its value (e.g. chloranil 2.78; bromanil 2.50; tetracyano-1,4-benzoquinone 3.40 eV).[64,146] In nucleophilic reactions therefore halogeno- and pseudohalogeno-quinones are the most reactive quinones. As nucleophilic reagents, neutral agents with a vacant electron pair and anions can be used. Next to halogens and pseudohalogens, other electron-acceptor groups capable of polarizing a C—X bond, can be employed.

3.1. *Reactions with* O- *and* S-*nucleophiles*

A classic example of nucleophilic substitution of quinones is the hydrolysis of halogen quinones resulting in the formation of hydroquinones. The replacement of a halogeno-substituent by a hydroxyl group proceeds most favourably in the presence of alkalies or pyridine. Acid-catalyzed hydrolysis is seldom performed. The completion of the reaction depends upon the effect of substituents in the quinone. Catalytic hydrolysis of substituted quinones proceeds rapidly and selectively.

In the presence of aqueous sodium hydroxide, chloranil is hydrolysed. If desired, mono- and di-substituted hydroxyquinones can be obtained. Bromanil and fluoranil react in a similar way during hydrolysis. In iodanil only one halogen atom is substituted.[150] Quinones containing alkoxy, aryloxy, alkylthio- and arylthio-groups as substituents, have a catalytic reaction with water: exchange of the substituent for a hydroxyl group takes place. 1,2-Quinones are hydrolyzed in a different way. The



initially formed hydroxy-1,2-quinone (**117**) is spontaneously transformed into the more energetically advantageous hydroxyl-1,4-quinone (**118**).[45] As a rule, the reaction of halogeno-quinones with alcohols and phenols takes place in the presence of catalysts such as alkaline metal alkoxides, phenolates, or alkalies. Alkoxylation or aryloxylation of quinones usually takes place, but hydrolysis and formation of hydroquinone can sometimes be observed.[151-153]

The alcoholysis of 2,3-dichloro-1,4-naphthoquinone was first investigated in the last century. This type of reaction is still used today especially for the synthesis of crown ethers with naphthoquinonoid residues.[152,153]

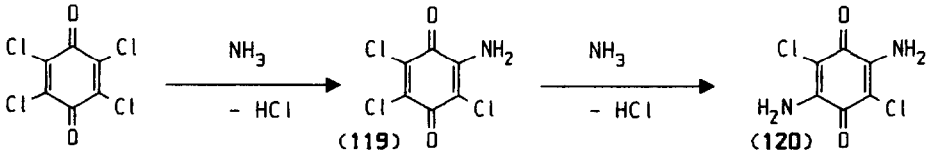
The reaction of substituted quinones with thiols and thiophenols is useful in synthesis, since it yields quinones with the sulfur-containing substituent in a known position. In the reactions with thiols, alkaline conditions are employed, whereas, in case of thiophenols, there is no need for catalysts.[45,64,154]

3.2. *Reactions with* N-*nucleophiles*

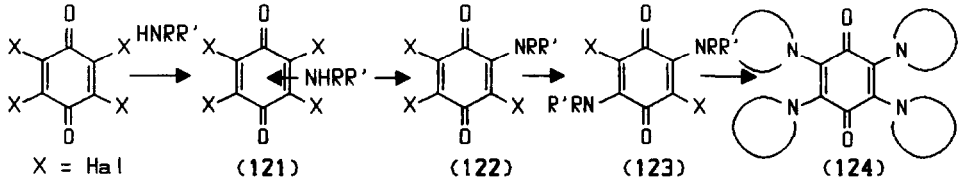
The reaction of substituted quinones with amines and other N-nucleophilic reagents is the most investigated type of nucelophilic substitution of quinones. The reactivity of N-nucleophiles decreases in the following series: hydrazines ⩾ ammonia > primary amines > secondary amines. Large substituents decrease the reactivity of aromatic amines. Electron-acceptor substituents in the benzene ring of aromatic amines also hinder the reaction.

Reaction of hydrazines with substituted 1,4-quinones yields hydrazinylquinones.[155-157]

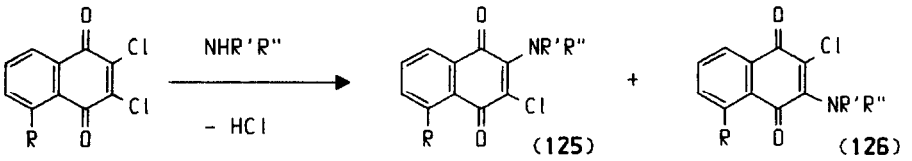
Ammonia reacts with chloranil, first forming monoaminoquinone (**119**) and then the diaminoquinone (**120**). The structures of the above compounds have been determined by X-ray crystallography.[158]



The reaction of halogenanils with amines having at least one N—H bond, consists of a complexing stage (**121**) then the subsequent transformation of the complex forming mono- (**122**), di- (**123**) and tetra-amination (**124**) products of quinone.[159-164] This type of substitution of all halogen



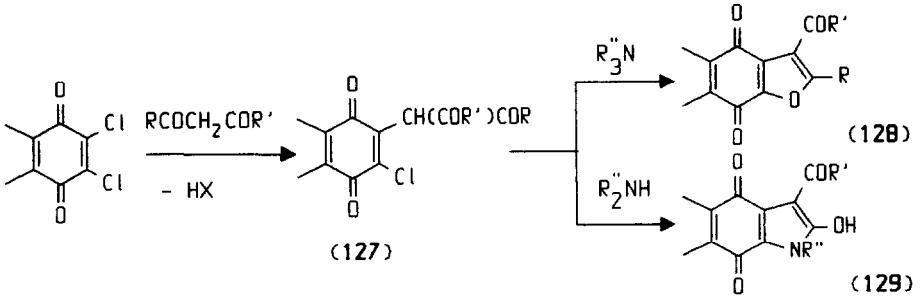
atoms can be carried out only with reactive cyclic amines such as pyrazoles, imidazoles, 1,2,3- and 1,2,4-triazoles.[165,166] Upon the reaction of halogen substituted naphthoquinones with amines,



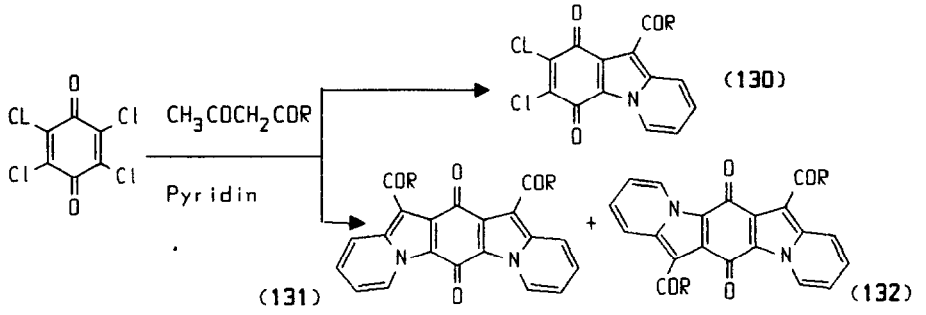
monoamination products (**125, 126**) are formed. Both halogen atoms can be substituted using nitrogen containing heterocycles.[167–185] It has been found that the ratio of yield of 2-chloro (**125**) and 3-chloro (**126**) substituted products depends on the reagent structures.[169–172] The effect of substituents on the reactivity of reagents and on spectral characteristics of products formed has been determined.[169] Optimum conditions for the synthesis of deeply dyed photosensitive materials have been established.[173] Further, a useful method of halogen naphthoquinone amination in the presence of a phase transfer catalyst has been discovered.[174] Water soluble naphthoquinone derivatives have been synthesized.[175,176]

3.3. *Reactions with C-nucleophiles*

Halogeno-quinones condense with *C*-nucleophiles yielding quinonoid products containing new carbon–carbon bonds. Olefins having an activated double bond react with chloranil, 2,3-dichloro-1,4-naphthoquinone yielding ethenylquinones.[177–180] A single stage reaction of acetylenes with halogen quinones proceeds in a similar way, resulting in the formation of alkynylquinones.[181] Cyclic hydrocarbons having mobile hydrogen also react with halogen quinones by nucleophilic substitution.[182,183] The products of the reaction, consisting of the combination 1,3-dicarbonyl compounds with halogeno-quinones, are quite diverse. The reaction begins with the substitution of a halogen atom and the formation of a quinone (**127**), which, under the influence of tertiary amines, is transformed into a furan derivative (**129**).[180,184–186]



Quite a number of the furans (**128**) and indoles (**129**) which have been synthesised display biological activity. Condensation of three reagents occurs during the reaction of halogeno-quinones with 1,3-dicarbonyl compounds and pyridine yielding either pyridoindole quinones (**130**) or benzodiindolizine quinones (**131, 132**).[180,187]



The reaction of 2,3-dichloro-1,4-naphthoquinone with indane-1,3-dione and pyridine exemplifies the general scheme of transformations taking place in a 3-component mixture. The formation of all products has been explained.[188]

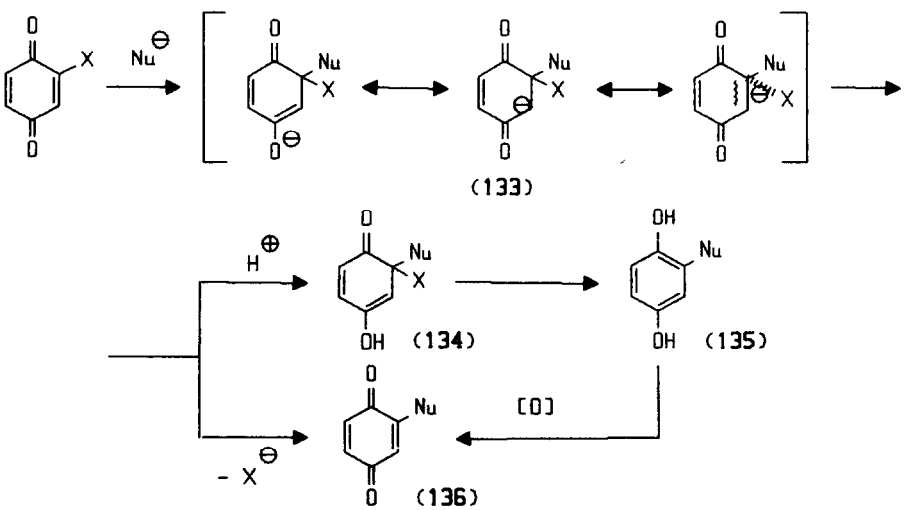
3.4. *Reactions with* P-*nucleophiles*

The scheme of nucleophilic substitution occurs as a rule, in the reactions of phosphorous compounds (such as phosphines, phosphites, amidophosphates) with polyhalogen quinones (such as chloroanil, 2,3-dichloro-1,4-naphthoquinone). The substitution products are either dipolar ions or phosphonates having a quinone substituent.[135]

4. CONCLUSION

Quinones are sometimes considered nominally as α,β-unsaturated carbonyl compounds. Even from a formal point of view, this approach, however, is incorrect as it does not take into account the specific character of the cyclic cross-conjugated structure of quinones. In order to orient oneself when dealing with the numerous reactions of quinones, one should keep in mind that:

1. The main characteristic feature of quinones and their derivatives is the tendency to form energetically favoured aromatic or semiquinone systems.
2. The important feature of quinones is the ability to exchange ring substituents without breaking the quinone structure.
3. In dealing with the reaction mechanism, it should be pointed out that a great number of reactions proceed by a heterolytic mechanism, resulting in the formation of adducts or substitution products. The scheme of nucleophilic reactions can be represented by a single process, the first stage of which being the same for both Ad_N and S_N reactions. It consists of the addition of a nucleophilic reagent Nu^- to a ring carbon, with the subsequent formation of compounds having a resonance structure (**133**). Stabilisation of such compounds is carried out by means of addition or substitution reactions. If an X substituent is a poor leaving group then addition of a counter ion H^+ takes place. The subsequent adduct (**134**) isomerises with the formation of hydroquinone (**135**) occurs. In case of high nucleophobic reactivity of the substituent X (Hal, RO, R_2N), stabilisation of the structures (**133**) is observed by means of anion X^- cleavage and the formation of quinone (**136**). The arrow linking the compounds (**135**) and (**136**) in the scheme indicates that hydroquinone (**135**) with donor substituents is capable of being easily oxidized to the quinone (**136**). In some cases, another scheme can be



applied. One electron is transferred from the nucleophilic reagent to the quinone forming a pair of radicals, whose recombination leads to the intermediate structure.[135]

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