NEW METHODS FOR THE SYNTHESIS OF HETEROCYCLIC QUINONES (REVIEW)

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New methods for the synthesis of heterocyclic quinones are examined.

New methods for the synthesis of heterocyclic quinones are described in the present review. In agreement with Baxter and Davis [1], only those compounds that contain condensed quinones and heterocyclic fragments are understood to be heterocyclic quinones (HQ). A great deal less study has been devoted to HQ than to benzo-, napththo-, and anthraquinones. Only quinoline-, indole-, and benzimidazolequinones are relatively well known, and, as a rule, there is more information available on p-quinones than on o-quinones. The peculiarities of the HQ are displayed most completely in the case of two-ring compounds that contain only a quinone ring and a heteroring, since the heterocyclic analogs of anthra- and phenanthrene-quinones, like their carbocyclic prototypes, are less reactive.

The practical value of the HQ is determined by the fact that compounds with high biological activity have been found among them in the last 10-15 yr. The natural HQ include a group of valuable antitumorigenic mitomycin antibiotics [2], streptonigrin [3], kinamycin [4], naphthyridinomycin [5], and a number of other antibiotics (for example, see [6] and [7-9]), precursors of melanins [10], and metabolites of fungi [6, 11, 12] and bacteria [13]. The difficulties involved in obtaining these compounds are indicated by the fact that not one of the important natural HQ has yet been synthesized, although efforts have been made in this direction. Of the synthetic HQ, let us note antagonists of ubiquinones with high antimalarial activity [14], aminochromes [15], which have hallucinogenic activity [16], substances with antimicrobial [17, 18], cytostatic [17-20], and herbicidal properties, and simulators of parthenocarpy [22, 23].

Since most of the biologically active quinones contain donor substituents — hydroxy, methoxy, amino, or alkyl groups — it might be expected that compounds of this type are most interesting from a practical point of view.

Both general methods and special methods are used for the preparation of HQ; some of them have a limited range of application but give a good idea of the diversity of the approaches to the solution of synthetic problems. The chemistry of some of the groups of HQ has sometimes been examined briefly in reviews and monographs devoted to the corresponding heterocycles, and the first review of the synthesis of HQ was published in 1971 [1]. New methods for the synthesis of HQ have been published and subjected to further development; they are examined below. References to the more recent papers (review papers where possible) are given in individual cases in order to preserve harmony in our presentation.

Methods Based on Oxidation

Oxidation of Bifunctional Derivatives. The oxidation of dihydric phenols, aminophenols, or diamines is still being used to obtain HQ. Oxidizing agents such as silver oxide, chromic acid, and ferric chloride [1] are widely used; however, the cerium(IV)—ammonium nitrate system sometimes gives better results [24].

The oxidation of 1-amino-4,7-dihydroxybenzotriazole (I) is an interesting example. Under the influence of silver oxide it gives unstable quinone II; however, the exceptionally labile dehydrobenzoquinone III, which was trapped in the form of adduct IIIa, was first obtained in the oxidation of I or II with lead tetraacetate [25]:

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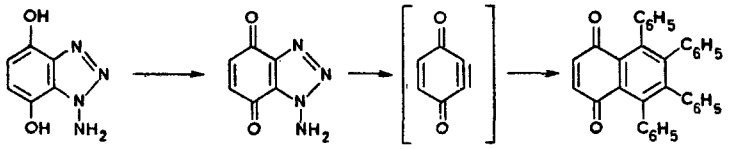
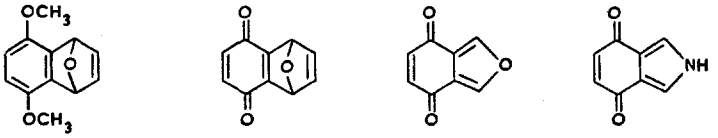


I II III IIIa

The application of the oxidative demethylation of dimethoxy derivatives with divalent silver oxide (AgO) in aqueous dioxane in the cold in the presence of strong acids to prepare difficult-to-obtain isobenzofuran- and isoindolequinones is noteworthy [26]; oxidation-sensitive double bonds and alcohol, aldehyde, and keto groups are not involved in the reaction in this case. Thus the adduct of dimethoxydehydrobenzene with furan (IV) was converted to a quinone (V), which undergoes a retrograde Diels–Alder reaction with splitting out of an acetylene fragment to give isobenzofuranquinone (VI) [27]:

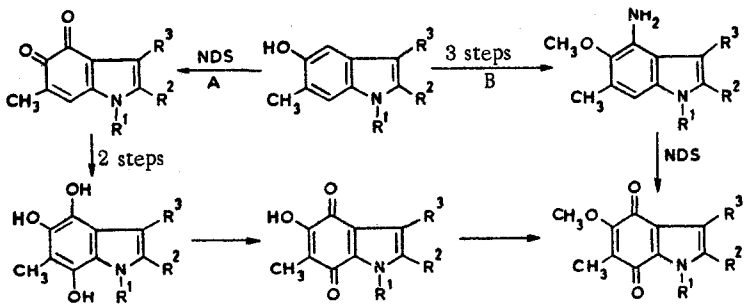


IV V VI VII

Isoindolequinone VII was similarly obtained. This method may evidently find application in the synthesis of other HQ.

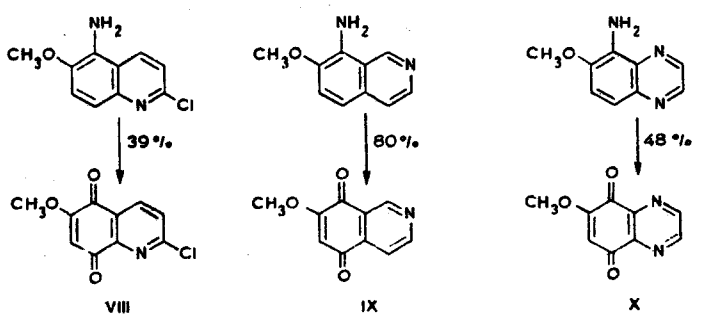
Teuber Reaction (Oxidation with Potassium Nitrosyldisulfonate). Methods for the synthesis of quinones based on the use of monofunctional derivatives, particularly phenols, have undergone a great deal of development in recent years. The oxidation of phenols is often difficult to control [28, 29]. The direct oxidation of phenols to quinones can be carried out only in some special cases [30, 31] or as applied to polycyclic [32] and highly substituted [33-36] phenols. However, the conversion of phenols and amines to quinones was simplified considerably by the introduction into practice of potassium nitrosyldisulfonate (Fremi's salt or NDS; see a previous review [37]). Numerous examples of the use of Fremi's salt for the preparation of HQ have been reviewed [1, 37]. The value of this reagent is also apparent from the following examples.

One of the major tasks in the synthesis of analogs of mitomycin antibiotics consists of the creation of the indolequinone fragment that is necessary for the manifestation of activity. Both of the developed variants of the synthesis specify oxidation with Fremi's salt (see [38] and previous communications of this series):



Variant B, which was developed later, usually gives better results.

Fremi's salt was also used for the preparation of quinone VIII during a search for methods for the synthesis of the antibiotic streptonigrin [39] and the synthesis of methoxyisoquinoline- (IX) and quinoxalinequinone (X) [40]:

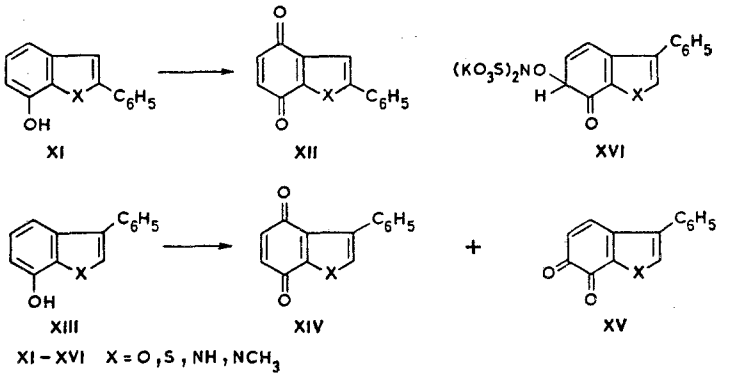


VIII IX X

Quinone IX was previously obtained from 7-methoxy-8-aminoisoquinoline by the traditional method in 17% yield [41], and the advantage of the Teuber method in this case is obvious.

In addition, dimeric C—C or C—O coupling products are formed in a number of cases by the action of Fremi's salt on heterocyclic phenols [37].

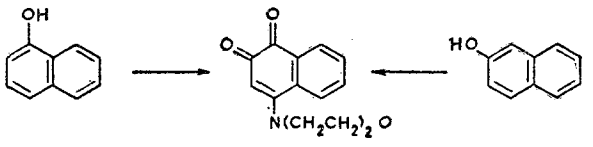
Steric and electronic effects play an important role in the oxidation of potassium nitrosyldisulfonate. The role of steric factors has been demonstrated thoroughly in the case of oxidation of 2- and 3-phenyl-7-hydroxybenzofurans, -benzothiophenes, and -indoles [42-44]. Whereas the 2-substituted compounds (XI) give only p-quinones (XII), the 3-substituted (XIII) and 2,3-diphenyl compounds form mixtures of p- and o-quinones XIV and XV. This difference is explained by the smaller steric strain of the o-quinoid intermediate (XVI) (as compared with the p-quinoid intermediate), which does not experience the effect of the bulky phenyl group attached to $C_{(3)}$.



The problem of the electronic effects in the oxidation of heterocyclic phenols with Fremi's salts is more complex. It has been shown in the case of the thoroughly investigated oxidation of substituted phenols that electron-donor substituents (alkoxy and alkyl groups) as a rule facilitate the reaction if they do not create steric hindrance. On the other hand, the presence of electron-acceptor substituents such as NO_2, CHO, and COOR completely inhibits the process [45-47]. Since a π-electron-deficient heteroring in heterocyclic phenols can be arbitrarily considered to be an electron-acceptor substituent, the failures in the attempts to oxidize hydroxyquinolones [24], hydroxyquinazolones [48], and 7-hydroxyisoquinoline and 6-hydroxyquinoxaline [49] with Fremi's salt can be explained from these positions. In any case, it is significant that most of the heterocyclic phenols that are oxidized by Fremi's salt contain π-electron-surplus heterorings, whereas there are fewer examples of the oxidation of phenols with π-electron-deficient systems, and side reactions are frequently observed in these cases. On the whole, the problem of the effect of the heteroring on the ability of the phenol to undergo oxidation by Fremi's salt requires further study.

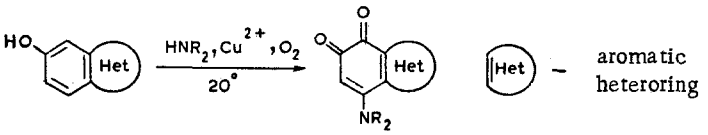
It should be noted that the need to work with aqueous solutions and the instability of the reagent impose additional restrictions on the use of the nitrosyldisulfonate for the preparation of quinones [50].

Catalytic Oxidation of Phenols. Treatment of phenol and α- and β-napthols with oxygen in the presence of the copper(II)—morpholine complex converts them to o-quinones containing a morpholine residue [51-55] (for example, XVII).



The reaction proceeds through steps involving o-hydroxylation, oxidation to an o-quinone, addition of morpholine, and oxidation. Despite the simplicity of the reaction and its extensive possibilities, it has not been studied with other compounds and has not found synthetic application. Primarily dimeric, trimeric, and polymeric products of C—C and C—O coupling are formed in the oxidation of substituted phenols (primarily alkylphenols) with oxygen in the presence of copper—amine complexes [56, 57].

In a series of studies (see [58] and subsequent papers) it has been shown that the oxidation of heterocyclic phenols XVIII with oxygen in the presence of copper(II)–secondary amine complexes is an efficient method for the synthesis of dialkylamino-o-quinones of the XIX type:



XVIII XIX

o-Quinones, and quinoline [58-64], indole [65, 66], acridine [58], isoquinoline [67-69], quinazoline [70-75], quinoxaline [76], benzofuran [77], and benzothiazole [78-80] derivatives have been obtained by this sort of oxidative amination.

Despite the data of Brackman and Havinga [51, 53], phenols are not oxidized in the presence of Cu^{2+}–primary amine complexes [81]. Of the secondary amines, the best results are obtained with piperidine, morpholine, dimethylamine, and pyrrolidine, and low yields are obtained when the reaction is carried out with secondary amines in which the nitrogen atom is more shielded. The competitive bonding of the copper with another ligand (rather than with the secondary amine) such as, for example, the starting heterocyclic phenol or the reaction products, slows down or even stops the reaction. Some heterocyclic phenols are therefore oxidized in the presence of piperidine or dimethylamine but remain unchanged in the presence of morpholine, since the latter is a weaker base and consequently has weaker complexing ability.

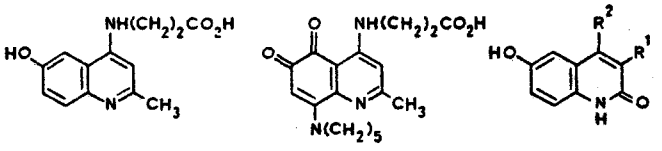
It has been shown in the case of hydroxyquinolines XX that, regardless of the presence in the 2, 3, and 4 positions of various substituents that are not involved under mild conditions, oxidation proceeds smoothly, and quinones XXI are obtained in high yields [58, 59, 61, 62, 64]:

XX XXI

$R^1 = H, CH_3, C_6H_5, CH=CHC_6H_5, OC_6H_5, N(CH_2CH_2)_2O$;
$R^2 = H, NHAlk, NR_2, COOH, COOAlk$

Thus numerous quinolinequinones, including 2-substituted compounds, which are of interest in connection with the search for methods for the synthesis of the antibiotic streptonigrin [82], have become accessible.

Like most of the other heterocyclic phenols, 6-hydroxyquinolines XX are oxidized to the corresponding quinones in the presence of catalytic amounts of a copper salt. However, some heterocyclic phenols are bonded so strongly to copper that oxidation becomes impossible. Thus 8-hydroxyquinoline or 5-hydroxybenzotriazole, which form extremely stable complexes with copper, cannot be oxidized. At the same time, XXII with a β-alanine residue, which inhibits oxidation, can be oxidized to quinone XXIII in the presence of an equivalent amount of copper salt [62].

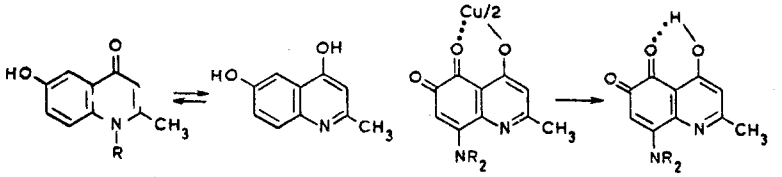


XXII XXIII XXIV a-c

XXIV a $R^1 = H, R^2 = CH_3$; b $R^1 = n\text{-}Bu, R^2 = Cl$; c $R^1 = n\text{-}Bu, R^2 = OH$

6-Hydroxy-2-quinolones XXIV, which also competitively form bonds with copper, can be oxidized to quinones in the presence of 0.25-1.0 equivalent of a copper salt [63]. It was shown that in the oxidation of quinolones XXIVa, b the copper is bonded to the starting compound and that the Cu^{2+}–secondary amine complex is necessary only in the hydroxylation step [63].

The oxidation of some heterocyclic phenols gives quinones that are strongly bonded to copper. The oxidation of such compounds is possible in the presence of an equivalent of cupric acetate, and the complex must be decomposed with strong acid to isolate the resulting quinones (or else the copper must be removed by means of EDTA). Thus quinones XXVII are obtained in good yields from 2-methyl-6-hydroxy-4-quinolone (XXVa) after oxidation and decomposition of complexes XXVI [60]:

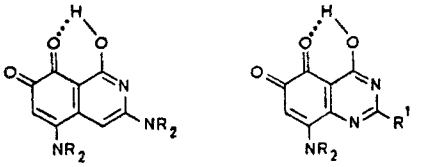


XXV a, b XXVc XXVI XXVII

XXV a R = H ; b R = CH_3

The assumption that quinolone XXVa is oxidized to a quinone that exists in hydroxy form XXVc is confirmed by the fact that quinolone XXVb, which is incapable of tautomeric transformations, is not oxidized in the presence of copper—secondary amine complexes [60].

The products of oxidation of 7-hydroxy-1-isoquinolone [68] and 6-hydroxy-4-quinazolones [72] also form strong bonds with copper, and the corresponding quinones (XXVIII and XXIX) were isolated only after decomposition of the complexes.

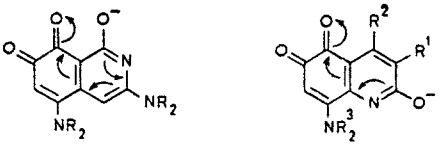


XXVIII XXIXa, b

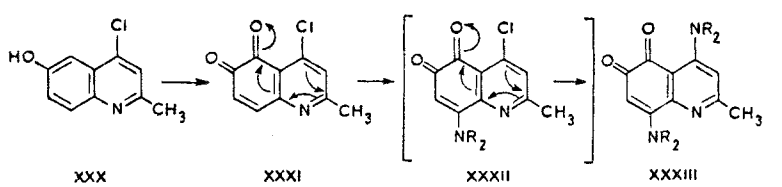
XXIX a $R^1 = N(CH_2)_5$; b $R^1 = C_6H_5$

Although 2- and 4-quinolones, 1-isoquinolones, and 4-quinazolones exist in the oxo form [83], quinones XXVII, XXVIII, and XXIXa exist in the hydroxy form stabilized by an intramolecular hydrogen bond in the solid state and in solution; this correlates well with their tendency to give copper chelates. This was demonstrated by a study of the IR and PMR spectra of quinones XXVII-XXIX and model compounds [68, 72, 84]. Thus a new type of stabilization of the hydroxy form of the heterocycles was found (see [85]). Substituents may have a pronounced effect on the strength of the intramolecular hydrogen bond. Thus both tautomeric forms, which exist in equilibrium, are detected in solutions of quinone XXIXb (in contrast to XXIXa) [86].

Compounds XXVII-XXIX and 2-quinolone-5,6-quinones are rather strong acids. Their ionization constants are at least four orders of magnitude larger than those of the corresponding oxoheterocycles [60]. This is explained by transmission of the effect of the quinone carbonyl groups:



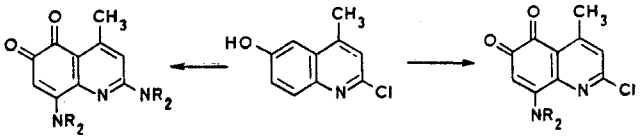
Secondary reactions involving the heteroring take place in a number of cases in the oxidative amination of heterocyclic phenols. They are explained proceeding from the concept of transmission of the effect of the quinone carbonyl groups, as a result of which the substituents in the heterocyclic fragment take on properties peculiar to substituents in the quinone ring. Thus quinones XXXIII are obtained in the oxidative amination of 2-methyl-4-chloro-6-hydroxyquinoline (XXX), i.e., the chlorine atom is replaced under very mild conditions [62]:



XXX XXXI XXXII XXXIII

This is associated with the formation of intermediate quinones XXXI and XXXII, in which the halogen is activated under the influence of the quinone $C_{(5)}$=O group. The high lability of the chlorine atom in 4-chloroquinoline-5,6-quinones is confirmed by the fact that the specially synthesized chloroquinone XXXI is converted to quinone XXXIII in good yield under oxidative amination conditions [62].

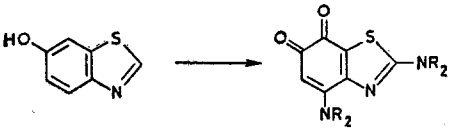
The oxidative amination of 2-chloro-4-methyl-6-hydroxyquinoline (XXXIV), which is an isomer of phenol XXX, under normal conditions (with excess secondary amine) leads to diaminoquinones XXXV; however, chloroquinones XXXVI are formed in satisfactory yields in the presence of 1 mole of amine [64]. Thus the sequence of the reactions that occur in the oxidation of 2(4)-chloro-6-hydroxyquinolines was proved.



XXXV XXXIV XXXVI

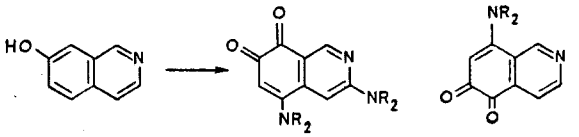
Both 2- and 4-haloquinolinequinones are extremely reactive compounds in which the halogen is readily replaced by the action of nucleophiles. For example, the reaction of chloroquinones XXXVI with amines proceeds rapidly at room temperature [64]. 2-Haloquinolinequinones are currently of interest as possible intermediates in the synthesis of streptonigrin [39].

The oxidative amination of, for example, 6-hydroxybenzothiazole [78, 80] formally recalls the Chichibabin reaction:



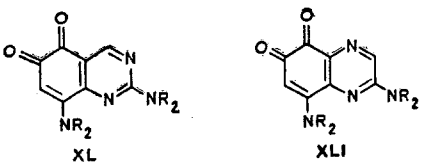
It is important that the amination of the heteroring is accompanied by increased oxygen absorption (2 moles per mole of phenol).

However, an analogy with the Chichibabin reaction cannot be pursued, since quinones XXXVIII are formed in the oxidative amination of 7-hydroxyisoquinoline (XXXVII) [67]. Thus a second electrophilic center [in addition to $C_{(5)}$] is found at $C_{(3)}$ in isoquinoline-7,8-quinones, although it is known that in the case of isoquinolines strong nucleophiles primarily attack $C_{(1)}$.



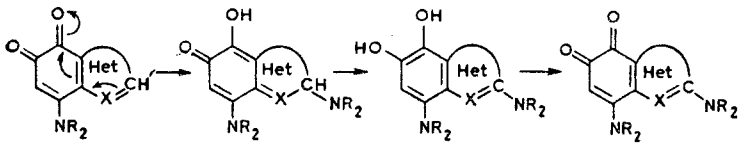
XXXVII XXXVIII XXXIX

It is important that the isomeric 6-hydroxyisoquinoline is not aminated at $C_{(3)}$ upon oxidation and gives quinones XXXIX [69]. Finally, 6-hydroxyquinazoline [70, 71], 6-hydroxy-4-quinazolone [72], 6-hydroxyquinoxaline [76], and 7-hydroxy-1-isoquinolone [68] are also aminated in the heterocyclic fragment in the presence of Cu^{2+}—secondary amine complexes to give quinones XL, XXIXa, XLI, and XXVIII, respectively.



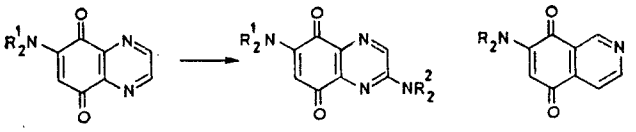
XL XLI

The ease with which amines add to quinones (1,4 addition) is well known. The amination of heterocycles can be represented as being the result of 1,6 addition of a secondary amine to intermediate o-quinone XLII with subsequent oxidation to XLIII:



XLII XLIII X = N, CH

A characteristic feature of p-quinones is their ability to undergo amination in the heterocyclic fragment: quinoxalinequinones XLIV react with secondary amines in the presence of metal ions to give diaminoquinones XLV [87, 88]. In this case, oxygen, the metal ion (Cu^{2+}, Ag^{+}, or Hg^{2+}), or the starting quinone may act as the oxidizing agent [88].

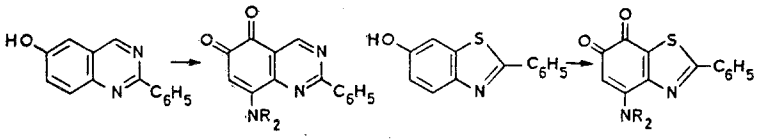


XLIV XLV XLVI

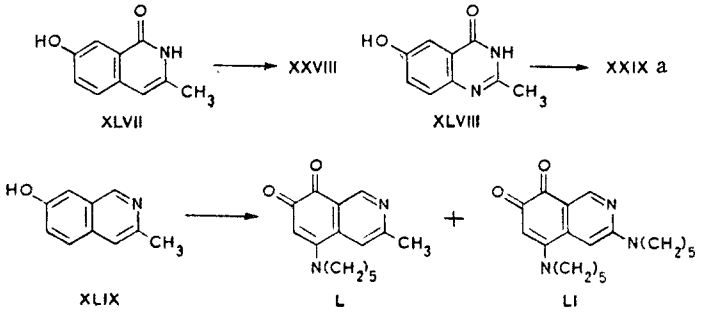
The observed transfer of the electrophilic center from $C_{(1)}$ to $C_{(3)}$ on passing from isoquinolines to isoquinoline-7,8-quinones [67] and from $C_{(4)}$ to $C_{(2)}$ for quinazolines and quinazoline-5,6-quinones [71] is associated with the effect of the strongly electronegative carbonyl oxygen atom, which hinders nucleophilic attack in the peri position of the quinones [$C_{(1)}$ and $C_{(4)}$, respectively].

The possibility of amination is determined not only by the acceptor properties and the aromatic character of the heteroring but also by the favorable orientation of the carbonyl group and the heteroatom. The amination reaction requires that the quinone carbonyl group conjugated with the site of attack be activated as a result of chelate formation. Quinone XLVI, which is not capable of forming chelate complexes, is therefore not aminated in the heterocyclic fragment under the reaction conditions.

If there is a phenyl group attached to the carbon atom at which amination is possible, the heteroring is not involved during the oxidation [71, 79]:



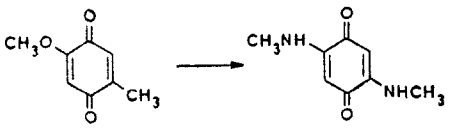
This is explained by participation of the phenyl group in delocalization of the charge on $C_{(2)}$. On the other hand, if there is a methyl group attached to this carbon atom, another unusual reaction — replacement of the methyl group by a secondary amine residue — is possible. It was shown that XLVII [68] and XLVIII [75] are converted to diaminoquinones XXVIII and XXIXa, respectively, under the oxidation amination conditions, whereas a mixture of quinones L and LI is obtained from 3-methyl-7-hydroxyisoquinoline (XLIX) [69]; quinone L is gradually converted to quinone LI under the reaction conditions:



XLVII XXVIII XLVIII XXIX a

XLIX L LI

Since splitting out of a methyl group does not occur in the case of oxidation and decarboxylation [75], it may be assumed that substitution reactions similar to those that are known in the benzoquinone series (see the previous review [89]) take place in this case. Thus 2,5-bis(methylamino)benzoquinone (LII) was obtained by the action of methylamine on 2-methyl-5-methoxy-1,4-benzoquinone:



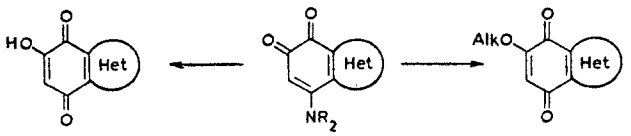
LII

Other similar examples have been presented in an earlier review [89]. There is evidence that methylquinones react in the hydroxyquinomethide form [90, 91]. The replacement of the methyl group in HQ is similarly explained under the assumption of transmission of the effect of the quinone carbonyl group through the heteroring [75].

It should be noted that there are a number of other quinoid heterocyclic systems that react with nucleophiles in the positions that are conjugated with the carbonyl group. Postovskii and co-workers studied phenoxazinones and phenothiazones, Gorelik studied anthraquinones containing an angularly condensed acceptor heteroring (see the previous review [92]), and Fokin investigated keramidonines [93]. Reactions involving nucleophilic substitution of the hydrogen in a number of quinones were examined in a review by Chupakhin and Postovskii [94] and they proposed a special symbol (S_NH) for such reactions. Thus the chemistry of the secondary processes that occur during oxidative amination is analogous to the chemistry of quinones.

The whole gamut of quinazolinequinones has been synthesized by oxidative amination [70-75], although other methods have been found to be less suitable for this purpose [48, 95]. Oxidative amination is beginning to receive acknowledgement and has been used for the preparation of quinones of the indole [96, 97], benzofuran [97], and quinoline [81, 98] series.

Let us note that simple methods for the conversion of dialkylamino-o-quinones XIX to substituted p-quinones have been developed:

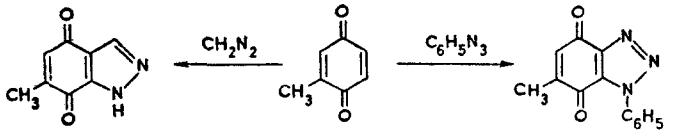


LIII XIX LIV

This may be accomplished either by saponification of o-quinones XIX to hydroxyquinones LIII or, which is of great interest, they may be converted to alkoxy-p-quinones LIV. The latter reaction, which was initially developed in the naphthoquinone series [99], usually gives the products in high yields. It has been applied to quinones of the quinoline [64, 100], isoquinoline [67], quinazoline [71, 73, 74], quinoxaline [87], and indole [101] series. In particular, in the indolequinone series this reaction, together with oxidative amination, is an alternative method for the construction of an indolequinone system of analogs of mitomycins.

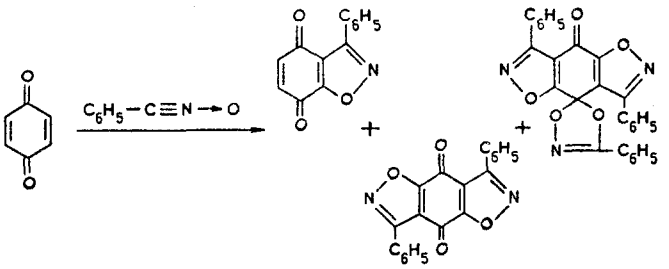
Syntheses Based on Quinones

Cycloaddition. Dipolar cycloaddition is a promising method for the construction of heterocyclic systems [102]. As applied to p-quinones, which are powerful dipolarophiles, two reactions that lead to HQ have been thoroughly studied. Quinones that contain a pyrazole ring are formed in the reaction of p-benzo- and naphthoquinones with diazoalkanes, whereas quinones that contain a triazole ring are formed in the reaction with alkyl(aryl) azides: (see earlier reviews [1, 89]):



Less study has been devoted to the reactions of the indicated reagents with o-quinones, and they do not have preparative value; o-quinones usually form products of addition to the C=O bonds on reaction with diazo compounds [89].

In addition to a benzisoxazolequinone, a three-ring quinone and products of addition to the C=O group are formed as a result of the reaction of nitrile oxides with p-benzoquinone [103, 104]:

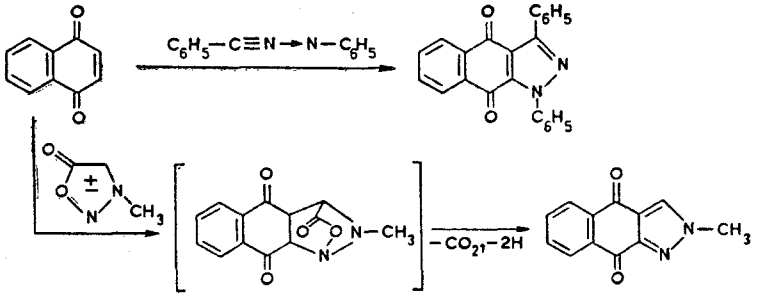


Quinones that contain an isoxazole ring and are stimulators of parthenocarpy have been obtained by this method [22, 23].

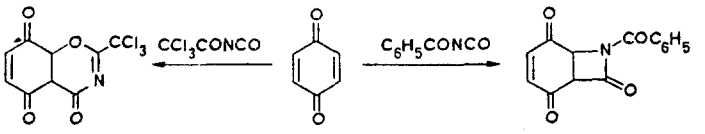
Sasaki and Yoshioka [105] have proposed a modification of this reaction based on the formation of nitrile oxides during the thermal decomposition of hydroxamic acid chlorides; this method sometimes gives better results [105].

Nitrile oxides initially add to the C=O bonds of o-quinones, and they are therefore unsuitable for the preparation of heterocyclic o-quinones [106].

There are unique examples of the addition of other dipolarophiles to quinones. Thus the nitrileimine that is formed in the thermolysis of 2,5-diphenyltetrazole adds to 1,4-naphthoquinone to give 1,3-diphenylnaphthopyrazolequinone in high yield [107], and the reaction of 3-methylsydnone with naphthoquinone gives, after oxidative decarboxylation, 2-methylnaphthopyrazolequinone [108].

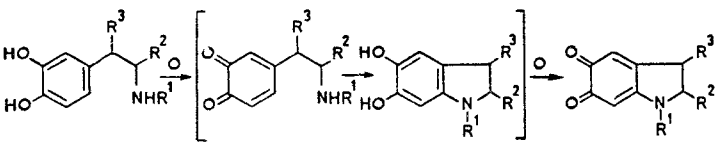


Arbuzov and co-workers [109] have shown that as a result of 1,3-cycloaddition, trichloroacetyl isocyanate reacts with benzoquinone to give an oxazine derivative, while benzoyl isocyanate reacts via a 1,2-cycloaddition mechanism to give a β-lactam:

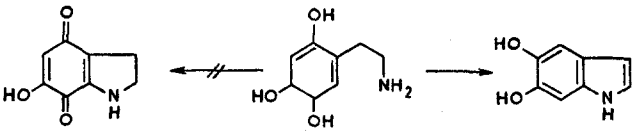


1,4-Naphthoquinone behaves similarly. Judging from the available data, both addition products exist exclusively in the oxo form and do not display a tendency to undergo enolization to hydroquinones.

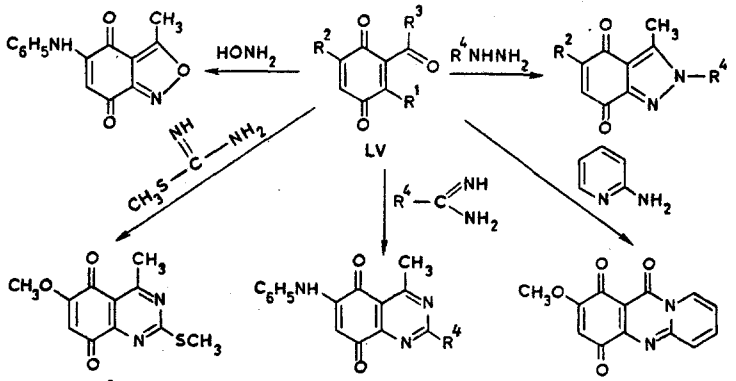
Syntheses Based on β-(Hydroxyphenyl)ethylamines. The oxidation of β-(3,4-dihydroxyphenyl)ethylamines, during which a heteroring is formed by intramolecular addition of the amino group to the o-quinone at the instant of its formation, is used for the preparation of aminochrome and 2,3-dihydroindole-5,6-quinone precursors and models of melanins:



Examples of reactions of this type have been presented in earlier reviews [1, 15, 110]. Studies of these reactions are continuing, and various one-electron oxidizing agents, oxygen, and even benzoquinone are used to carry out the oxidation [111]. It should be noted that despite earlier data, oxidative cyclization to indole-4,7-quinones is not observed [112]:

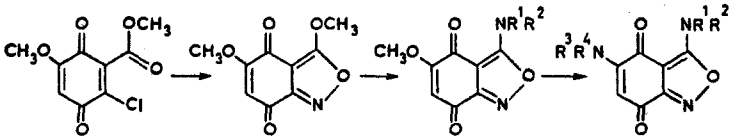


Syntheses Based on Acetyl(carbalkoxy)benzoquinones. A number of HQ have recently been synthesized from substituted 2-acetyl(carbomethoxy)-1,4-benzoquinones (LV). Owing to the concerted effect of the quinone and exocyclic carbonyl groups, nucleophilic addition and substitution reactions take place primarily at $C_{(3)}$ in the case of quinones of this type. Using this property and an exocyclic carbonyl group, Schafer and co-workers [113, 114] obtained quinones that contain five- and six-membered heterorings:



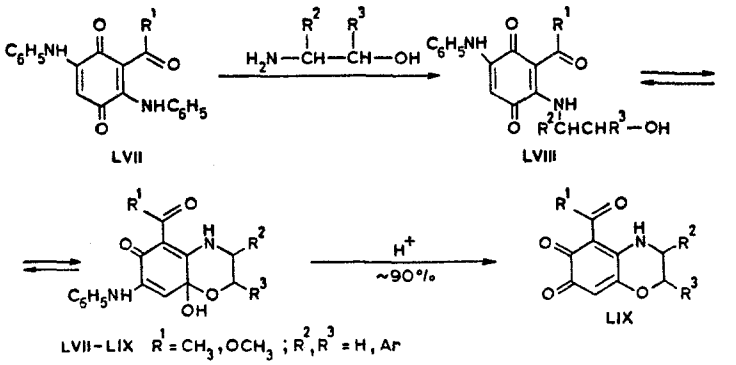
LV $R^1, R^2 = OCH_3, Cl, NHC_6H_5$; $R^3 = CH_3, OCH_3$

2-Carbomethoxy-3-chloro-6-methoxy-1,4-benzoquinone can be converted by treatment with sodium azide to 3,5-dimethoxy-2,1-benzisoxazole-4,7-quinone (LVI), the methoxy groups of which are capable of being replaced successively by residues of primary or secondary amines [115]:



LVI

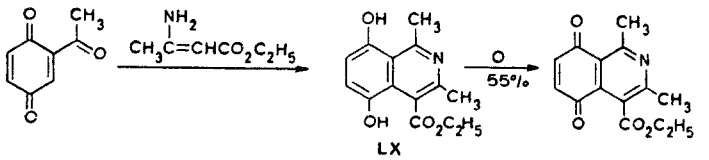
Dianilino derivative LVII reacts with β-amino alcohols to give substituted hydroxyethylaminoquinones LVIII, which split out aniline when they are treated with acid to give 2,3-dihydro-1,4-benzoxazine-6,7-quinone derivatives (LIX) [116].



LVII-LIX $R^1 = CH_3, OCH_3$; $R^2, R^3 = H, Ar$

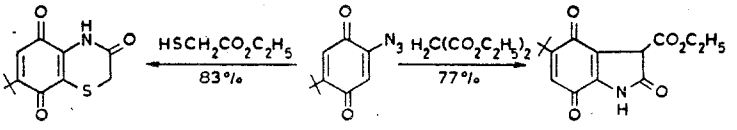
Some substituted benzofuran- [117] and indazolequinones [118] have also been synthesized from acetylbenzoquinones.

It is interesting to note that, in contrast to other quinones, acetylbenzoquinone reacts with ethyl β-aminocrotonate to give isoquinoline LX, which is oxidized to the corresponding quinone, rather than a substituted 5-hydroxyindole (the Nenitzescu reaction) [119]:



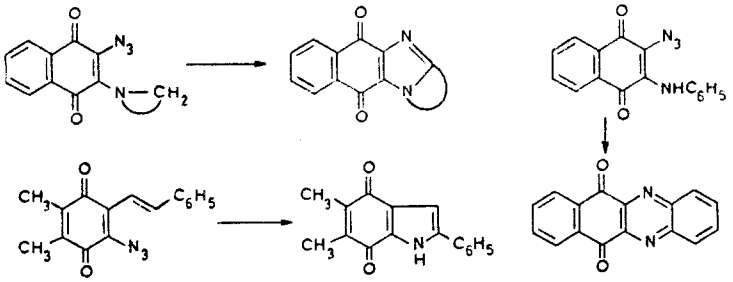
LX

Syntheses Based on Azidoquinones (See the Previous Review [120]). Azidohydroquinones, which are obtained by the addition of nucleophiles to azidoquinones, readily undergo disproportionation through nitrenes to the corresponding aminoquinones. Correspondingly, 2-azido-5-tert-butyl-1,4-benzoquinone (LXI), the tert-butyl group of which hinders attack at C(6), forms quinones of the 2,3-dihydrobenzothiazine and indole series on reaction with thioglycolic and malonic acid esters:



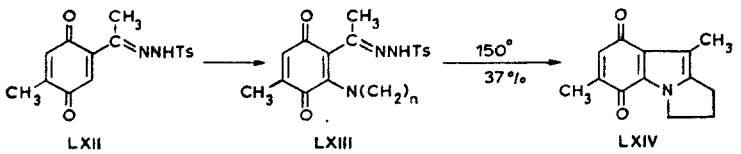
LXI

Some polycyclic quinones have been synthesized by thermolysis of 3-substituted 2-azidonaphthoquinones, and indolequinones have been obtained from 2-azido-3-vinylbenzoquinones:



The thermal or photochemical rearrangements of azidoquinones have been used for the synthesis of other polycyclic quinones that contain a pyrrole ring [120].

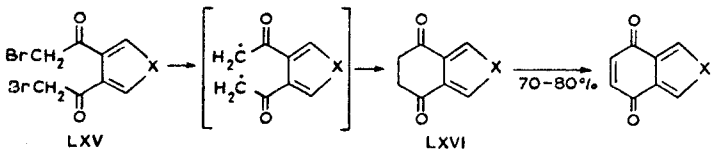
In 1974 Takada and co-workers [121] described a new method for the synthesis of systems similar to mitomycins from 2-acetyl-5-methyl-1,4-benzoquinone tosylhydrazone (LXII) [121]. In contrast to azidoquinones, in this case the reactive intermediate is a carbene rather than a nitrene. The addition of cyclic secondary amines to quinone LXII and subsequent oxidation give quinones LXIII. Brief heating of the pyrrolidine derivative (LXIII, n = 4) at 150°C leads to pyrrolo[1,2-a]indolequinone LXIV. Thermolysis is accompanied by splitting out of toluenesulfinic acid and nitrogen and cyclization of the resulting carbene with subsequent disproportionation to a pyrroloindolequinone.



LXII LXIII LXIV

Methods for the Formation of a Quinone Ring

Syntheses Based on o-Bis(bromoacetyl)heteroaromatic Derivatives. A new method for the synthesis of isobenzofuran-, thiophene-, and indolequinones from dibromo compounds LXV was recently proposed [122]:

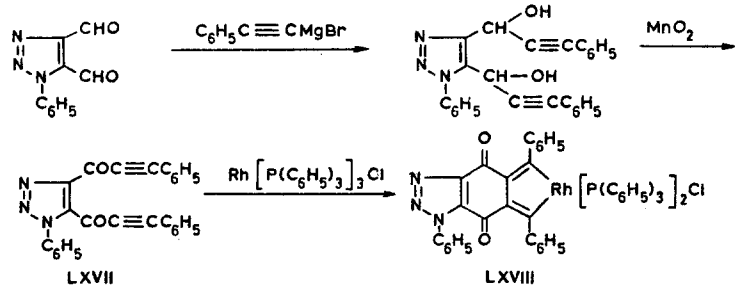


LXV LXVI

LXV, LXVI X = O, S, NH

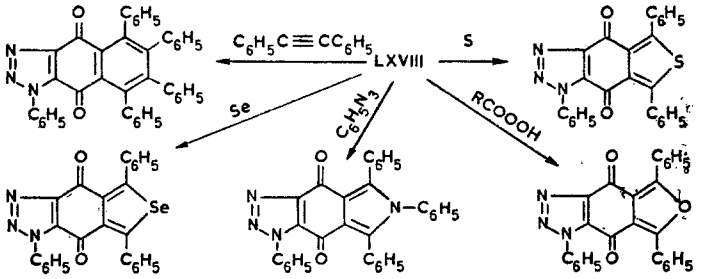
The diradicals formed in the reduction of LXV with a zinc-copper couple undergo cyclization to diketones LXVI in 50-60% yields. The latter are not inclined to undergo enolization and exist in the oxo form; however, they are dehydrogenated to quinones under the influence of dicyanodichloroquinone or chloranil.

Syntheses Based on o-Bis(arylalkynyl) Ketones. In a series of studies Muller and coworkers (see [123] and subsequent communications of this series) used rhodium complexes of o-bis(arylalkynyl) ketones (for example, LXVII), synthesized from the corresponding dialdehydes, for the preparation of polycyclic (including heterocyclic) quinones [124]:

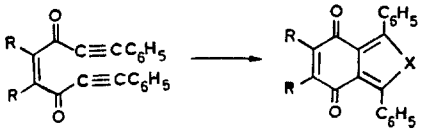


LXVII LXVIII

Diketone LXVII reacts with tris(triphenylphosphine)rhodium (I) chloride to give complex LXVIII, which is capable of reacting with acetylenes, sulfur, selenium, phenyl azide, and peracids:



Two-ring quinones can be obtained (although in low yields) from aliphatic dialkynyl ketones via a similar scheme [125]:



X = O, S, Se, NC_6H_5

The mechanism and range of application of these reactions are not yet completely clear. Despite the low accessibility of the starting compounds and the apparent limitations in the sense of their selection, this fundamentally new approach to the synthesis of quinones is of interest.

Several methods that were recently developed as applied to aromatic compounds are evidently suitable for the preparation of many HQ. The study of oxidizing agents such as cerium(IV)—ammonium nitrate [126, 127], thallium trifluoroacetate [128], and cobalt complexes [129, 130] and a method for the selective conversion of phenols to o-quinones [131] are particularly noteworthy.

After we had prepared this review for publication, a number of interesting papers, the citations to which are advisedly included in our review, appeared. Thus the preparation of indole-4,7-quinones by oxidative demethylation has been reported [132], the cycloaddition of sydnones to quinones has been studied [133], an original synthesis of indazole-quinones has been accomplished [134], the range of application of acylbenzoquinones for the preparation of HQ has been extended [135-137], and new photochemical and thermochemical reactions of substitution of carbocyclic quinones that lead to HQ have been described [138-140]. Communications by a group of researchers from Harvard University regarding the first total synthesis of mitomycin antibiotics — mitomycins A and C [141] and porphyromycin [142] — were a significant event. The authors of these publications succeeded in developing a new approach to the synthesis of the four-ring system of mitomycins. The two key steps in the synthesis are intramolecular cyclization of the substituted benzoquinone to give an eight-membered heteroring and transannular cyclization [143].

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SYNTHESIS AND NONCHAIR CONFORMATIONS OF 2,2-DISUBSTITUTED 4,4-DIMETHYL-1,3-DIOXANES

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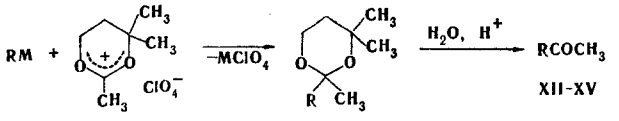
The fundamental possibility of the synthesis of 2-substituted 1,3-dioxanes by reaction of 1,3-dioxanium perchlorates with organometallic compounds is demonstrated. A method for the synthesis of acyl derivatives of heterocycles was developed on the basis of these compounds. The existence of 2,2,4,4-substituted 1,3-dioxanes in the twist conformation was shown by ^{1}H NMR spectroscopy; the twist conformation is explained by the effect of nonbonded 1,3-syn-axial interactions.

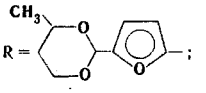
We have studied the synthesis and stereochemistry of new 1,3-dioxane systems that have not been previously described in the literature and have a gem-dimethyl grouping attached to the $C_{(4)}$ atom in all cases. The most convenient method for the synthesis of 1,3-dioxanes [1] is condensation of carbonyl compounds with 1,3-diols. However, it is difficult to prepare ketals by this method [2]. Having a convenient method for the synthesis of 1,2-dioxanium perchlorates [3] at our disposal, we deemed it expedient to use these salts for the preparation of new 1,3-dioxanes. 1,3-Dioxanium systems have an electrophilic center at the meso carbon atom of the $O-\overset{+}{C}-O$ fragment and can readily undergo nucleophilic attack [4-6].

Reactions of 2,4,4-trimethyl-1,3-dioxanium perchlorate (I) were first carried out with lithium aluminum hydride (LAH), a Grignard reagent, and Li derivatives of the heterocyclic series, as a result of which cyclic acetals and ketals that are difficult to obtain by other methods were obtained. The reduction of perchlorate I with LAH leads to 2,4,4-trimethyl-1,3-dioxane (II) in high yield (Table 1). 1,3-Dioxanes III-V were obtained by mixing the Grignard reagent with perchlorate I at room temperature and subsequent decomposition of the excess Grignard reagent with water.



I III-XI XII-XV

M = MgBr, Li; III R = CH_3; IV R = C_2H_5; V R = n-C_3H_7; VI R = n-C_4H_9;

VII R = 1-methyl-2-benzimidazolyl; VIII, XII R =  ;

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