REACTIVITIES OF HETEROCYCLIC QUINONEIMINES (REVIEW)

G. B. Afanas'eva, V. I. Vysokov, and O. N. Chupakhin

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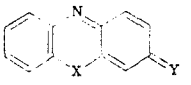
Data on the reactions of phenazine, phenoxazine, and phenothiazine derivatives in which the bridge nitrogen atom is included in a quinoneimine fragment are correlated. The effect of the nature of the second bridge heteroatom, benzo annelation, and activation of the substrate and the reagent on the reactivities of the heterocyclic quinoneimines cited above is discussed.

The range of the application of derivatives of related heterocycles – phenoxazine, phenothiazine, and phenazine – is vast and is undergoing continuous expansion in connection with new requirements of public health and technology [1-6]. Among the large number of compounds of this series one can single out the group of so-called heterocyclic quinone-mono- and -diimines (HQI) with the general formula 1, in which the nitrogen atom of the central heteroring is included in a quinoneimine (Y = O) or quinonediimine (Y = NH, NP, NAr, $\overset{+}{N}<$) fragment.



1

X=O, S, NR, NAr

Diverse dyes, redox and acid-base indicators, antimicrobial agents, anticancer antibiotics, etc. are found among HQI of the 1 type (here and subsequently, both mono- and diimines are included in this term) and are widely used. Reviews [7-14] of the individual areas of the synthesis and application of phenoxazines, phenothiazines, and phenazines are available.

In the present brief review we examine for the first time the principal factors that determine the specific reactivities of HQI; attention is directed exclusively to reactions that directly involve the polycyclic ring.

Heterocyclic quinoneimines can be formally regarded as both substituted noncyclic quinoneimines and as the corresponding phenoxazine, phenothiazine, or phenazine derivatives. However, in HQI the presence of a unified system of conjugation that includes the quinoneimine fragment and the central azine heteroring leads to substantial differences in the reactivities from both the corresponding heterocycles and the noncyclic quinoneimines. Thus the reactivities of phenoxazine, phenothiazine, and phenazine are determined by their clearly expressed π-surplus character and significant transfer of electron density to the benzene rings [15]. In contrast to the parent heterocycles (and the noncyclic analogs [16]), HQI molecules are planar [17, 18], and the π-deficient quinoid part of the molecule, which is responsible for their increased electrophilic properties, has the principal effect on their chemical behavior. The affinity of HQI for nucleophiles makes it possible to synthesize C-substituted phenazines, phenoxazines, and phenothiazines and their derivatives by direct nucleophilic substitution of hydrogen and nucleofugal atoms or groups. Alternative methods of synthesis of HQI derivatives by means of cyclizations are often hindered by the low accessibility of the corresponding synthones [19, 20]. The domination of the electrophilic properties determines the smaller degree of occurrence in the HQI series of reactions with electrophilic reagents. Radical and photochemical processes also seldom occur in this series.

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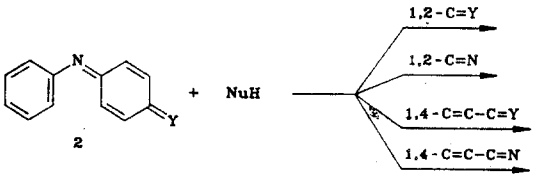
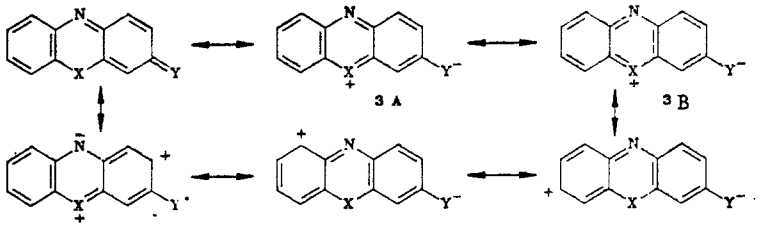
1. REACTION OF HETEROCYCLIC QUINONEIMINES WITH NUCLEOPHILES

The structural similarity between heterocyclic quinoneimines of the 1 type and noncyclic 1,4-benzoquinone-4-arylimines 2 is responsible for a number of analogies in their chemical behavior with respect to nucleophiles. Thus, 1,2-C=Y and 1,2-C=N additions and nucleophilic substitution of hydrogen attached to the ethylene bond are common in both series. In the latter case one initially observes 1,4 addition of the nucleophile to the C=C–C=Y or C=C–C=N fragments of the quinoneimine with the formation of adducts with a hydroquinone structure, which, in the presence of a suitable oxidizing agent, are converted to the corresponding substituted quinoneimines [21].



2

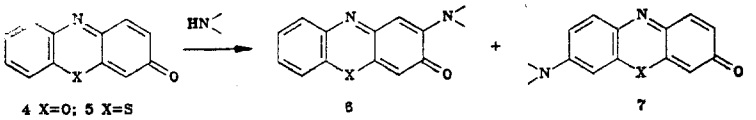
Quantum-chemical calculations and an analysis of the ^{13}C NMR spectra provide evidence that HQI differ considerably more substantially from 1,4-benzoquinone-4-arylimines than the products of ordinary substitution in quinoneimine 2 molecules [22, 23]. The second bridge heteroatom, by forming an azine ring, due to the unshared pair of electrons stabilizes betaine anthracenelike quinoneazine system 3 (A and B), thereby increasing its aromatic character. At the same time, the significant degree of degeneracy of o-quinoid structures 3A and 3B makes it possible to explain the anomalously high activity of the aryl fragment in nucleophilic substitution reactions. In addition, attack by the nucleophile at the central heteroring (at the C–X bond), which may be accompanied by a transformation of the ANRORC type, also becomes possible in HQI.



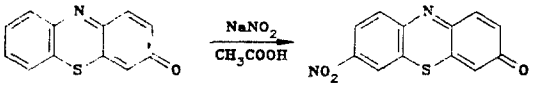
1.1. Effect of the Bridge Heteroatom on the Reactions of Heterocyclic Quinoneimines with Nucleophiles

A characteristic peculiarity of HQI is competition between nucleophilic attack at the quinoneimine fragment and nucleophilic substitution of hydrogen in the aromatic ring; the reactivity parameters depend on the electronegativity of the second bridge atom X and its ability to transmit electronic effects between the quinoneimine and aromatic fragments of the molecule. Research [24, 25] has been devoted to a comparative investigation of the reactivities of HQI with respect to nucleophiles.

The reactions of HQI with N and S nucleophiles have been studied to the greatest extent. Unsubstituted 3H-phenoxazin-(4) and 3H-phenothiazin-3-ones (5) react smoothly with both aromatic and aliphatic amines (with the exception of tertiary amines) and cycloalkylimines to give, in the presence of an oxidizing agent, products of substitution in both the quinoid and aromatic (in the para position relative to the nitrogen atom) fragments. The reactions with weakly basic amines are accelerated when mineral acids are added. The principal products in all cases are 2-amino derivatives (6), and (7)-amino derivatives – the result of competitive activated aromatic substitution – are also formed in small amounts [26-32].



Phenoxazin-3-one (4) reacts with ammonia to give 2-aminophenoxazin-3-one in poor yield [27]. The nucleophilic nitration of phenothiazin-3-one (5) with sodium nitrite in glacial acetic acid has been described; however, the incorporation of a nitro group in the 7 position of the molecule cannot be considered to be proved in connection with the absence of spectral confirmations in the study [33].



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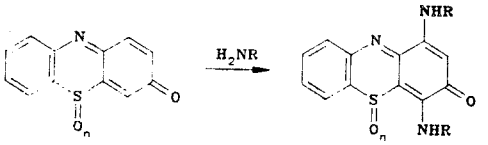
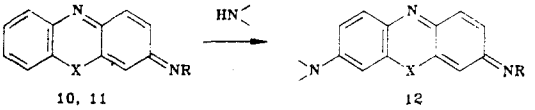
A change in the regioorientation of the attack by various nucleophiles was noted for phenothiazin-3-one 5-oxides 8. The latter are extremely reactive compounds and at the instant of formation give adducts involving the 4 position even with the weak nucleophiles (water, methanol). 1,4-Diaminophenothiazin-3-one 5-oxides 9 are formed in the presence of amines [34].



8 n=1, 2 9

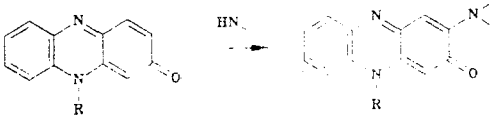
It is interesting that phenoxazine and phenothiazine 3-imino derivatives 10 and 11 on reaction with arylamines and dialkylamines manifest (in contrast to the corresponding quinoneimines 4 and 5) a clearly expressed tendency to form products of substitution in the aryl fragment of the molecule – evidently as a consequence of a decrease in the local π-deficient character of the electrophilic center in the quinoneimine ring due to the donor effect of the imino group [35-38]. 3,7-Diamino derivatives 12 have become widely known as dyes (methylene blue, etc.).



10, 11 12

10 X=O; R=H, Ar; 11 X=S; R=H, Ar

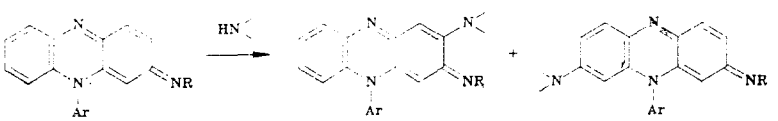
The reactions of 5-alkyl- and 5-arylphenazin-3-ones 13 with amines of any nature proceed with considerably greater difficulty than for HQI that contain an oxygen or sulfur atom as a second heterobridge and lead to the regioselective formation of 2-amino derivatives 14 [39-44].



13 14

13, 14 R=Alk, Ar

3-Arylimino-5-arylphenazines 15 react with amines under severe conditions to give both 2- (16) and 7-amino (17) derivatives. The reactions may be complicated by transamination processes [45-47].

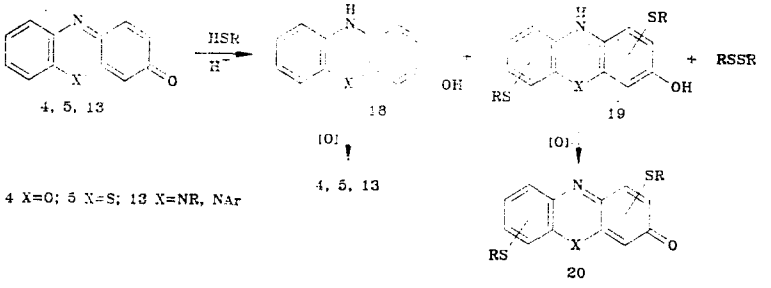


15 16 17

Instances of the attack by nucleophiles in the central heteroring and 1,2 addition to the exocyclic C=O or C=N bond, which will be examined below, have also been noted in the reactions of HQI with amines.

The high nucleophilicity of thiols leads to low selectivity of their reaction with heterocyclic quinoneimines. Thus the least reactive 5-R-phenazin-3-ones 13 in the presence of mineral acids give 2-mono- and 2,7-dithio derivatives [24]. Phenoxazin-3-one (4) reacts with thiophenols to give 2-arylthio-, 7-arylthio-, 2,7-diarylthio-, and 2,7,9-triarylthio-substituted compounds [48, 49]. In addition to the principal products – 2-thio derivatives – phenothiazin-3-one (5), depending on the mode of activation of the reagents, gives 7-monothio derivatives and 1,2-dithio-, 2,4-dithio-, and 2,7-dithiophenothiazin-3-ones in up to 20% yield [24, 50].

In contrast to "hard" amines, "soft" S nucleophiles on reaction with heterocyclic quinoneimines do not give rise to destruction of the central heteroring and do not give stable products of 1,2 addition to the exocyclic double bond. The reactions with thiols proceed under milder (as compared with amines) conditions; decolorization of the reaction mass, which constitutes evidence for the formation of dihydro derivatives of both the substrate and the substitution products (18 and 19, respectively), which can be isolated in pure form, is always observed [51]. The introduction into the reaction of an external oxidizing agent sharply increases the yield of quinoneimine thio derivatives 20 owing to the fact that the HQI is not consumed as the dehydrogenating agent [26].

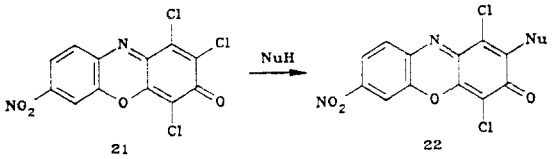


In summarizing the data on the reactivities of heterocyclic quinoneimines it might be concluded that, with respect to their tendency for nucleophilic substitution of hydrogen, 3H-phenoxazine and 3H-phenothiazine derivatives, as expected, substantially surpass 3H-5-alkyl(aryl)phenazines.

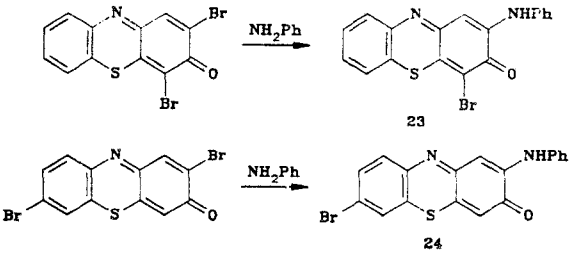
A comparative investigation of the reactivities of HQI and 1,4-benzoquinone-4-arylimines shows that the formation of the central heteroring leads to a strong mutual effect of the quinoid and aromatic fragments, to a decrease in the overall electrophilic reactivity, and to the development of an electrophilic center in the aromatic ring.

The reactions of nucleophiles with heterocyclic quinoneimines that have atoms or groups that are capable of anionic stabilization in the electrophilic centers most often proceed as competitive processes, the selectivity of which depends on the relative ease of substitution of the nucleophile with respect to substitution of the hydrogen atom.

Ipso substitution in the 2-position of the quinoneimine fragment of the molecules proceeds most readily. Thus the reaction of 2- and 1,2,4-trihalo-7-nitrophenoxazin-3-ones 21 with a number of N and S nucleophiles has been described in a patent [52]; the principal products were 2-substituted compounds 22.



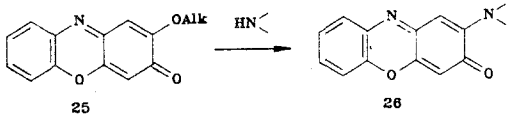
2-Bromophenothiazin-3-one and 2-bromo-5-arylphenazin-3-ones also react with various N and S nucleophiles to give products of ipso substitution of the bromine atom [40, 43]. Only 2-phenylamino derivatives 23 and 24 are formed in the reaction of 2,4- and 2,7-dibromophenothiazin-3-ones with aniline [53].



23

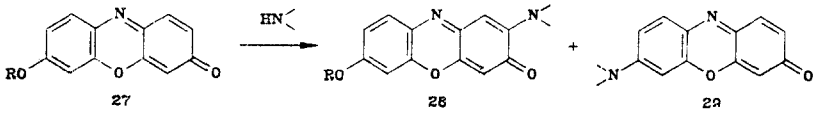
24

2-Alkoxyphenoxazin-3-ones 25 react with aryl- and alkylamines to give exclusively products of substitution of the alkoxy group for an amine residue (compounds 26). Substitution of a hydrogen atom in the free electrophilic center of the aromatic ring does not occur [54].



25 26

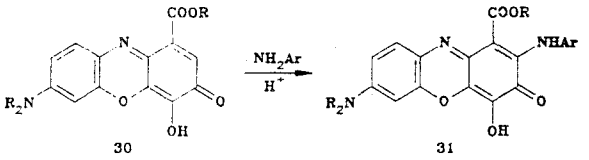
Substitution of a hydrogen atom in the quinoneimine fragment also takes place primarily when an acetoxy or ethoxy group is present in the 7 position. An increase in the nucleophilicity of the amine (on passing from arylamines to alkylamines) makes it possible to carry out the substitution of an ethoxy group also in 7-ethoxyphenoxazin-3-one (27); a mixture of 28 and 29 is formed [55].



27 28 29

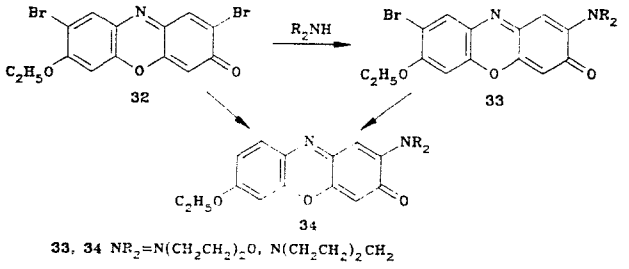
27, 28 R=Alk, CH_3CO

In halocyanine methyl ester 30, in which only the electrophilic center in the quinoneimine fragment is free, the reaction with aniline leads to the formation of 2-arylamino derivative 31 [56].



30 31

Both thiols and amines react with 2,8-dibromo-7-ethoxy-phenoxazin-3-one (32) to give 2-substitution products 33 [57]; heating 32 or 33 with morpholine in the absence of a solvent, in addition, leads to debromination in the 8 position, and 2-cycloalkylamino-7-ethoxy derivative 34 was isolated in good yield [58].



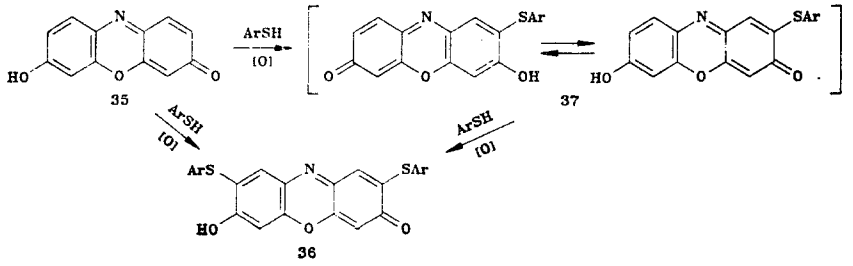
32 33 34

33, 34 $NR_2=N(CH_2CH_2)_2O$, $N(CH_2CH_2)_2CH_2$

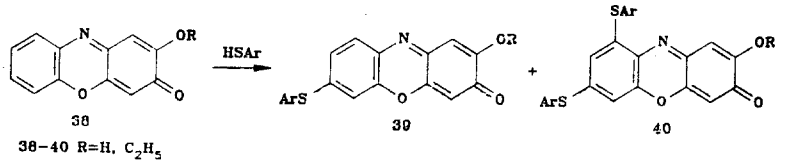
Methods for the preparative dehalogenation of HQI in a reductive medium containing amines have been developed [59-63].

A number of anomalous reactions of heterocyclic quinoneimines with thiols have been described. 7-Hydroxyphenoxazin-3-one derivatives (resorufin, 35), which are inclined to

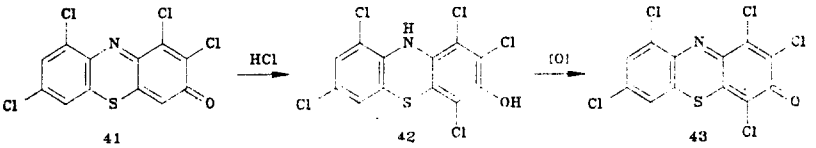
undergo symmetrization of the molecule on protonation, react with thiols to give 2,8-disubstitution products 36 [57]. The incorporation of the nucleophile in the phenolic part of the molecule here is associated with a two-step reaction mechanism that includes the formation of a monosubstituted quinoneimine that has 8-arylthiophenoxazin-3-one structure 37.



Only products 39 and 40 of aromatic nucleophilic substitution were isolated in the reaction of 2-hydroxy- and 2-ethoxyphenoxazin-3-ones 38 with thiophenols [49].

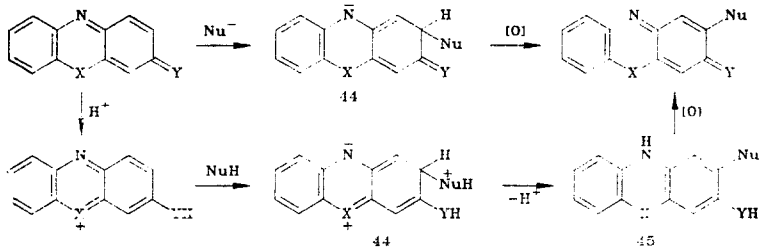


Among other reactions of HQI one may note the addition of hydrogen chloride to polyhalophenothiazin-3-ones 41, which proceeds through the intermediate formation of dihydro derivatives 42, which are then oxidized to polyhalosubstituted 43 [64].



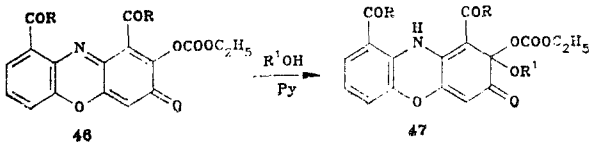
A number of studies [65-69] have been devoted to the nucleophilic functionalization of the chromophore of the antibiotic actinomycin D, which is a 1,2,4,6,9-substituted phenoxazin-3-one. On the whole, here one observes the same basic principles as in the above-examined examples.

It is apparent from the data presented that in reactions involving the nucleophilic substitution of hydrogen HQI, regardless of the site of primary addition of the nucleophile, behave like quinones, forming only products of reaction at the functional group of the reagent with arylamines and thiophenols. In this respect HQI differ from activated aromatic or heteroaromatic substrates, for which the products of S or N addition (kinetic control) are converted to the more stable σ adducts with a C–C bond, which correspond to arylation products [70, 71]. In the HQI series adducts 44, which are formed under kinetic-control conditions, are readily converted, due to irreversible prototropic rearrangement, to the thermodynamically stable dihydro derivatives 45, in which the possibility of dissociation at the newly formed bond is absent [21].



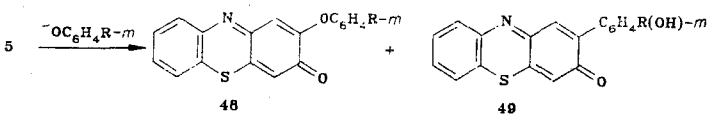
When sigmatropic rearrangement is hindered, the isolation of σ complexes of HQI with nucleophiles is possible. An example of the addition of aliphatic alcohols to activated

phenoxazin-3-ones 46 with the formation of adducts 47 is known [72]. This occurrence of the reaction indicates the relationship of nucleophilic substitution in the quinoid and aromatic rings.



46 47

In the case of nucleophiles that have pronounced ambident character such as phenoxide anions, the formation of products of arylation of the substrate (compounds 49) in addition to products of reaction at the functional group (compounds 48) was observed in the reaction with phenothiazin-3-one (5) [73].



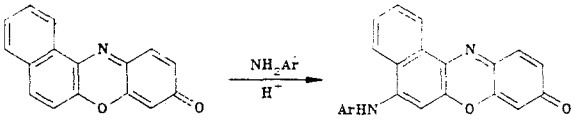
48 49

Thus, in the reactions of nonannelated heterocyclic quinoneimines of the 1 type (Y = O), regardless of the nature of the second heteroatom X, substitution of the hydrogen atom in the 2 position of the quinoneimine fragment takes place more readily than substitution of the atoms or groups in other alternative reaction centers. For the corresponding quinonediimines, on the other hand, the principal pathway of reactions with nucleophiles is the formation of products of aromatic nucleophilic substitution of the hydrogen in the 7 position.

1.2. Effect of Benzo Annelation on the Reaction of Heterocyclic Quinoneimines with Nucleophiles

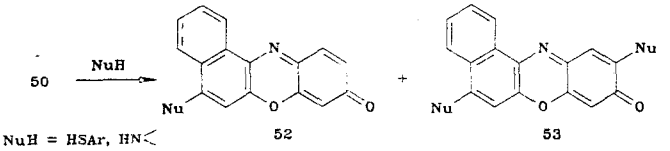
The reactivities of heterocyclic quinoneimines depend substantially on the number and position of benzo-annelated rings. In this respect only a number of phenoxazine derivatives have been studied in sufficient detail. The quantum-chemical calculation of phenoxazinone molecules by the Pariser–Parr–Pople (PPP) [74] and MO LCAO methods within the Hückel [75] and CNDO/2 [76] approximations has been carried out. In addition to the overall effect on the electrophilic properties of the molecules, benzo annelation may substantially change the reactivities of HQI due to blocking of certain electrophilic centers.

Of all of the benzo-annelated phenoxazinones, only benzo[a]phenoxazin-9-one (50) has, like nonannelated phenoxazin-3-one, both electrophilic centers free. Annelation of the [a] type leads to a change in the regioorientation of attack by nucleophiles. The arylamination of 50 with the formation of 5-arylamino derivatives 51 had already been described in 1903 [77]



50 51

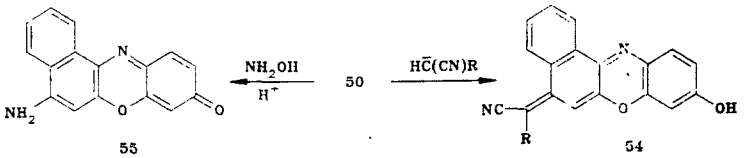
Regioselective substitution of the hydrogen atom in the 5 position of the aromatic fragment also occurs under mild conditions in the reaction of 50 with thiophenols [78, 79] and arenesulfonic acids [80]. Under more severe conditions S nucleophiles as well as cycloalkylamines, also give 5,10-disubstituted derivatives 53 in addition to 10-monosubstitution products 52 [81, 82].



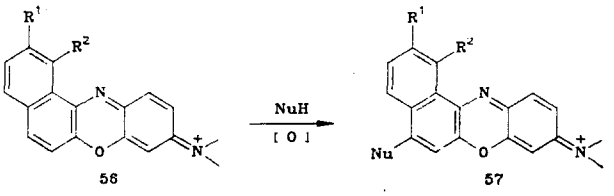
NuH = HSAr, HN< 52 53

Anionic C nucleophiles react with 50 to give products of aromatic nucleophilic substitution 54 with a naphthoquinoid structure [83].

5-Amino derivative 55 was obtained in the reaction of quinoneimine 50 with hydroxylamine [84].

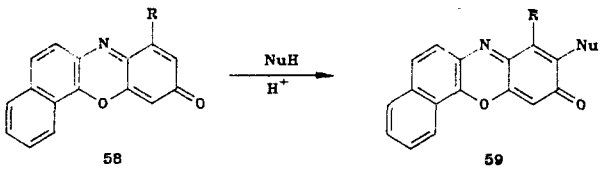


Benzophenoxazonium salts 56 react with nucleophiles also to give 5-substituted compounds 57 [85-96].



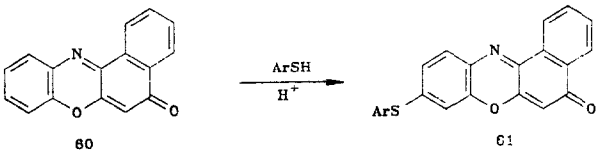
Nu = N<, HNHet, HNAr, SAr, SO_2Ar, OH

Blocking of the electrophilic center in the aromatic part of the phenoxazin-3-one molecule directs the nucleophilic attack of thiophenols and arylamines under conditions of acidic activation of the substrate exclusively to the quinoneimine fragment of the molecule of 50 and its 1-methyl derivative 58; 2-monosubstitution products 59 are formed [82, 97].

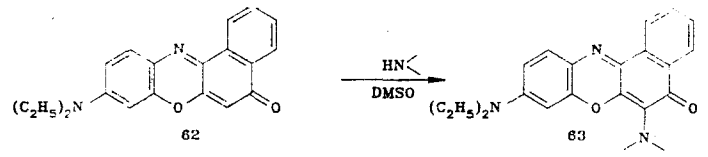


R = H, CH_3

The benzo annelation of phenoxazin-3-one in the quinoneimine fragment is accompanied by a sharp decrease in its electrophilicity (which is also confirmed by the results of polarographic reduction [98]), the result of which is significant hindering of the reaction of nucleophiles with benzo[a]phenoxazin-5-one (60). The reaction of thiophenols with the latter proceeds with the formation of 9-arylthio derivatives 61 and requires more severe conditions than the analogous reaction with quinoneimines 50 and 58 [82].

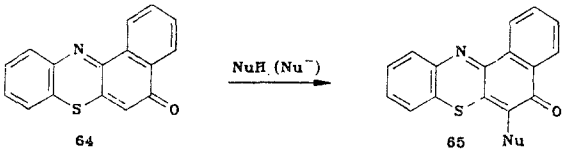


9-Diethylaminobenzo[a]phenoxazin-5-one (62), with a blocked electrophilic center in the aromatic ring, forms 6-amino derivatives 63 on prolonged heating with cycloalkylimines in DMSO [99].

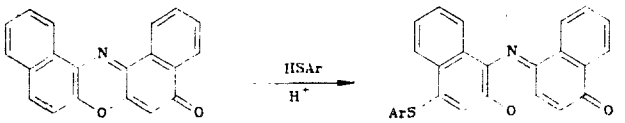


A decrease in the reactivity with respect to a large number of nucleophiles was also noted for benzo[a]phenothiazin-5-one (64). Regardless of the type of nucleophile (N, O, S),

exclusively 6-monosubstituted compounds 65 are formed in the reactions with compounds 64 [100-102].



Annelation of two rings to phenoxazine of the [a] type leads in the case of dibenzo[a, j]phenoxazin-5-one (66) to a further decrease in the electrophilic reactivity. Thus, the attack by N nucleophiles takes place only under very severe conditions and, according to the data in [103], leads to 9- and 13-monosubstituted compounds; on prolonged refluxing in ethanol in the presence of acidic catalysts thiophenols form 9-arylthio derivatives 67 [104].



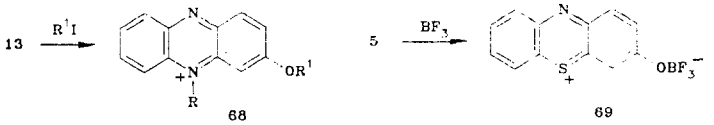
1.3. Effect of the Mode of Activation of the Reagents on the Reaction of Heterocyclic Quinoneimines with Nucleophiles

The substitution of hydrogen and other atoms or groups in heterocyclic quinoneimines by nucleophiles can be facilitated substantially either due to activation by the charge of the substrate or reagent or by simultaneous activation of both reaction partners (reagents); in a number of cases only one of the indicated modes proves to be effective. By varying the mode of activation one can purposefully change not only the rates but also the regiospecificity of the reactions of HQI with nucleophiles.

Cationic activation of the substrate has been widely used in the above-examined reactions of HQI with N nucleophiles (with the exception of strongly basic amines) and thiols. It can be accomplished under the influence of mineral acids and Lewis acids or due to autocatalysis (HS nucleophiles).

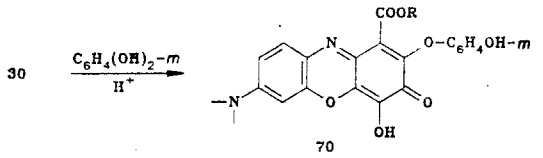
According to the data of spectrophotometric investigations [105, 106], protonation of molecules of unsubstituted HQI and their benzo analogs occurs primarily at the exocyclic heteroatom. Quantum-chemical calculation of the molecules of heterocyclic quinoneimines also gives preference to primary protonation at the exocyclic heteroatom [74, 76].

Of the entire series of HQI, only quinonediimines [107] and quinoneimines of the phenazine series that have sufficient basicities [108] form stable protic and quaternary salts. The alkylation of 5-R-phenazin-3-ones 13 with alkyl halides leads to salts 68 with an o-quinoid structure in which the alkyl group is attached to the oxygen atom of the exocyclic carbonyl group [109]. Phenothiazin-3-one (5) reacts with BF_3 etherate to give deeply colored complex 69, which evidently has a similar structure [110].

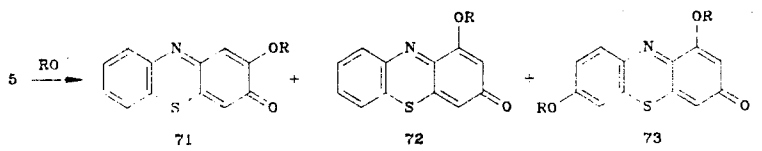


The tendency for protonation at the exocyclic heteroatom in unsubstituted heterocyclic quinoneimines may be due to the great possibilities of localization of the positive charge by the bridge oxygen, sulfur, and, particularly, nitrogen atoms, which leads to significant polarization of the HQI molecules in the ground state [105, 106] (the extreme instability of S-oxides of quinoneimines of the phenothiazine series also indirectly indicates the same thing [34]). At the same time, judging from the data in [111], alternative protonation is also possible in substituted heterocyclic quinoneimines.

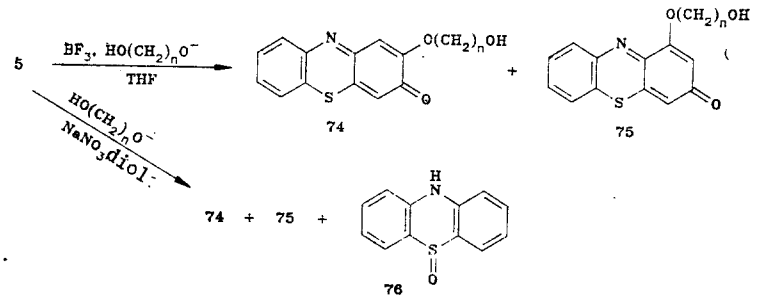
Cationic activation of HQI is sufficiently effective only in reactions with N and S nucleophiles. Weaker O and C nucleophiles, even under severe conditions, are inert with respect to the cations of unsubstituted heterocyclic quinoneimines. Only additional activation of the substrate by an electron-acceptor substituent in halocyanines 30 made it possible to accomplish their aroxylation by resorcinol to 2-substituted 70 in the presence of sulfuric acid [112].



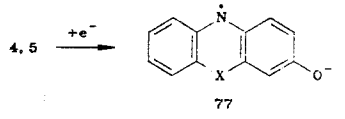
The problem of the direct introduction of most O and C nucleophiles into HQI can be solved by using anionic activation of the nucleophile. Thus, alkali metal alkoxides react with phenothiazin-3-one (5) under mild conditions to give 2-alkoxy (71), 1-alkoxy (72), and 1,7-dialkoxy (73) derivatives in a ratio of 9:4:1; this constitutes evidence for a small difference in the electrophilicities of the 1 and 2 positions in the unactivated HQI molecule [113].



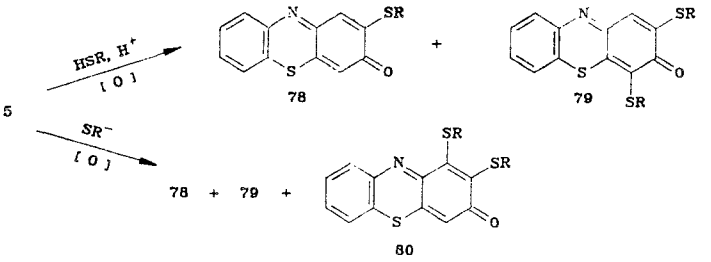
The effectiveness of the simultaneous activation of both reagents was demonstrated in the case of the reaction of compound 5 with glycolates. Activation of the substrate with boron trifluoride makes it possible to carry out the reaction with glycolates even at room temperature. In the direct reaction of compound 5 with glycolates final products 74 and 75 were formed only after prolonged refluxing of the reaction masses. It is interesting that the addition of an external oxidizing agent ($NaNO_3$) in the latter case led to the formation of significant amounts of phenothiazine 5-oxide (76), the mechanism of the formation of which is evidently the reverse of the known mechanism for the formation of phenothiazin-3-one from the S-oxide [105, 110].



The reaction of HQI with "hard" anionic nucleophiles (alkoxides, glycolates) is complicated by dimerization and destruction processes [110, 113]. In strongly polar aprotic solvents (DMSO, DMF) alkoxides reduce HQI to the corresponding stable anion radicals of the semiquinone type 77; nucleophilic substitution is completely inhibited [113]. This fact and the absence of a correlation between the spin densities on the carbon atoms of HQI obtained from the EPR spectra [114] and the directions of nucleophilic attack make it possible to negate the participation of anion radicals 77 in the realization of nucleophilic substitution.



The mode of activation substantially changes the rate and regioorientation of the reaction of HQI with thiols. The reaction of phenothiazin-3-one (5) with thiolates proceeds instantaneously at 0°C; under the same conditions thiols in the presence of an acid react only slowly with the substrate. Although the principal reaction product in both cases is 2-thio derivative 78, the incorporation of a second alkylthio residue under conditions of activation of the substrate leads to the formation of 2,4-dithio derivatives 79, while thiolates under the same conditions form primarily 1,2-dithio derivatives 80 [50].

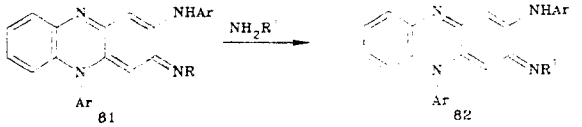


78 79 80

The formation of 1-substituted derivatives both in the case of attack by "hard" alkoxides and "soft" thiolates indicates that the direction of attack by the nucleophile in HQI depends not only on the nature but also on the covalent or ionic state of the reagent.

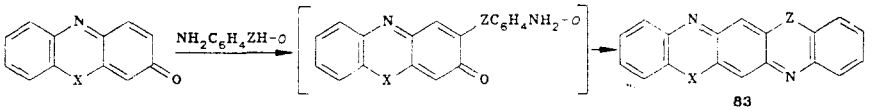
1.4. 1,2 Additions to Heterocyclic Quinoneimines and Reactions in the Central Heteroring

Only a few examples of nucleophilic addition to the exocyclic C=O group are known in this series of heterocyclic quinoneimines [104, 115]. This is evidently explained by both the pronounced competition on the part of alternative 1,4-addition and nucleophilic substitution processes in the aromatic fragment and by the more saturated (as compared with true quinones) character of the exocyclic double bond as a consequence of the donor effect of the bridge heteroatom. At the same time, in heterocyclic quinonediimines 1,2 addition to the exocyclic C=N bond sometimes has synthetic value – most often this involves the hydrolysis of quinonediimines to quinoneimines or transamination [11, 116-119]. Thus, 5-arylphenazine derivatives 81 give the corresponding 3-alkylimino derivatives 82 under the influence of alkylamines under severe conditions [43].



81 82

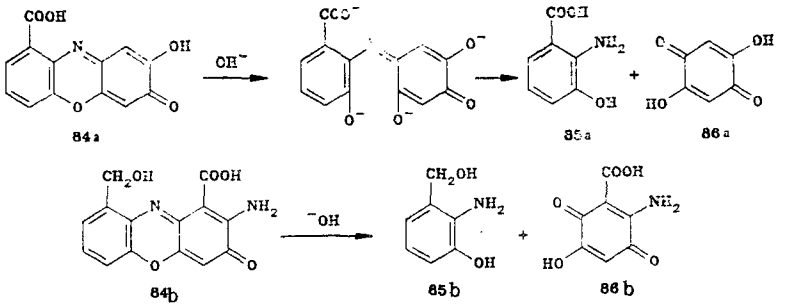
Sterically favorable possibilities for the occurrence of 1,2 addition to the exocyclic C=O group arise in the case of the reactions of HQI with dinucleophiles such as o-aminothiophenol and o-phenylenediamine derivatives. Polycyclic quinonediimines 83 are formed in all cases [54, 120-122].



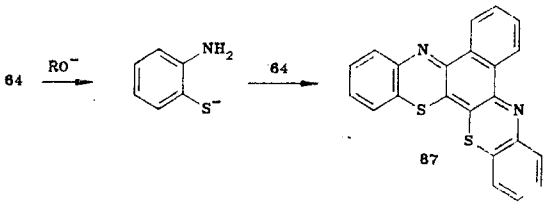
83

Z = S, NH

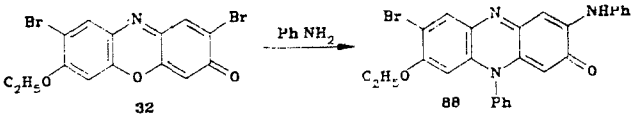
Other rarely encountered alternatives to the above-examined reactions of HQI with nucleophiles are reactions with opening of the central heteroring. Judging from the results of quantum-chemical calculations [75, 76], the carbon atoms attached to the heteroatoms of the central ring are "hard" electrophilic centers, and "hard" anionic nucleophiles in polar solvents are therefore capable of attacking the central ring of HQI. The alkaline cleavage of phenoxazinones 84 to the corresponding o-aminophenols 85 and quinones 86 has been used to establish their structures [123-125].



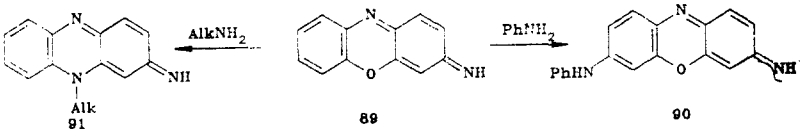
This sort of cleavage has also been noted for benzo[a]phenothiazin-5-one (64). The latter in reactions with alkoxides forms benzo[a] [1,4]benzothiazino[3,2-c]phenothiazine (87) as a minor product; this constitutes evidence for partial destruction of the ring leading to o-aminothiophenol, which condenses smoothly with starting substrate 64 [101].



Electron-acceptor substituents facilitate reactions of a similar type, and in this case even weaker nucleophiles – primary aromatic amines – may attack the heteroring. Thus the corresponding 5-arylphenazinone 88 was obtained from phenoxazinone 32 on reaction with aniline [126].

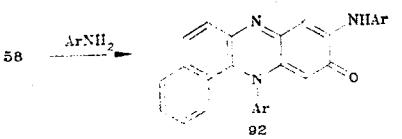


Judging from the data in [127], heterocyclic quinonediimines are capable of the "oxazine–diazine" transformation to an even greater extent than the quinoneimine analogs. Depending on the reaction conditions and the type of amine, 3-iminophenoxazine 89 gives either products of substitution of hydrogen in the 7 position of the molecule (compound 90) or products of transformation of the oxazine ring 91 [127].

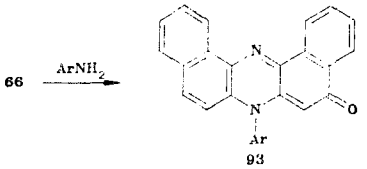


The primary act of attack by the nucleophile in the heteroring can be formally regarded as nucleophilic substitution of the aroxy(arylthio) group in the quinoneimine. However, with primary amines the process ultimately leads not to destruction of the oxazine ring but to transformation to the corresponding phenazine via an "addition–ring opening–ring closing" scheme; this makes it possible to regard the reaction as an ANRORC process.

The transformation to a phenazine proceeds quite readily for benzo[c]phenoxazin-3-one (58). The latter on refluxing with arylamines in alcohol in the absence of acidic activation forms 2-arylamino-5-arylbenzo[c]phenazin-3-ones 92 as the principal products; the central heteroring initially undergoes attack by the amine [97].

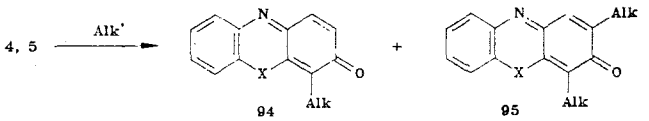


Dibenzo[a,j]phenoxazin-5-one (66) on refluxing with arylamines without a solvent gives 7-aryldibenzo[a,j]phenazin-5-ones 93 in almost quantitative yields; in this case products of substitution of the hydrogen atom are not formed at all [104].

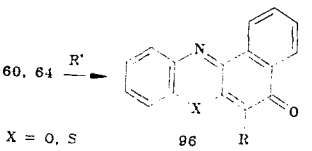


2. RADICAL AND PHOTOCHEMICAL REACTIONS OF HETEROCYCLIC QUINONEIMINES

A series of new studies by Ueno [128-130] were devoted to the reactions of heterocyclic quinoneimines with radicals. Thus, alkyl radicals generated in the oxidation of carboxylic acids with peroxydisulfate in the presence of a silver catalyst react with phenoxazin- (4) and phenothiazin-3-ones (5) to give 4-alkyl (94) and 2,4-dialkyl (95) derivatives; the primary site of attack by the radicals is the 4 position, which, in conformity with calculations by the Hückel MO method, has the maximal free-valence index [128-130].

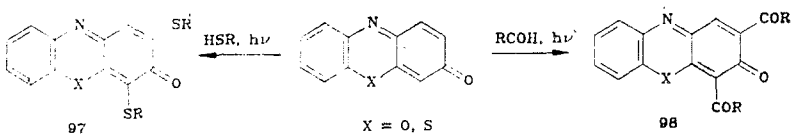


In benzo-annelated derivatives (60, 64) the 6 position (to give compounds 96) undergoes regioselective attack by the alkyl and acyl radicals generated from carboxylic acids, aldehydes, or acetone; the nature of the heteroatom has little effect on the conditions under which the reactions are carried out and the yields of the final products [131-136].



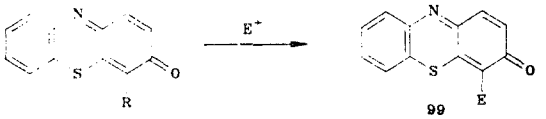
The radical bromination and iodination of non-benzo-annelated HQI also take place in the 4 position [137-139].

Under photochemical-initiation conditions aldehydes and thiols replace hydrogen in HQI in the same way as radical reagents. The yields of the corresponding thio derivatives 97 or ketones 98 usually do not exceed 40%.



3. REACTIONS OF HETEROCYCLIC QUINONEIMINES WITH ELECTROPHILES

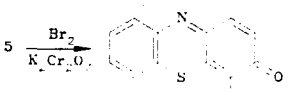
The reactions with electrophilic reagents in the HQI series have found only limited practical application primarily for obtaining halo and nitro derivatives. One's attention is drawn to the contradictory character of the literature data on the site of incorporation of the substituent in reactions with electrophiles; this was associated with the absence, prior to the development of the NMR method, of reliable methods for establishing the structures of polysubstituted HQI. The usual electrophilic mechanism of nitration and halogenation of HQI also seems unlikely. Thus, in the case of the nitration of phenothiazin-3-one (5) and its halo derivatives it was shown that the reaction with the electrophile leads to substitution of a hydrogen atom and halogens in the 4 position of the quinoneimine fragment (to give compounds 99) and not in the more nucleophilic aryl ring [145-147].



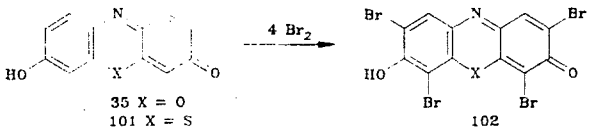
R = H, Hal

This regioorientation is typical for radical substitution in HQI molecules. At the same time, truly electrophilic reactions of HQI, as expected, are markedly hindered. For example, sulfonation in the ring and Friedel–Crafts alkylation have not yet been described. The addition of sulfuric acid to nitric acid in the nitration of phenothiazin-3-one not only does not promote but even hinders the formation of a nitro derivative. In connection with the information set forth above the data on the formation of 6- and 6,8-dinitro derivatives in the nitration of polyhalophenothiazin-3-ones evidently need to be verified [146, 148].

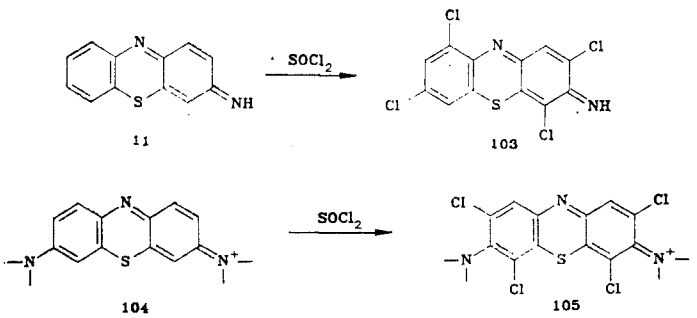
Halogenation reactions extremely graphically confirm the predominance of electrophilic properties in the chemical behavior of HQI. Thus, the halogenation of phenothiazin-3-one (5) proceeds quite selectively in the 4 position (to give compound 100) only in the presence of potassium dichromate. In the absence of an oxidizing agent the resulting hydrogen bromide reacts immediately with the substrate or its bromo derivative to give a product of nucleophilic addition; this ultimately leads to the formation of polyhalo-substituted compounds in the reaction mixture [145, 149-151].



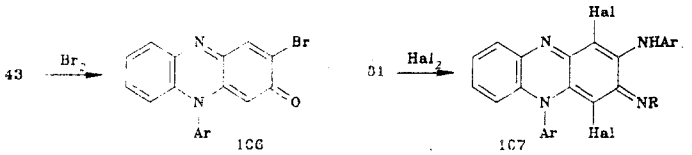
Resorufin (35) and thionol (101) react like phenols and give 2,4,6,8-tetrabromo derivatives 102, which have strong fluorescence, on bromination under mild conditions [152, 153].



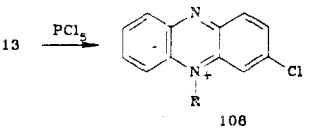
The chlorination of 3-iminophenothiazine (11) with thionyl chloride leads to 2,4,7,9-tetrachloro derivative 103; under similar conditions 3,7-diaminophenazothionium salts 104 are chlorinated to 2,4,6,8-tetrachloro-substituted compounds 105 [154].



In 5-arylphenazin-3-one and imine molecules the donor effect of the bridge arylamino group leads to an overall increase in the nucleophilic properties of the molecules. The bromination of 5-phenylphenazin-3-one (13) takes place in the 2 position of the quinone-imine fragment (to give compound 106) [40] or in the 1 and 4 positions (to give compounds 107) in the case of 2-substituted 3-arylimino-5-arylphenazines 81 [43].



3-Chloro-5-ethylphenazinium chloride (108) was obtained in the chlorination of 5-ethylphenazin-3-one (13) with phosphorus pentachloride [108].



Thus, HQI substrates are convenient substrates for diverse reactions in which they manifest the rather rare (in the heterocyclic series) ability to undergo functionalization under mild conditions by both nucleophilic and radical and electrophilic reagents.

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