RECENT ADVANCES IN THE CHEMISTRY OF PHENAZINE OXIDES (REVIEW)

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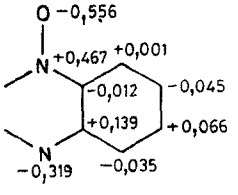
Data on the electronic structures and spectral characteristics of phenazine 5-oxides and 5,10-dioxides are correlated. Methods for the synthesis of N-oxides of the phenazine series and their reactions (reduction, electrophilic and nucleophilic substitution, and photochemical transformations) are examined. Data on the natural compounds of this series are presented.

The chemistry of phenazine oxides, except for the material that is discussed in detail in the classical book by Swan and Felton [1], is examined in the present paper.

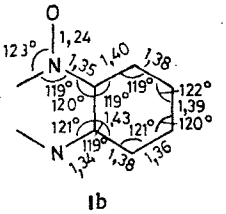
Electronic Structures. The electronic structures of phenazine 5-oxide (I) and 5,10-dioxide (II) have been calculated by the Pariser–Parr–Pople (PPP) method [2, 3]. The electron-density distribution (calculated by the complete neglect of differential overlap (CNDO) method [4]) is depicted in molecular diagram Ia. The photoelectronic spectra [5, 6] of oxide I and the effect of substituents are in agreement with the calculated values (CNDO) [5]. The absorption bands in the photoelectronic spectra were assigned as follows: upper occupied molecular orbital (UOMO), −8.00 eV, a π orbital with b_2 symmetry, similar to the $2b_{2g}$ UOMO of anthracene; second occupied orbital, −9.21 eV, π_{a_2}, almost identical to the $2b_{3g}$ orbital of anthracene; fifth occupied orbital, −9.38 eV, localized on the oxygen atom; seventh occupied orbital, −11.10 eV, similar to the $2b_1$ orbital of anthracene.

Electronic Spectra. The absorption spectra of oxides I and II are extremely similar to the spectra of anthracene, although their shift to the long-wave region is evident. The L_a and L_b bands of monoxide I are found, respectively, at 267 (log ε 5.2) and 423 nm (3.95), while those of dioxide II are found at 287 (4.95) and 484 nm (4.1) (in alcohol) [2, 7, 8]. The solvent has little effect on the absorption spectra, in contrast to what is observed in the case of N-oxides of the lower amines. The spectra can be interpreted completely on the basis of MO calculations and calculations of the polarization of the fluorescence spectra [2]. The energy of the first absorption band corresponds to the difference in energy between the UOMO and lower vacant molecular orbital (LVMO) calculated from the difference in the oxidation and reduction potentials [3]. Compound I has weak fluorescence in aprotic solvents and moderate fluorescence (Φ = 0.15, λ_{max} 485 nm) in water [9], and II also fluoresces (λ_{max} 505 nm) [2]. The fluorescence of both oxides changes in acidic media when pH > pK_a. This fact indicates that the basicity of the excited state is higher than that of the ground state [7]. Phosphorescence was not detected.

Other physicochemical characteristics of phenazine oxides — the dipole moment (1.76 D, I) [10, 11], dissociation constant (pK_a 1.13 in water, I) [12], IR spectrum [13], and bond lengths and valence angles (Ib) [14, 15] — have been presented.



Ia



Ib

The PMR spectra of oxides I and II, the parameters of which were calculated by an iteration method [16, 17], and the ^{13}C NMR spectrum of 1,6-dimethoxyphenazine 5-oxide [18] have

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been described. The mass spectra of I and II have been studied: the molecular ion of I splits out O, CO, CN, and N_2O [19-21]. The ESR spectra of the radical anions of I and II [22-24] and the radical cation of II [25-28] have also been interpreted. The radical cation of II undergoes an interesting dimerization reaction.

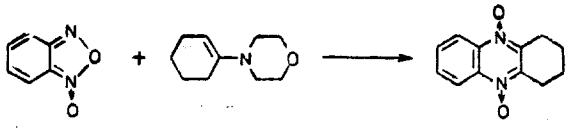
Preparative Methods

Many N-oxides or N,N'-dioxides can be obtained by direct oxidation of the corresponding phenazines. The reaction usually proceeds readily in a solution of hydrogen peroxide in acetic acid at 50-55°C with subsequent dilution of the reaction mixture with water. m-Chloroperbenzoic acid has been used in some cases, and tert-amyl hydroperoxide in the presence of $MoCl_5$ has recently been proposed as the oxidizing agent [29].

The oxidation reaction depends on electronic and steric factors. Rozum and Kiprianov [30] have shown that oxidation takes place more readily at the nitrogen atom with the higher electron density. The selective oxidation of 2-methoxyphenazine to the 10-oxide derivative is therefore possible under certain conditions [30, 31]. However, the selectivity decreases when most other substituents are introduced, and this method is not of great preparative value. From this point of view it may be assumed that derivatives of the 5,10-dioxide can be easily obtained from β-substituted phenazines. The steric effects of substituents in the α position are of great importance: the N-oxidation of 1-substituted phenazines gives only the 5-oxides, except for those cases in which the substituent is a strong electron donor (OH or OR).

N-Monoxides have sometimes been obtained by partial reduction of the corresponding N,N'-dioxides [32], but if the two nitrogen atoms are nonequivalent, this method is completely unsuitable because of the low selectivity of the reduction. In this connection, it should be pointed out that phenazine N,N'-dioxides undergo dc polarographic reduction with one four-electron wave. A peculiar example is the reduction of benzo[a]phenazine 7,12-dioxide with hydrogen peroxide and acetic acid to the 7-oxide (in 16% yield) [33]: deoxygenation of the substrate occurs initially in this case and is followed by regeneration of the N-oxide. Oxygen is possibly split out from both nitrogen atoms [34], while reoxidation of the substrate occurs only in the 7 position, since approach to the 12 position is sterically hindered.

Until recently, in addition to the direct oxidation of phenazines, the Wohl—Aue condensation of nitrobenzenes and anilines in the presence of bases was practically the only method for the synthesis of phenazine N-oxides. Recently developed preparative methods have facilitated the approach to known compounds and have made it possible to synthesize new compounds. The original method of Haddadin and co-workers [35] is based on a completely new principle for the construction of the phenazine ring. The authors have observed that benzofuroxan (III) reacts with 1-morpholinocyclohexene to give 1,2,3,4-tetrahydrophenazine N,N'-dioxides.

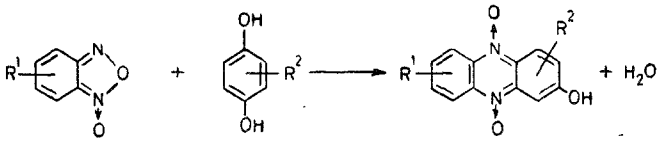


III

Other cyclohexanone derivatives (for example, some azomethines [36]) also react similarly. Derivatives of 1,2,3,4-tetrahydrophenazine 5-oxide have been obtained by reaction of azomethines and cyclohexanone enamines with benzofurazan in triethylamine [3].

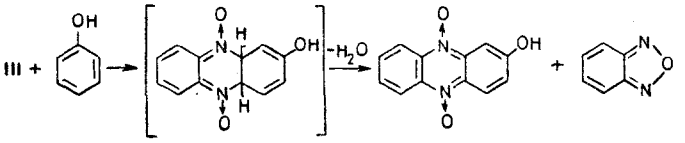
The reaction of benzofuroxans with enamines proceeds formally through a step involving 1,4-cycloaddition. However, benzofuroxan does not react with tetracyanoethylene or other dienophiles [37]; this excludes four-center addition of the Diels—Alder type in the first step. The authors propose that the reaction with enamines is similar to the reaction with enolate anions [38] (which leads to substituted quinoxaline 1,4-dioxides) in the sense that in both cases the negative center (the β-carbon atom of the enamine or the enolate carbanion) attacks the benzofuroxan, after which the intermediate undergoes cyclization and, respectively, deamination or dehydration. It was later observed that benzofuroxans react with hydroquinones [39] in an aqueous alkaline suspension and also with phenols and naphthols [40] in the presence of a base to give phenazine N,N'-dioxide derivatives. In the latter

case the reaction is more complex and in the case of the simplest reagents includes reduction of a portion of the benzofuroxan to a benzofurazan.



R^1 = H, alkyl, CH_3O, C_2H_5O, halogen, COOR

R^2 = H, alkyl, aryl, halogen, SO_2R, NO_2, COOH, CH_2CONR_2

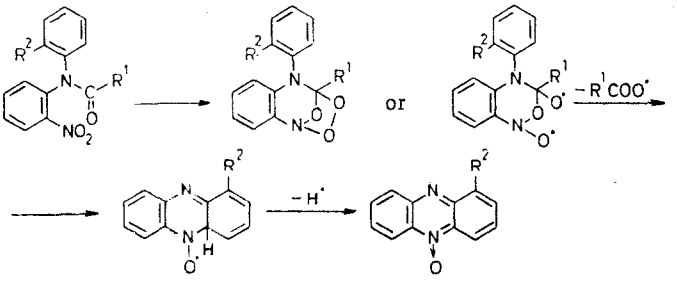


Reactions used for the synthesis of the phenazine ring constitute the basis of other preparative methods. In a study of the mechanism of the Wohl—Aue reaction, Serebryanyi [41] assumed potential intermediates in addition to nitrosodiphenylamines and 2-nitrodiphenylamines, but the latter did not undergo cyclization under the typical conditions of the Wohl—Aue reaction (refluxing in benzene or in toluene in the presence of potassium hydroxide). In contrast to these data, Cross and co-workers [31] were able to accomplish the cyclization at higher temperatures (130-150°C). The range of application of this reaction has not yet been studied, and the only example up until now has been the cyclization of 4-chloro-2-nitrodiphenylamine to 2-chlorophenazine 10-oxide in 30-39% yield.

Cyclization of 4'-substituted 2-nitrodiphenylamines can occur in the presence of fuming sulfuric acid [31], for example,

2,2'-Dinitrodiphenylamines have been used as starting materials for the preparation of phenazines. These compounds form N-oxides [31] under mild reduction conditions in alkaline media.

The cyclization of nitrodiphenylamines can also be accomplished by irradiation with UV light. Good yields were obtained only if the resulting N-oxide does not undergo subsequent photoisomerization with a considerable quantum yield [42]. N-Acyl-2-nitrodiphenylamines are formed in this reaction. Transfer of an oxygen atom from the nitro group to the N-acyl group occurs initially and is followed by elimination of an $R^1COO^\bullet$ radical:



Base-catalyzed reactions of 2,2'-bis(hydroxylamino)diaryl sulfones [43] and 2-hydroxylaminocyclohexanone oxime [44], which lead to octahydrophenazine N,N'-dioxides, have less practical value.

Nevertheless, one should note that some phenazine N-oxides have also been obtained by the Wohl—Aue method [45].

TABLE 1. Reduction Half-Wave Potentials Measured with Respect to a Saturated Calomel Electrode

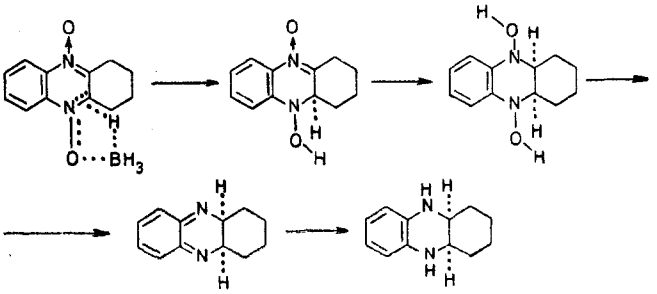
Compound	$E_{1/2}$, V
Phenazine	−0,32
1-Methoxyphenazine	−0,34
2-Methoxyphenazine	−0,37
2-Nitrophenazine	−0,19; −0,47
1-Phenylphenazine	−0,30
2-Phenylphenazine	−0,29
Phenazine 5-oxide	−0,23; −0,38
2-Methoxyphenazine 10-oxide	−0,29; −0,42
2-Methoxyphenazine 5-oxide	−0,24; −0,38
2-Nitrophenazine 10-oxide	−0,17; −0,51
2-Phenylphenazine 10-oxide	−0,20; −0,33
2-Phenylphenazine 5-oxide	−0,19; −0,33
1-Phenylphenazine 5-oxide	−0,22; −0,32

Reduction

Splitting out of oxygen from phenazine oxides occurs very readily as compared with N-oxides of simpler azines.

A complete list of reducing agents that are usually employed in reactions of this type is presented in [1, 45, 46], and we will therefore not repeat it here. We note only that in many cases (for example, in the catalytic hydrogenation or reduction by metals) the reduction of phenazine oxides bypasses the phenazine step and leads to 5,10-dihydrophenazines.

The interesting reduction of N-oxide groups and the azine ring was reported in [47]: cis-1,2,3,4,4a,5,10,10a-octahydrophenazine is formed in the reaction of 1,2,3,4-tetrahydrophenazine 5,10-dioxide with sodium borohydride. It has been proved that neither the tetrahydrophenazine itself nor its N-monoxide is the intermediate in this stereospecific reduction. A reaction mechanism in which the boron atom of the borohydride group and the oxygen atom of the N-oxide are coordinates with simultaneous hydride-ion transfer to the C_{5a} atom has been proposed.



The ability of phenazine oxides to undergo facile splitting out of oxygen atoms is also apparent from polarographic data. For example, the following reduction half-wave potentials are presented in [48]: pyridine 1.018, quinoline 1.164, acridine 0.854, quinoxaline 0.650, and phenazine 0.218 V.

The polarographic characteristics of phenazines and their oxides have been widely used in connection with the fact that one of the reasons for the biological activity of phenazine derivatives is the presence in them of a labile redox system. A detailed discussion of all of the polarographic data obtained under various conditions goes beyond the limits of our review.

Data cited in one of the papers [49] are presented in Table 1.

The data presented in Table 1 and in [50-58] make it possible to establish that in aqueous ethanol mixtures the polarographic reduction of phenazine N-oxides proceeds in two steps, the first of which corresponds to two-electron (or four-electron in the case of the dioxide) splitting out of the oxygen atoms, the second of which corresponds to two-electron reduction of the phenazine system to the 5,10-dihydro base. The $E_{1/2}$ value of the second step is somewhat higher than the $E_{1/2}$ value of the corresponding phenazine. Electron-donor

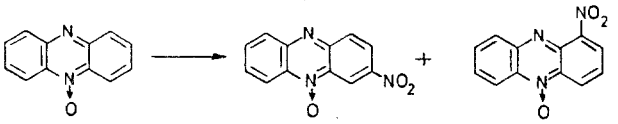
substituents lead to more negative potentials than the potential of the base compound, while electron-withdrawing substituents display the opposite effect; an α or β orientation of the substituent and the position of the substituent with respect to the N-oxide group usually have a negligible effect. A review of the polarographic reduction of azine N-oxides is presented in [46].

It has been reported [23] that in dimethylformamide (DMF) some N,N'-dioxides give two well-resolved one-electron waves. A linear dependence of $\Delta E_{1/2}$ on the σ_p constants and the energy of the first free π orbital is observed under these conditions. Data on the polarographic characteristics of oxides I and II for alternating current have been obtained: the height of the peak of the ac polarogram and the half-wave potential ($E_{1/2}$) of the first wave are approximately linear functions of the stabilities of the radicals [53].

Electrophilic and Nucleophilic Substitution

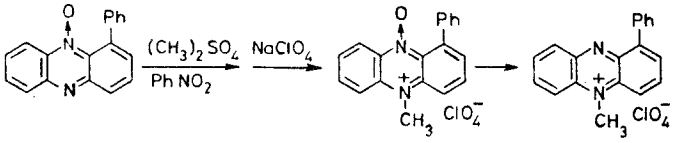
The 5-N-oxide group in phenazine N-oxides activates the condensed benzene ring, particularly in the 3 and 1 positions, with respect to electrophilic and nucleophilic reagents.

The nitration of phenazine 5-oxide [54-56] leads to 3-nitrophenazine 5-oxide (which will subsequently be called 2-nitrophenazine 10-oxide) and to the 1-nitro isomer, which is formed in smaller amounts. However, phenazine is nitrated exclusively in the α position.



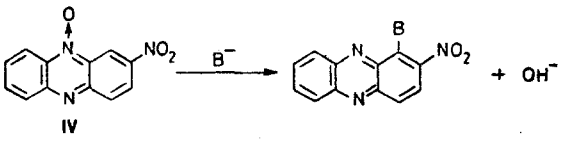
The direction of attack [45] in the nitration of substituted phenazine N-oxides [45] corresponds to the scheme presented above and to the electronic effects of the substituents. Some electrophilic reactions with phenazine 5-oxide are similar to the reactions of azine N-oxides. For example, acetic anhydride reacts with 4-tetrahydrophenazine N,N'-dioxide [57] to give 1-acetoxy-1,2,3,4-tetrahydrophenazine 5-oxide and 1,4-diacetoxy-1,2,3,4-tetrahydrophenazine via a mechanism that is probably similar to the mechanism (which has been studied in detail) [45] of the reaction of α-picoline N-oxide. Tosyl chloride reacts with phenazine 5-oxide to give 1-hydroxyphenazine [58].

The oxygen atom of the N-oxide function is sometimes used as a protective group; thus N'-methylphenazinium perchlorate N-oxide is formed in the reaction of dimethyl sulfate with substituted N-oxides [59, 60]. Substituted phenazinium derivatives, the structure of which is completely unambiguous, are obtained by reduction.



Nucleophilic substitution in the aromatic ring is accomplished quite readily owing to the presence of two nitrogen atoms in the molecule. Substitution occurs more readily if one or both nitrogen atoms are oxidized to the N-oxide. Vivian [61] was the first to report activation of the halogen by the oxide group in 1- or 2-halophenazine oxides, and this fact was subsequently confirmed by many authors. Amines [62], RS^- [63], OH^- [61], and RO^- [64] have been used as nucleophilic reagents. The reaction is accompanied by a certain degree of reduction of the N-oxide group. Tada [63] has presented an important example of nucleophilic substitution. Methylthiophenazines are formed from 1- and 2-chlorophenazine 5-oxides in 4 and 18% yields, respectively, together with a large amount of the corresponding N-oxides, under identical conditions and in the case of equimolar amount of CH_3S^-. Other leaving groups may be SO_2CH_3 and NO_2. For example, 2-hydroxyphenazine 5,10-dioxide is formed in quantitative yield when 2-methylsulfonylphenazine 5,10-dioxide is heated with potassium hydroxide, and the reaction of 2-nitrophenazine 10-oxide (IV) with methoxide ion gives 2-methoxyphenazine 10-oxide in good yield [66].

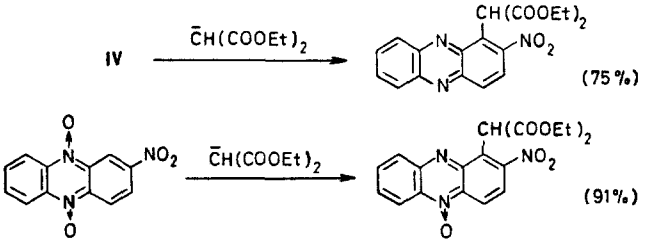
If the phenazine N-oxide molecule is activated to a sufficient extent by, for example, a nitro or sulfo group, a hydrogen atom of the benzene ring may be the leaving group.



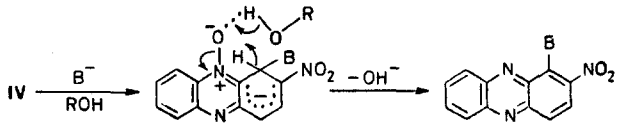
IV

In the case of nitrophenazine N-oxides the reaction proceeds at room temperature and frequently gives the products in high yields with many nucleophilic reagents: potassium cyanide [67], amines [67], the conjugate bases of ketones [68], β-diketones, β-keto esters, and β-cyanoesters [69], imidazole, pyrazole [70], and indoles [71]. In nucleophilic substitution of this type the oxygen atom of the N-oxide group not only has an activating effect but also plays an important role in the elimination of a hydride ion. This step is usually the most difficult one in nucleophilic reactions of aromatic and heteroaromatic compounds, since the hydrogen atom leaves with its electron pair only in the presence of a suitable oxidizing agent. Oxidation can take place intermolecularly under the influence of another reagent (for example, potassium chlorate in the synthesis of alizarin from anthraquinone-β-sulfonic acid) or by means of a second molecule of the substrate.

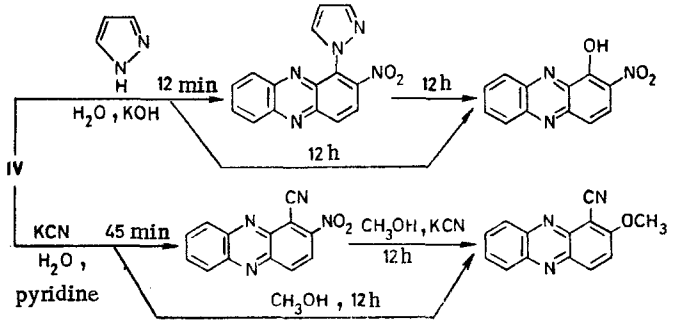
Elimination of H^- may also take place intramolecularly in the step involving the intermediate, and in this case the reaction proceeds more readily. This is observed when the nucleophilic group or the group in the intermediate can be reduced. The well-known amination of aromatic nitro derivatives by means of $NHOH^-$ and the reactions of nitrophenazine N-oxides under discussion here are examples of these two variants. In the latter reactions the closeness of the oxygen atom to the site of attack by the nucleophilic reagent is important [72]:



According to the mechanism proposed in [72] with allowance for the distance between the hydrogen atoms in the 1 position and the oxygen atom in the 10 position, a solvent molecule assists in splitting out of a hydride ion:

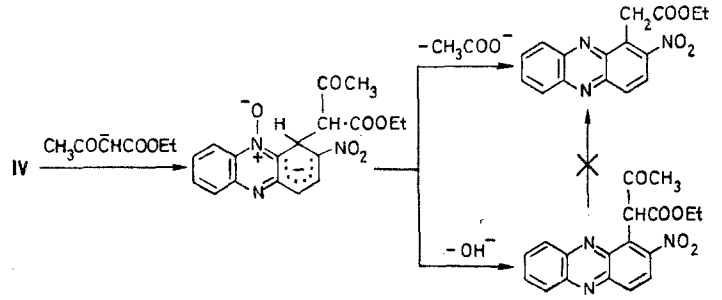


In some cases the overall scheme is much more complex than the scheme presented above. This is the case if the product of the "normal" reaction undergoes further transformations, for example [67, 70]:

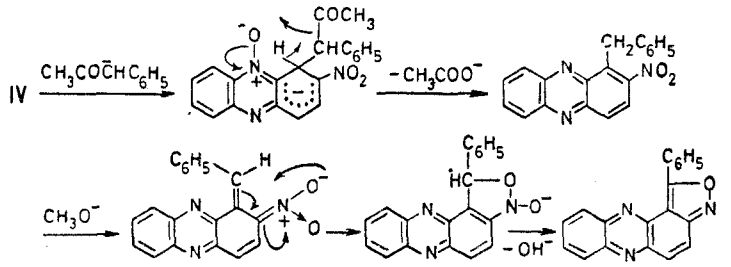


The reaction also proceeds in a more complex manner if another pathway for substitution of the hydride ion is possible. The presence of an oxygen atom in the N-oxide group also plays the chief role in this case. As an example we present the reaction of 2-nitrophenazine 10-

oxide (IV) with acetoacetic ester. In this case ethyl 2-nitro-1-phenazylacetate is formed along with the "normal" condensation product — ethyl 1-(2-nitro-1-phenazyl)acetoacetate [69].



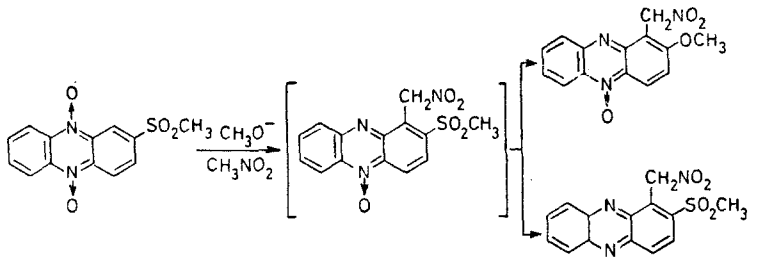
The "unusual" reaction product may undergo further changes: for example, oxide IV reacts with benzyl methyl ketone in the presence of CH_3O^- to give 1-phenylisoxazolo[4,3-a]-phenazine [68] instead of the "unusual" 1-benzyl-3-nitrophenazine.



The assumption that the closeness of the oxygen atom to the site of attack in the case of 2-nitrophenazine 10-oxide is of significance is confirmed by the fact that the reaction of 1-nitrophenazine 5-oxide with the pyrazolyl anion leads to 1-nitro-2-(1-pyrazolyl)phenazine 5-oxide, whereas the reaction with aliphatic amines, which attack the 4 position, gives 1-nitro-4-alkylaminophenazines [73].

The reaction schemes are based on the assumption of the formation of an intermediate σ complex. This hypothesis has recently been confirmed experimentally: a σ complex was detected in the reaction of 2-nitrophenazine 10-oxide with amines [74].

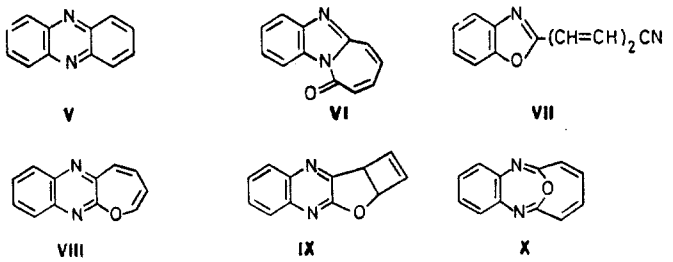
Direct nucleophilic substitution in 2-methylsulfonylphenazine 5,10-dioxide was reported in [65].



Photochemistry

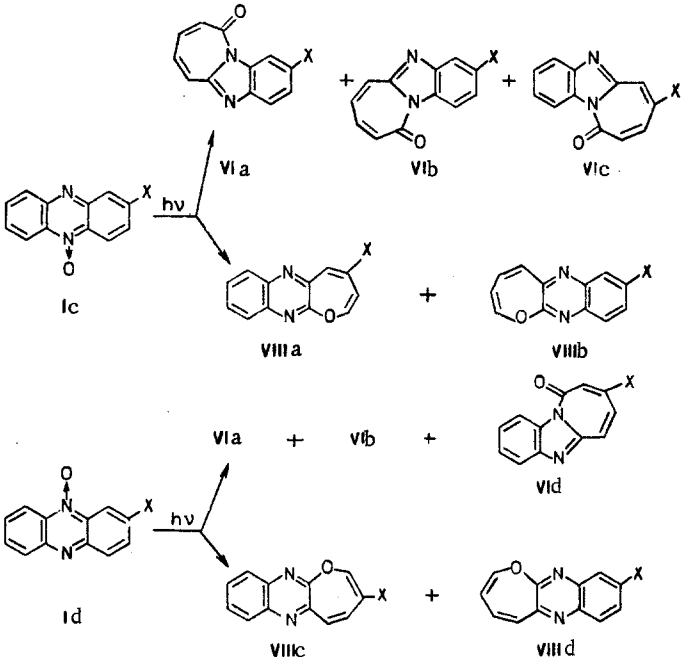
Irradiation of phenazine 5-oxide I in benzene, acetonitrile, and other solvents leads to phenazine V and isomerization products — lactam VI, nitrile VII, oxepinoquinoxaline VIII and its photorearrangement product (IX), and annulene X [75]. In contrast to photoreduction to phenazine, which gives the products in higher yields in alcohols and is slowed down by oxygen, photoisomerization is possibly realized through the singlet state. (See scheme on following page).

The primary photochemical mechanism and thermal transformations that lead to isomerization products VI-X have been studied. Judging from the amounts of structural isomers VI and VIII obtained in the photoisomerization of a pair of substituted phenazine N-oxides (Ic and



Id), any possibility of occurrence of the reaction through annulene to give lactams VI and oxepinoquinoxalines VIII is excluded [76].

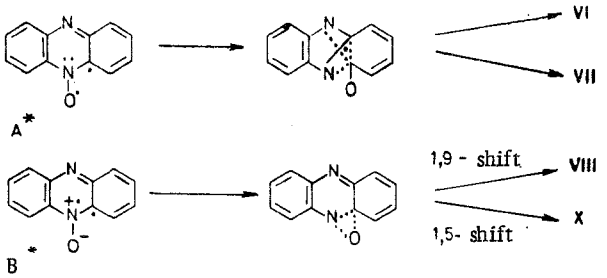
The distribution of structural isomers VIa-d also proves that the carbocyclic ring should be perpendicular to the plane of the molecule during the I → VI isomerization. These data and the solvent effects observed in the photoisomerization of I in a mixture of acetonitrile and water [77] make it possible to assume that there are two different pathways for the formation of oxepinoquinoxalines VIII and lactams VI. In fact, the quantum yields of VI (and VII) are intimately associated with the percentage of water in the mixture of solvents and decrease markedly as the water concentration increases. The quantum yields of compounds of the VIII type are almost independent of the composition of the solvents. The difference in the two photochemical pathways of the reaction is related to the differences in the active excited states, since the change in the first band of the absorption spectrum of oxide I on passing from acetonitrile to a mixture of acetonitrile with water corresponds to the change in the quantum yields of lactams VI.



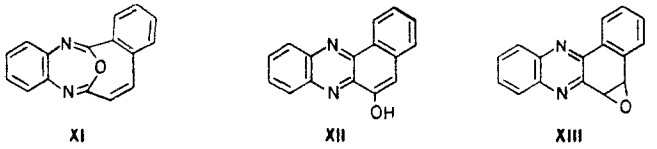
In conclusion, we note that the formation of compounds of the VI and, possibly, VII type includes excitation of the free pair of electrons of the oxygen atom. The resulting π* state is bent in such a way that the carbocyclic ring is oriented perpendicular to the plane of the remainder of the molecule. The process recalls isomerization of the benzene → benzvalene type. There are no stable intermediate particles between the excited state and compounds of the VI type. Compounds of the VIII type are formed from the pure ππ* state, and in this case simple migration of oxygen takes place without any structural rearrangements. In the following scheme (see following page), the two electronic structures that make up the active excited state are designated A* and B*.

In conformity with the results of calculation by the CNDO (complete neglect of differential overlap) method [4] for oxide I, the nπ* transition (2.575 eV, f = 0.0000) is realized more readily than the ππ* transition (3.238 eV, f = 0.328). Both types of reactions are observed for most phenazine N-oxides, and this suggests that the two excited singlet states are close to one another.

The predominance of one of the reactions is therefore determined by the changes in the character of the substituents, as well as by the effect of solvents. If the active state of

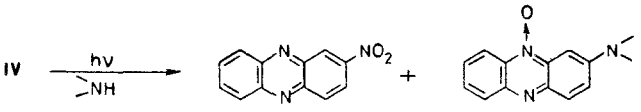


phenazine N-oxides has pure ππ* character, reaction of only one type occurs, as, for example, in the case of benzo[a]phenazine 7-oxide, irradiation of which leads almost exclusively to products of oxygen migration without structural rearrangements — to annulene XI [78], 6-hydroxybenzo[a]phenazine (XII), and 5,6-dihydrobenzo[a]oxireno[c]phenazine (XIII) [19].



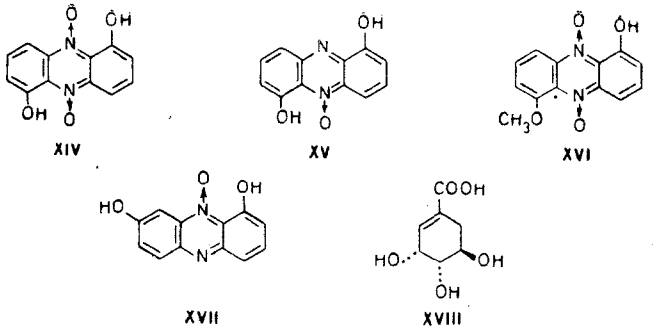
The skeletal rearrangements observed in the fragmentation of the molecular ion of I to $(M - CO)^{+\cdot}$ and $(M - CN)^{+\cdot}$ ions and the photoisomerization processes have been correlated [21], and two ionic structures responsible for the fragmentation of oxide I have been proposed.

It was recently confirmed that reduction to 2-nitrophenazine and substitution to give 2-alkylaminophenazine 10-oxides also occur during irradiation of 2-nitrophenazine 10-oxide in the presence of primary and secondary amines [74].

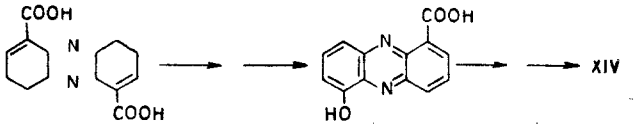


Natural Compounds

Several natural phenazine oxides — 1,6-dihydroxyphenazine 5-oxide (XV) [80], myxin (XVI) [81], 1,8-dihydroxyphenazine 10-oxide (XVII) [82] — have been synthesized from microbiological sources. Their structures are similar to the structure of the known [1, 45] iodinin (XIV).



The biosynthesis of phenazine pigments is still under thorough study. It has been observed [83, 84] that 6-hydroxyphenazine-1-carboxylic acid can be converted to iodinin (XIV) and that shikimic acid is the only source of carbon in the construction of the phenazine skeleton [85]. Some disagreement relative to the schemes of incorporation of labeled XVIII has developed between the two chief groups [83, 84] of researchers engaged in the study of this problem. The Holliman group recently adopted the scheme proposed by the Hollstein group. The reliably established steps in the biosynthesis of phenazines are shown in the following scheme:



The high degree of interest in myxin (XVI) is due to its antibiotic properties [86]. An incorrect structure was initially proposed for it [87] but was immediately corrected [88, 89].

Iodinin analogs have been synthesized as possible antimicrobial agents [90]. Other derivatives have been reported in patents. Myxin (XVI) in the form of a labeled complex displays antimicrobial activity and is used for the treatment of skin bacterial infections of dogs and cats [91].

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METHANOLYSIS AND HYDROLYSIS OF DERIVATIVES OF METHYL 2,5- AND 4,5-DIHYDROFURAN-2-CARBOXYLATES

D. O. Lolya and K. K. Venter

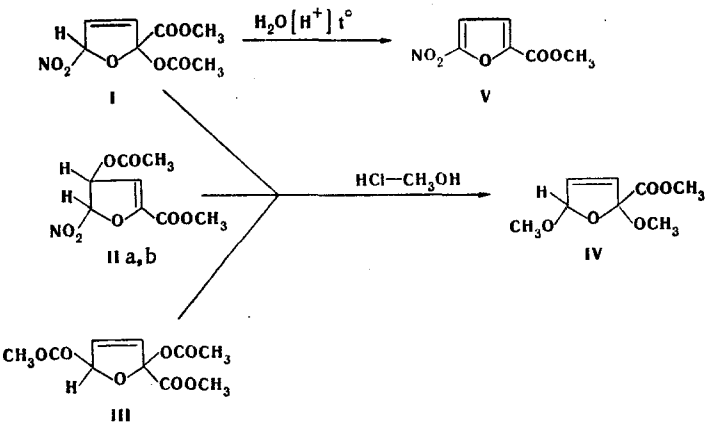
UDC 547.722.5'724:543.544:542.938

Methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate is formed in the reaction of HCl—CH_3OH with methyl 5-nitro-2-acetoxy-2,5-, 5-nitro-4-acetoxy-4,5-, and 2,5-diacetoxy-2,5-dihydrofuran-2-carboxylates, whereas methyl 2,5-dioxo-3-pentenoate bis(2,4-dinitrophenylhydrazone) and 4-oxo-2-penten-1,5-dioic acid 2,4-dinitrophenylhydrazone are isolated in the presence of 2,4-dinitrophenylhydrazine. Methyl 5-nitrofuran-2-carboxylate is formed by treatment of methyl 5-nitro-2-acetoxy-2,5-dihydrofuran-2-carboxylate with aqueous solutions of acetic or phosphoric acid.

Acid hydrolysis with identification of the products in the form of hydrazones is frequently used for the establishment of the position of the substituents in the furan and dihydrofuran rings [1-4]. The possibilities of the method for the establishment of the structures of methyl esters of some 2,5- and 4,5-dihydrofuran-2-carboxylic acids (I-III) were determined in the present research [5].

We first found that esters I-III are not cleaved by the action of HCl in methanol but readily undergo nucleophilic substitution of the nitro and acetoxy groups by a methoxy group to give the same product (IV) — methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate. Moreover, isomerization to give a 2,5-dihydrofuran ring occurs in the case of II in the form of the cis and trans isomers (IIa, and IIb, respectively). We also obtained III in addition to methyl 5-nitrofuran-2-carboxylate (V) by a process similar to the isomerization we observed for IIb in [6] when it was treated with sodium acetate.

Despite the indications in [4], I was not converted to V by the action of HCl in methanol. We observed that I is capable of undergoing "aromatization" to V under the influence of acid reagents in the presence of water, for example, when it is heated with 1% acetic acid or 10% phosphoric acid.



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