EFFECT OF THE ACID-BASE PROPERTIES OF HETEROAROMATIC COMPOUNDS ON THEIR ELECTROPHILIC SUBSTITUTION REACTIONS (REVIEW)

L. I. Belen'kii

UDC 547.562'72'732'771'787'789'796.04:543:87(047)

The effect of the properties of heteroaromatic compounds as acids and bases on their behavior in electrophilic substitution reactions was examined. The established peculiarities were compared with the behavior of functional compounds of the benzene series. The specific characteristics of the mechanisms of electrophilic substitution in the heteroaromatic series due to the acidic and basic properties of the heteroaromatic compounds are discussed.

This review is dedicated to the memory of Professor Yakov Lazarevich Gol'dfarb, in whose research the problem of the effect of the acid-base properties of heterocycles on their reactivities, primarily on the specificity of various substitution reactions, was one of the major concerns. Gol'dfarb's contribution to the chemistry of thiophene, furan, and benzene was particularly significant in this respect.

Individual problems related to the topic under discussion were not only the subject of original papers but were also correlated in reviews; this makes it possible, where appropriate, to condense the exposition in the present review. In addition, the problem as a whole has not been duly reflected in monographs dealing with both aromatic substitution (for example, see [1, 2]) and general problems in the chemistry of heterocycles, for which it is particularly essential, although in a previously published book [3] this gap was partially bridged with respect primarily to compounds of the pyridine series. Taking into account the information stated above, we will begin our exposition with the general problems of the mechanisms of electrophilic substitution in the aromatic series and the effect of the acid-base properties of functional substituted benzenes on such reactions; this makes it possible to emphasize the peculiarities of the behavior of heteroaromatic systems.

Electrophilic substitution is the most important and widely investigated class of reactions in the aromatic and heteroaromatic series. Moreover, one cannot help being struck by the fact that, despite the great diversity of substrates and reagents, virtually all electrophilic substitution reactions are usually considered to be reactions that proceed via a single mechanism, viz., through the intermediate formation of σ complexes; the differences, for example, between nitration and halogenation are basically reduced to the peculiarities of the conditions for the generation of the electrophilic agent E^+, which participates in the above-mentioned single mechanism:

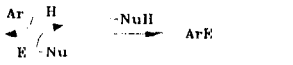
$$ArH + E^+ \longrightarrow [ArHE]^+ \xrightarrow{-H^+} ArE \qquad (1)$$

This sort of treatment sheds no light on the problem regarding the steps of the reaction that precede or accompany the formation of the σ complex, which include reaction of the substrate not only with the electrophilic particle E^+ but also with catalysts or condensing agents that are usually present in the reaction mixture. We will not discuss here the problem of the intermediate formation of π complexes and the role of one-electron transfer in electrophilic substitution reactions. The task of this review includes an examination of the effect of the reactions of aromatic and heteroaromatic substrates with protic and aprotic acids, in which these substrates act as bases and are converted to nv or σ complexes (in the latter case, however, the complexes are not converted to the desired electrophilic substitution products). Problems associated with the effect of the acidic properties of the substrates on electrophilic substitution will also be discussed. This aspect is of substantial significance not only within the framework of the "classical" mechanism described by Eq. (1) but

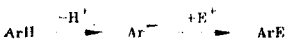
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 749-773, June, 1986. Original article submitted November 1, 1985.

0009-3122/86/2206-0587$12.50

takes on particular interest in connection with the fact that concepts regarding different mechanisms of electrophilic aromatic substitution have recently emerged. These concepts are formulated in the most general and precise form in [4], in which the possibilities of the occurrence of electrophilic substitution reactions via concerted mechanism (2) and through a carbanion (3) are examined:

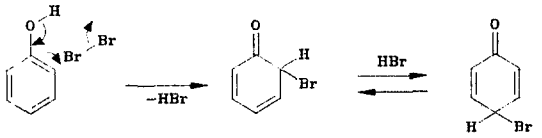


(2)



(3)

We do not know of cases in which a concerted mechanism for electrophilic substitution has been rigorously proved. However, let us present a description of a similar process in which, moreover, the acidic properties of the substrate play an essential role [5]:



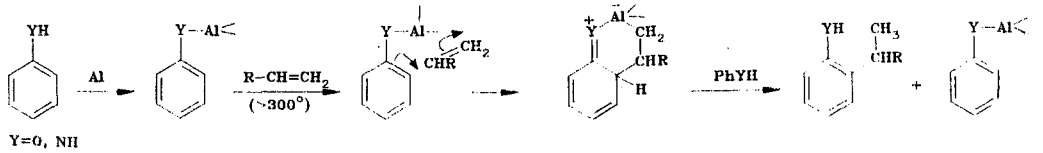
It might be assumed that electrophilic substitution reactions of activated heteroaromatic compounds in which condensing agents are not used also proceed via a concerted reaction. A vulnerable feature of this mechanism is the inevitable formation during the reaction of a protic acid, which, if special measures are not taken, may serve as a catalyst.

The carbanionic mechanism is considerably more substantiated. Practically speaking, the direct metallation of aromatic and heteroaromatic compounds, which is accompanied by treatment of the reaction mixture with the electrophile, proceeds via this scheme. The similar bromination of 1,3,5-tribromobenzene with tert-butyl hypobromite in the presence of potassium tert-butoxide is described in [4]. Specific variants of such processes, which include the intermediate formation of relatively stable ylids, are known in the heteroaromatic series and will be examined in a special section of this review.

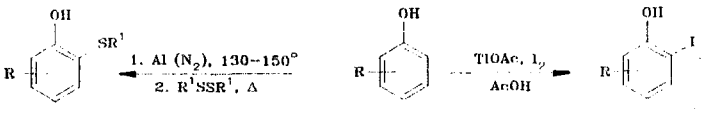
1. Effect of the Acidic Properties of Aromatic Compounds on Their Electrophilic Substitution Reactions

In addition to reactions that proceed via a carbanionic mechanism in which the CH acidity of the substrate is manifested, numerous examples of electrophilic substitution in which NH and OH acidities play a substantial role are known. This is the case of phenols, anilines, and carboxylic acids. Data published up to 1970 were correlated in a previous review [6]. To give a complete picture, some of these data will be presented below; however, principal attention will be directed to newer publications. The transformations that precede substitution itself are far from being proven in all cases. In most cases one can arrive at a judgment regarding them from indirect data, primarily from the preferred formation of ortho-substituted compounds.

The methods for the preparation of o-alkylphenols and o-alkylanilines by the action of olefins on phenols and anilines in the presence of aluminum metal or aluminum phenoxide have found substantial preparative value and use in industry [1, 6]. In particular, the method is used for the synthesis of sterically hindered phenols that are used as antioxidants [7].

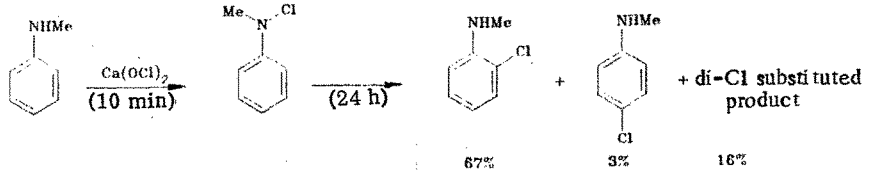


It is possible that the thiylation of aluminum phenoxides by disulfides [8] and the iodination of phenols in the presence of thallium acetate [9] proceed via a similar mechanism.

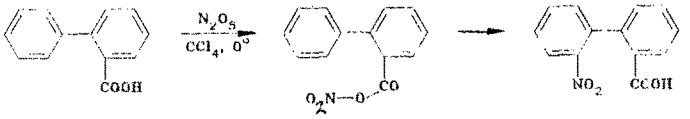


Cases of the primary ortho halogenation of phenols have been described in the literature; intermediate replacement of the hydrogen of the hydroxy group by the halogen is assumed [6]. Data on the effect of the pH of the medium on the ratio of the products of the chlorination of phenols by the action of sodium hypochlorite are in agreement with this assumption [10]: The ortho/para ratio increases sharply on passing from an acidic medium to an alkaline medium (from 0.64 at pH 4 to 4.3 at pH 10). It is interesting to note that in the case of anisole a change in the pH of the medium does not affect this ratio, which remains within the limits 0.63-0.66.

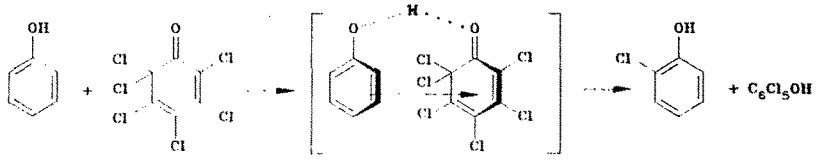
The intermediate formation of a product with replacement of a hydrogen atom of a functional group, which then undergoes isomerization to an o-substituted product, was established by means of the IR spectra for the chlorination of N-methylaniline by calcium hypochlorite (the yields of the compounds formed are indicated under the formulas) [11]:



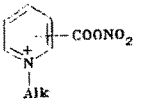
The formation of an o-nitro-substituted product by the action of nitrogen pentoxide on biphenyl-2-carboxylic acid fits into the same scheme [12].



Reagents of a new type that ensure selective ortho or para substitution of phenols, due, in the opinion of the authors, to the formation with the substrate of an intermediate complex in which the phenol acts both as a proton donor for a hydrogen bond and as a π donor, have recently been proposed [13-15]. 2,2,3,4,5,6- and 2,3,4,4,5,6-Hexachlorocyclohexadienones have been proposed as chlorinating agents of this type. In particular, the first agent in the chlorination of hydroquinone monomethyl ether gives compounds with a chlorine atom in the ortho position relative to the OH and OMe groups in the ratio of 95:5. The same reagent gives only p-chloroanisole in the chlorination of anisole.



Phenol is converted to o-nitrophenol with high selectivity by the action of mixed anhydrides of nitric and N-alkylpyridiniacarboxylic acids [15].



In the case of anisole and potassium phenoxide, in which the formation of a hydrogen bond with the reagent is impossible, nitration proceeds unselectively.

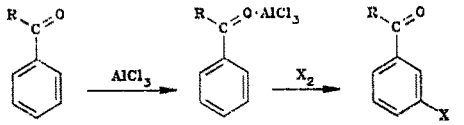
2. Effect of the Properties of Aromatic Compounds as Bases on Their Electrophilic Substitution

The presence in an aromatic compound of a functional group that has an unshared pair of electrons creates the possibility of the formation of an nv complex with an aprotic acid or protonation of this group under the influence of a protic acid; this leads to a pronounced change in the orienting ability of the substituent. Thus the halogenation of aniline and dimethylaniline leads only to o- and p-substituted products; however, the halogenation of complexes of the same anilines with $AlCl_3$ gives $\sim$20% meta isomers, and 50-60% meta isomers are formed in the case of the ammonium compounds $PhNR_2^+HAlCl_4^-$ [16]. The bromination of dimethylaniline in sulfuric acid by bromine in the presence of silver sulfate gives a similar effect

[17]. The nitration of dimethylaniline in sulfuric acid is a convenient method for the synthesis of an m-nitro-substituted compound [18].

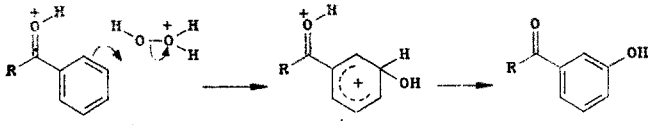
The situation is more complex in cases in which the onium grouping develops with the participation of the attacking electrophile. For example, in the sulfonation of aniline the slow step is the formation of the similar onium ion $PhNH_2SO_3H$, which then is rapidly converted (inter- or intramolecularly) to products of sulfonation in the para and ortho positions but not in the meta position [19]. The nitration of acetanilide and some of its m-substituted derivatives with acetyl nitrate or nitronium tetrafluoroborate leads to a mixture of o- and p-nitro-substituted products with a substantial preponderance of the former [20]. In the opinion of the authors, the reason for this is preceding coordination of NO_2^+ at the nitrogen or oxygen atom of the amide group. The well-known instances of the selective formation of o-nitro-substituted products in the nitration of anisole [21-23] and methyl phenylethyl ether [22, 24] can also be explained by similar coordination of the nitronium cation at the ether oxygen atom. Thus the intermediate formation of an onium center with the participation of a cation reagent does not lead to a fundamental change in the orienting effect of activating substituents and can only increase the formation of o-substituted products.

Complexing or protonation at the functional group in the case of carbonyl compounds has an extremely substantial effect on the specificity of substitution. It is well known that replacement of the hydrogen atoms of the α-methylene group in the case of ketones (for example, see [25, 26]) and, not infrequently, an aldehyde proton [27], is observed under ordinary conditions in many electrophilic substitution reactions. However, various electrophilic substitution reactions are directed to the meta position of the aromatic ring when a strong aprotic acid in amounts above the equimolar amount or excess protic acid is used. As examples of such reactions, let us cite the chlorination and bromination of benzaldehyde and acetophenone in a large excess (2.5 moles) of anhydrous $AlCl_3$ without a solvent [28, 29] or the bromination of these compounds with 1 to 1.5 moles of $AlCl_3$ in a solvent [30].



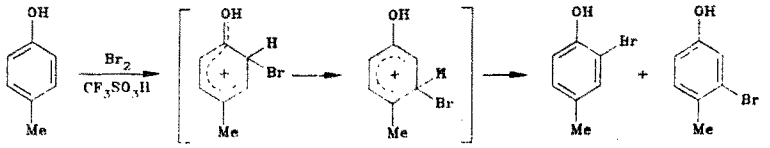
Bromination by the action of bromine in concentrated sulfuric acid in the presence of Ag_2SO_4 on benzaldehyde [31] and acetophenone [32] is also directed to the meta position. Acetophenone in the form of a complex with $AlCl_3$ is converted smoothly to m-(chloromethyl)-acetophenone by the action of various reagents, viz., mono- [33] and bis(chloromethyl) [34] ethers, as well as a mixture of paraformaldehyde with $AlCl_3$ [35].

An interesting example of the effect of protonation on the specificity of a reaction is the electrophilic hydroxylation of benzaldehyde and acetophenone with 70% hydrogen peroxide in $HF-SbF_5$ super acid [36]. It is well known that in conditions under which complete protonation of both components is not achieved, oxidation to benzoic acid and the Baeyer–Villiger rearrangement to give the phenyl formate and phenyl acetate, respectively, occur [37].

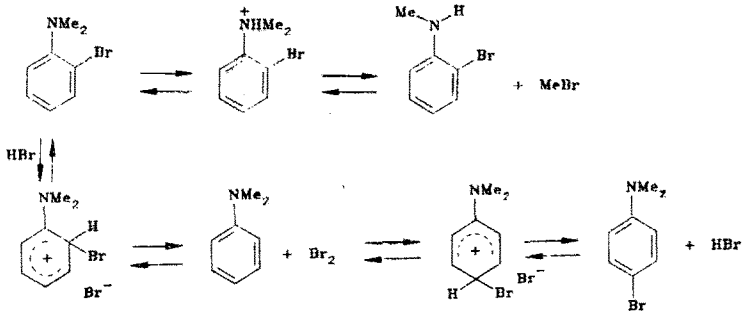


In interpreting the unusual specificity of electrophilic substitution reactions one must specially demonstrate that complexes with protic and aprotic acids are actually formed under the reaction conditions and that the products of their transformations differ from the substances obtained from the corresponding aromatic compounds that are not tied up in complexes. Such data are available for many of the examples examined above. In particular, complexes of carbonyl compounds of the benzene series were identified in solutions by diverse physical methods, including IR, UV, PMR, and ^{13}C NMR spectroscopy [30, 38-42], as well as calorimetry, dielectrometry, and cryoscopy [43]. At the same time, instances in which the real transformations do not, it would seem, fit into an extremely plausible scheme are known. Such "deviations" are known primarily for the halogenation and alkylation of phenols and anilines, and they are due to the possibility of C protonation of the activated aromatic ring and the associated reversibility of the indicated reactions, which is manifested even under mild conditions. Thus the bromination of p-alkyl- and o,o-dialkyl-substituted phenols and anisoles in a super acid medium proceeds in the meta position relative to the hydroxy or methoxy group; this was explained by Jacquesi and co-workers [44] as being the result of

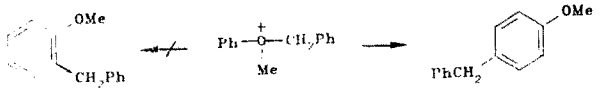
protonation at the oxygen atom, as a consequence of which, the orienting effect of an oxygen-containing substituent of the first order also changes. However, in actuality, as demonstrated in [45] in the case of p-cresol, protonation is not directed to the oxygen atom but rather to the carbon atom in the ortho position relative to the hydroxy group. Bromine also enters the same position, but this is then followed by slower conversion of the kinetically controlled product to the thermodynamically more favorable isomer, the amount of which increases significantly when the reaction mixture is allowed to stand for a long time.



Similar transformations are also known for aniline derivatives. In particular, the transformations of o-bromo-N,N-dimethylaniline under the influence of HBr to dealkylation, debromination, and isomerization products have been studied [46].



A study of the alkylation of anisole using various alkylating agents and catalysts [47] under kinetic-control conditions (at a low temperature and a low catalyst concentration) showed that o- and p-alkyl-substituted products are formed in a ratio close to the statistical value (2:1) and that the amount of meta isomers does not exceed 3%. Isomerization of the substances is observed under more severe conditions; the amount of the ortho isomer decreases, and the amounts of the para and meta isomers increase. In the same study in the case of the benzylmethylphenyloxonium ion generated at −90°C it was shown that initial attack of the electrophile at the heteroatom of the functional group, in contrast to the prevailing opinion, does not at all ensure the formation of o-substituted products: When the temperature is increased, the indicated cation is converted exclusively to a product of intermolecular transfer, viz., p-benzylanisole.



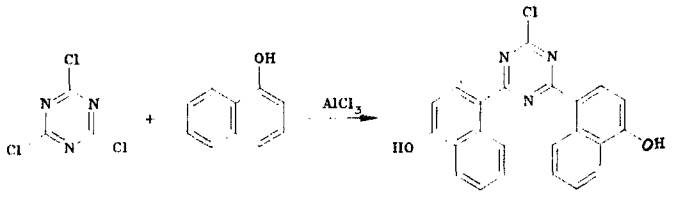
3. Basicities of Heteroaromatic Compounds and Their Electrophilic Substitution Reactions

In the preceding section it was shown how the basic properties due to the presence in the benzene ring of appropriate substituents lead to the formation of complexes with protic and aprotic acids, a consequence of which is a change in the specificity of electrophilic substitution as compared with the free bases. Similar effects, which are determined by complexing at the functional group, are also manifested in the heteroaromatic series, as will be stated below. However, in heterocycles even the first members of the series and homologs are essentially functional compounds in which the ring heteroatom acts as a function. It is therefore clear that phenomena similar to those described above are usually widespread in the heteroaromatic series. Considering the enormous diversity of the types of heteroatomatic systems, one must sharply limit the subject of the discussion.

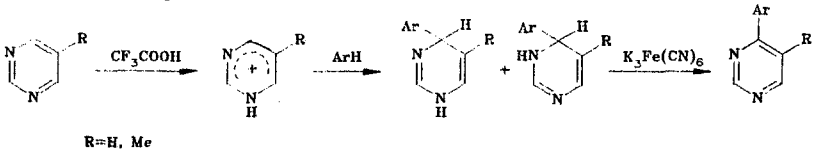
Principal attention will be focused on monocyclic five-membered heterocycles with one heteroatom, compounds of the pyridine series, and azoles. We will not touch upon condensed systems, since in them the peculiarities of the electrophilic substitution reactions of interest to us turn out to be either similar to those of monocyclic heterocycles or to those

of functional compounds of the benzene series. Oxygen and sulfur analogs of pyridine, viz., pyrylium and thiopyrylium cations, do not react with electrophilic agents. The reaction of electrophilic agents with azines that contain several nitrogen atoms, however, usually does not lead to substitution products but rather to onium salts involving one or two nitrogen atoms. Electrophilic substitution becomes possible only when activating substituents are present in such compounds.

At the same time, it must be pointed out that π-deficient di- and triazines under certain conditions can act as electrophilic reagents with respect to various aromatic and heteroaromatic compounds. Thus some halogen-substituted pyrimidines and sym-triazines, which can be regarded as analogs of imido chlorides, undergo condensation with aromatic compounds in the presence of Lewis acids [48-50].

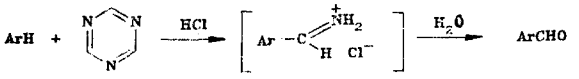


The conversion of azines to azinium cations by protonation, alkylation, or acylation makes it possible to realize the so-called "hetarylation" of active aromatic and heteroaromatic compounds [51, 52]. N-Acyloxyazinium salts formed in the acylation of N-oxides can also serve as hetarylating agents [53]. Hetarylation often proceeds under very mild conditions. For example, pyrimidine, 5-methylpyrimidine, and the corresponding benzo-annelated compounds react readily in trifluoroacetic acid with active aromatic and heteroaromatic compounds to give aryl(hetaryl)dihydropyrimidines, which can be aromatized by the action of potassium ferricyanide [54-56].



R=H, Me

The reaction of sym-triazine with aromatic compounds initiated by means of hydrogen chloride, which can serve for the synthesis of aldehydes [57], evidently also has similar character.



Pyrylium [58, 59] and thiopyrylium cations [60] can also undergo hetarylation.

Turning now directly to the problem of the properties of heteroaromatic systems as substrates in electrophilic substitution reactions, let us note that the heterocycles under discussion differ substantially from one another with respect to their strengths as bases. The pK_a values of a number of monocyclic compounds and some of their substituted derivatives at 20-25°C in water or aqueous sulfuric acid, taken for 2,5-dimethylfuran, 2,5-dimethylthiophene and 2,5-dimethylpyrrole from [61], and for 2-acetylthiophene from [62] (the remaining values are presented from data in [3, pp. 126, 127] and are supplemented and partially corrected from the data in [63]), are presented in Fig. 1. It is not difficult to see that the differences in basicities exceed 17 orders of magnitude between the strongest base (imidazole) and the weakest bases (furan and thiophene, for which data are not available but which should be weaker bases than their 2,5-dimethyl-substituted derivatives) It is apparent that such colossal differences in basicities also predetermine the extremely different behavior of the examined systems with respect to protic and aprotic acids.

The protonation of heteroaromatic compounds or their complexing with a Lewis acid under the reaction conditions leads to slowing down of electrophilic substitution; this is due to two reasons: 1) a decrease in the substrate concentration as a consequence of tying up of a significant amount of the substrate in a deactivated complex with a protic or aprotic acid; 2) a sharp decrease in the reactivity of the substrate when it is completely converted to the complex. Katritzky and co-workers have made comprehensive studies that make it possible in many cases to draw conclusions as to the form (free base or conjugate acid) in which various heteroaromatic compounds react. Criteria based on measurement of the reaction rate constants

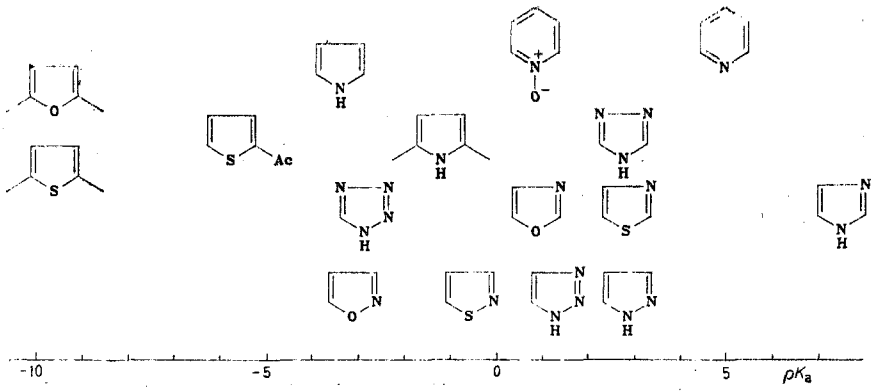
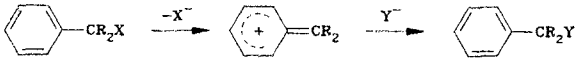


Fig. 1. Ionization constants of the conjugate acids of heteroaromatic compounds.

at various acidities of the medium, determination of the activation parameters, and comparison of the observed rate with the reaction rate of a related compound known to exist in the ionic form (for example, pyridine methiodide in a study of the reactions of pyridine in an acidic medium) were developed [64]. The same group of researchers obtained comparable quantitative data on the reactivities of heterocycles of various classes. Data extrapolated for hydrogen isotope exchange in a moderately acidic medium (pD 0) at 100°C [65-67] are presented in Fig. 2, and, in the case of "standardized" constants for nitration by nitric acid, scaled for 25°C and H_0—6.6 (75% sulfuric acid) [68-72], are presented in Fig. 3. We will subsequently use these data in an examination of various groups of heteroaromatic compounds. Here, however, we will make some general comments. The differences in the relative reactivities of the heteroaromatic compounds as compared with benzene (Fig. 2) in the case of hydrogen exchange reach 30 orders of magnitude; for the same compound in the form of the neutral base and the conjugate acid these differences amount to 6-9 orders of magnitude. It is important to note that 1,2-azoles (in the free base form) in the case of acid-catalyzed hydrogen isotope exchange are more active than benzene and approach thiophene and N-methylpyrrole in this respect, which differ substantially from pyridine. In a more acidic medium (see the data on nitration in Fig. 3) the same 1,2-azoles are substantially inferior in reactivity to not only thiophene but also to benzene; they are similar in activity to deactivated acetophenone. Such differences can be explained by the fact that at H_0—6.6 the substrates are almost completely protonated, and the true concentration of the free base is very low. If the conjugate acid undergoes the reaction, the reaction rate again decreases by several orders of magnitude, so that, with respect to their activity, the protonated forms resemble nitrobenzene. The smaller range of differences (12 orders of magnitude) in the case of nitration as compared with hydrogen isotope exchange is due to both the higher rate (and the lower substrate selectivity) of nitration and the absence of data for the "extreme" members of the series, viz., the pyridinium ion and the protonated pyridine N-oxide, on the one hand, and N-methylpyrrole, on the other.

An idea as to what relative activities various heteroaromatic compounds had in electrophilic substitution reactions, if one could completely exclude their reaction with protic and aprotic acids, was given by the results of experiments on the solvolysis of analogs of benzyl halides and benzyl ethers, which were carried out in neutral media such as aqueous ethanol, methanol, or acetone. It is assumed that the intermediates of such reactions resemble cationic σ complexes:



In each case a linear correlation of the Hammett type with the utilization of electrophilic substituent constants σ^+ is observed when various substituents are introduced into the benzene ring:

$$\lg k_{Ar}/k_{Ph} = \rho \cdot \sigma_{Ar}^{+}.$$

A similar correlation is also observed for heteroaromatic analogs; each heteroaromatic residue can be characterized by a "substituent" constant that formally corresponds to replacement of one or two vinylene groups in the phenyl residue by NH, O, S, or —N=CH—. Data on

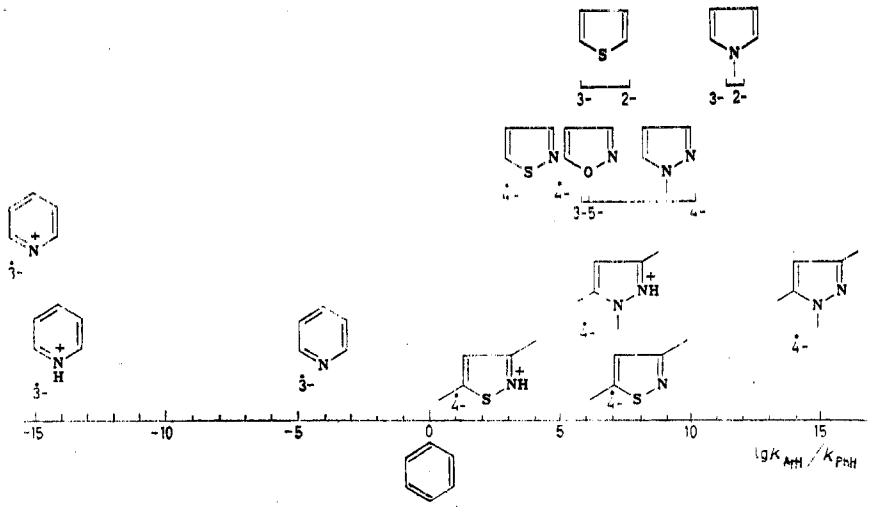


Fig. 2. Logarithms of the factors of the partial rates of hydrogen isotope exchange in heteroaromatic compounds (pD 0, 100°C). The positions of the ring for which the partial rate factors are presented are indicated under the formulas.

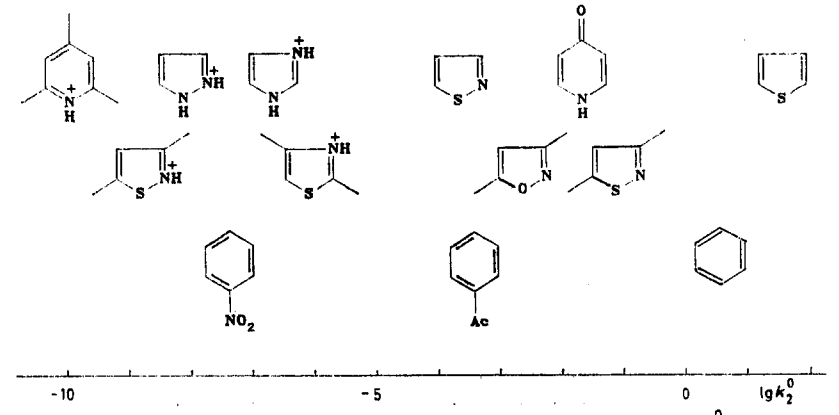


Fig. 3. "Standardized" constants of nitration (k_2^0) of some heteroaromatic compounds by the action of HNO in sulfuric acid (H_0—6.6, 25°C). The positions of the ring for which the nitration rate constants are presented are indicated under the formulas.

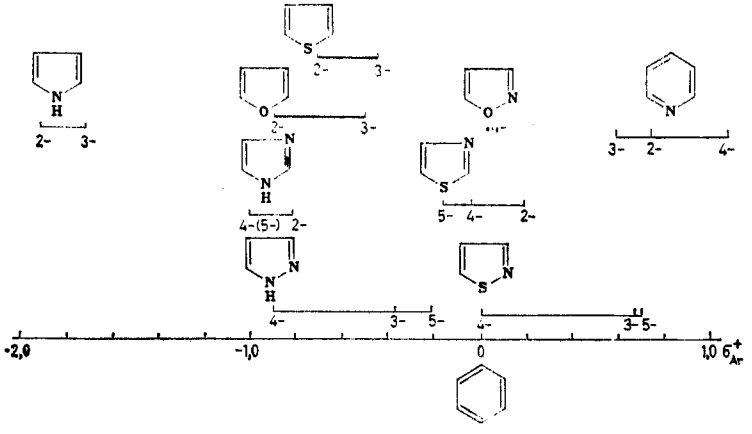
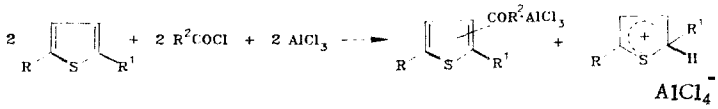


Fig. 4. The σ_{Ar}^{+} constants of some heteroaromatic compounds for the solvolysis of heterocyclic analogs of benzyl halides and benzyl ethers. The positions of the heterocycle that are bonded with the side chain in the heteroanalogs of compounds of the $Ar—CR_2X$ are indicated under the formulas.

the σ_{Ar}^{+} values for various hetaryl systems obtained primarily by Noyce and co-workers [73-81], as well as in [82-84], are presented in Fig. 4; the heterocycles are depicted above the σ_{Ar}^{+} values corresponding to the ring positions that are most reactive in electrophilic substitution. It is clearly seen in Fig. 4 that the heterocycles under discussion are distributed between pyrrole and pyridine in two groups, in one of which imidazole and pyrazole are included along with furan and thiophene, whereas the other is made up of other 1,2- and 1,3-azoles, the σ_{Ar}^{+} values of which are close to that of benzene ($\sigma_{Ar}^{+}\equiv 0$ for phenyl).

3.1. Five-Membered Heterocycles with One Heteroatom. Furan, thiophene, pyrrole and their homologs are not only the weakest bases of the heterocycles under consideration but also differ fundamentally from pyridine and azoles with respect to the structure of the protonated part. Five-membered heteroaromatic systems with one heteroatom are not protonated at the heteroatom but rather at the α-carbon atom; this was demonstrated clearly by physical methods, primarily by means of PMR spectroscopy; it is important to note that in the case of pyrrole [85-88] and thiophene [89-95], the resulting heteroarenium ions (σ complexes), as a consequence of the stabilizing effect of the heteroatom, are quite stable in acidic media at ordinary temperatures for the first members of the series, whereas in the case of furan they are stable for the sterically hindered di- and trialkyl-substituted compounds [96-99].

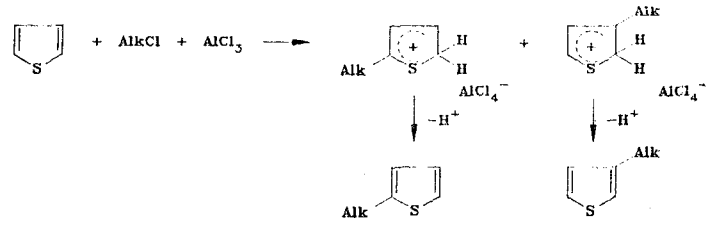
The well-known acidophobic character of five-membered heterocycles is due to the formation of C-protonation products: Heteroarenium ions can act as electrophilic agents with respect to free heteroaromatic molecules, which leads to products of acidic oligo- and polymerization, which are often formed under the conditions of electrophilic substitution carried out in the presence of protic and aprotic acids (see a previous review [100] for a more detailed discussion). One should, however, bear in mind that oligomerization is often observed in the presence of relatively small amounts of acid and that stable heteroarenium ions can be formed in excess protic acid; the bonding in the form of this sort of ion may create a distorted idea regarding the reactivity of the heteroaromatic compounds. In our opinion, the lower activity of thiophene as compared with benzene in the case of alkylation in liquid hydrogen fluoride observed in [101] can be explained precisely by the formation of C-protonation products, which are incapable of reacting with the electrophilic agent. Such complexes can develop under electrophilic substitution conditions even without the addition of a protic acid from the outside due to the protic acid liberated during the reaction if the aprotic acid used in an equivalent amount forms a stable anion, as we observed in the acylation of thiophene and its homologs by means of carboxylic acid chlorides in the presence of 1 mole of $AlCl_3$ [94], in which case up to half of the substrate was found to be tied up in the form a a C-protonation product and did not participate in the primary reaction.



a R=R¹=H; b R=Me, R¹=H; c R=R¹=Me; R²=Me, CH_2Cl

Replacement of the aprotic acid, in this case for example, by stannic chloride, prevents the formation of stable σ complexes. However, when stabilizing substituents are present in the substrate molecule, σ complexes can also be formed in the presence of $SnCl_4$ [93].

The formation of stable σ complexes can also be used for preparative purposes. Thus it makes it possible to avoid the production of di- and polyalkyl-substituted compounds if the alkylation is carried out in the presence of an equivalent amount of $AlCl_3$ [102].



Substituted thiophenium ions undergo disproportionation, the driving force of which is conversion of the less stable cations to more stable cations. In the case of alkylmercapto-substituted [92] and tert-alkyl-substituted compounds [94] these processes take place at a quite high rate (after a few hours) even at room temperature. Compounds with secondary and primary alkyl groups behave similarly, but their transformation proceeds very slowly or requires heating [94, 95]. Disproportionation can serve for the preparative synthesis of 2,4-bis(alkylmercapto)thiophenes [92] and 2,4-dialkylthiophenes [95] from the 2,5-substituted isomers and also makes it possible to convert a mixture of 5- and 3-tert-butyl-2H-thiophenium ions formed in the alkylation of thiophene by the method in [102] and containing ~15% of the 3-substituted compound to practically pure 2-tert-butylthiophene [94]. The mechanism of the disproportionation under discussion, which was examined in [92, 94, 95], is similar to the transformations described above for the products of alkylation and halogenation of activated compounds of the benzene series, viz., phenol and aniline derivatives [45-47]. Disproportionation is due to the reversibility of the formation of σ complexes and the possibility of transfer of the substituent split out in the form of an electrophilic particle to a free molecule that already bears a substituent. The unsuccessful attempts to obtain alkylmercaptothiophenium ions by the action of sulfenyl chlorides on thiophene in the presence of an equivalent amount of $AlCl_3$ [103] can be explained by the ease of splitting out and redistribution of the alkylmercapto groups in the presence of $AlCl_3$ and also by oligomerization.

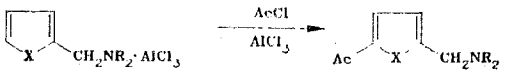
The well-known difficulties involved in the production of 2-bromothiophene, which is generally formed by bromination in a mixture with 2,5-dibromothiophene, are probably due to the facile disproportionation of the intermediately formed σ complexes. In this connection let us note that our attempts to obtain bromothiophenium ions by the action of bromine on thiophene in the presence of $AlCl_3$ under conditions close to those described for alkylation [102] were unsuccessful, and the deprotonation product contained significant amounts of 2,5-dibromothiophene. It seems to us that the successful production of 2-bromothiophene by the action of a bromide–bromate mixture on thiophene by the method in [104] is due to the fact that ether, which ensures deprotonation of the resulting σ complexes, was used as the solvent. Data indicating that 2,5-dibromo-2H-thiophenium ions are readily converted to 3,5-dibromo-substituted compounds [105] are in agreement with the information stated above. Let us also note that the diverse chloro-substituted thiophenium ions described in [106, 107], which are generated by protonation of chlorothiophenes at −40°C to −70°C, evidently undergo rearrangement and (or) polymerization at temperatures above −30° C, i.e., they behave like 2,5-bis(alkylthio)-2H-thiophenium ions (see [92]).

Thus, with respect to their behavior toward acids, the first members of the series of five-membered heterocycles with one heteroatom resemble activated aromatic compounds, viz., phenols, anilines, and polyalkylbenzenes. To an even greater degree this pertains to pyrrole, thiophene, and furan derivatives that have a substituent of the first type. Let us note in this case that C protonation can also be observed for such derivatives of heterocycles that have substituents that are the site of protonation in the case of the benzene analogs. Thus C protonation of sulfides of the thiophene series was noted frequently above, whereas, according to the data in [108, 109], alkyl phenyl sulfides are protonated at the sulfide sulfur atom. Even when a strongly basic center such as an amine nitrogen atom is present in the substituent, C protonation is observed for heteroaromatic compounds. This occurs in the case of aminofurans [110], including those in which the nucleophilicity of the ring is reduced by the presence of a negative substituent (CN) [111].

R=Me, Ph; R + R=$(CH_2)_4$

It is appropriate here to note that anilines and diphenylamine form stable products of protonation at the nitrogen atom [112]. Carbazole also behaves in the same way [113]. Stable C-protonation products are observed only for 1,3,5-triaminobenzene [114] and 1,3,5-tris-(dialkylamino)benzenes [115], which form σ complexes that are stabilized by three amino groups. It might be assumed that the discussed differences between functional substituted benzenes and their five-membered heterocyclic analogs are due to the lower aromatic character of the latter; the energy expenditures associated with the loss of aromatic stabilization in the formation of a heteroarenium ion are fully compensated by the gain due to charge delocalization with participation of the multiple bond and the ring heteroatom, as well as the substituents. If the amino group is not conjugated with the heteroaromatic ring, protonation and complexing with the Lewis acid are directed to the nitrogen atom. This circumstance can be used for preparative purposes. Thus "blocking" of the amino group by means of $AlCl_3$ makes

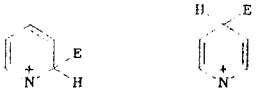
it possible to prevent both cleavage of 2-thenyl- and 2-furfurylamines at the N–C_{Het} bond and N acylation in the case R = H [116].



a X=S, R=H; b X=S, R=Me; c X=O, R=Me

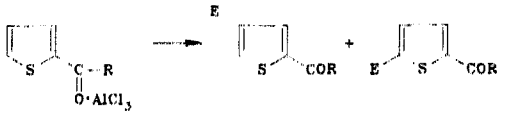
In pyrroles, furans, and thiophenes that have second-order substituents the basicity center, as in the benzene analogs, is the substituent heteroatom. Exceptions are known only for compounds that have additional substituents that increase the electron density in the heteroring, like the above-mentioned amino nitriles of the furan series [111] or polyalkylated carbonyl compounds of the pyrrole series [117, 118]. The effect of complexing and protonation at the substituent heteroatom on electrophilic substitution reactions has been widely studied for thiophene and furan derivatives, chiefly by Ya. L. Gol'dfarb and co-workers (see the previous reviews [100, 119, 120], as well as [121, Chap. 1]) and by Anderson and co-workers in the pyrrole series [122]. Here, one should recall only that for the first members of the series in electrophilic substitution reactions the activity changes in the order pyrrole $\gg$ furan > thiophene, whereas the selectivity (the α–β ratio) changes in the order furan $\gg$ thiophene > pyrrole. The reasons for the disparity between the activity and selectivity series were examined in [100]. It is important to bear in mind only the fact that the same orders are also retained for substituted heterocycles. With respect to their behavior in reactions with electrophilic agents, the β-substituted compounds, for which the m-orienting effect of the substituent is in accord with the α-orienting effect of the heteroatom, are most similar to the benzene analogs. A peculiarity that is due to the higher activity of the system is the appreciable formation of other isomers, chiefly the 2,3-disubstituted compounds. In the case of α-substituted compounds the orienting effects of the substituent and the heteroatom do not coincide, and mixtures of 2,4- and 2,5-disubstituted compounds are often formed. If complexing and protonation at the functional group are prevented (chiefly carbonyl-containing substituents were studied), the reactions are then directed exclusively to the 5 position for furan derivatives and exclusively or primarily to the 5 position for thiophene derivatives. Primarily 2,4-disubstituted compounds are formed in the case of pyrrole derivatives. Conversion of a free functional substituted compound to a complex with a protic or aprotic acid markedly intensifies the electron-acceptor properties of the substituent (see [42] for quantitative estimates of the σ_p^+ constants of various substituents modified by complexing with AlX_3). In conformity with the selectivity order presented above the complexing under consideration makes it possible to readily suppress the σ-orienting effect of the heteroatom in the case of pyrrole compounds and to obtain diverse 2,4-disubstituted pyrroles [122]. In the case of thiophene derivatives the desired effect is achieved only for the strongest meta orientators, viz., formyl and acetyl groups modified by complexing or protonation. In the case of 2-(ethylsulfonyl)thiophene [123] and 2-cyanothiophene [124] complexing with AlX makes it possible to obtain primarily 4-bromo-substituted products in bromination. Selectivity in substitution is virtually absent in the case of the thiophene-2-carboxylic acid ester. Protonation of the carbonyl group gives virtually the same results as conversion to a complex with $AlCl_3$. When sulfuric acid, which evidently does not form a true protonated form as in the case of $HSbCl_6$, but rather a hydrogen-bonded complex, is used the selectivity is appreciably lower. The corresponding data are presented in Tables 1 and 2. In the case of furan compounds the σ-orienting effect of the heteroatom cannot be overcome. Primarily 4-bromofurfural is formed in the bromination of the complex of furfural with $AlCl_3$ [130].

3.2. Pyridine. Because of the deactivating effect of the pyridine nitrogen atom, electrophilic substitution reactions proceed with great difficulty and are directed to the 3 position of the heteroring. The unfavorability of the formation of 2- and 4-substituted compounds can be explained by the instability of the corresponding σ complexes because of the contribution of structures with a positively charged divalent nitrogen atom.



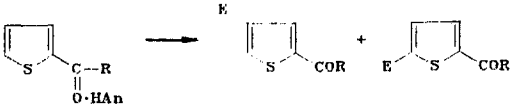
Protonation or complexing at the nitrogen atom substantially decreases the reactivity but does not change the specificity of electrophilic substitution in the pyridine series. It is easy to see that extremely unfavorable structures with a doubly charged trivalent nitrogen

TABLE 1. Specificity in the Electrophilic Substitution of Complexes of Carbonyl Compounds of the Thiophene Series with $AlCl_3$



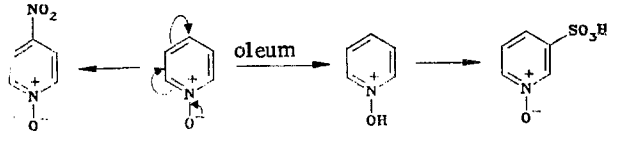
R	E	Reagent	Ratio of the 2,4 and 2,5 isomers	Literature
H, Me	Br	$Br_2/AlCl_3$ in $CHCl_3$	99 : 1	[125]
Me	Br	Br_2 in excess $AlCl_3$ without a solvent	99,5 : 0,5	[126]
Me	CH_3CO	CH_3COCl in excess $AlCl_3$ without a solvent	94 : 6	[127]
H, Me	CH_2Cl	$(ClCH_2)_2O/AlCl_3$ in $CHCl_3$	>99 : <1	[128]
H, Me	CH_2Cl	$(CH_2O)_x/AlCl_3$ in $CHCl_3$	>99 : <1	[35]

TABLE 2. Specificity in the Electrophilic Substitution of Complexes of Carbonyl Compounds of the Thiophene Series with Protic Acids



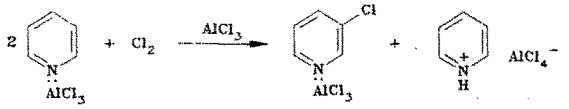
R	An	E	Reagent	Ratio of the 2,4 and 2,5 isomers	Literature
H	$SbCl_6$	Br	$Br_2/AlCl_3$ in $ClCH_2CH_2Cl$	98 : 2	[124]
Me	$SbCl_6$	Br	$Br_2/AlCl_3$ in $ClCH_2CH_2Cl$	96 : 4	[124]
H	$SbCl_6$	NO_2	$NO_2^+BF_4^-$ in $ClCH_2CH_2Cl$	94 : 6	[41]
Me	$SbCl_6$	NO_2	$NO_2^+BF_4^-$ in $ClCH_2CH_2Cl$	89 : 11	[41]
MeO	$SbCl_6$	NO_2	$NO_2^+BF_4^-$ in $ClCH_2CH_2Cl$	59 : 41	[41]
H	HSO_4	NO_2	KNO_3 in excess H_2SO_4	75 : 25	[60]
Me	HSO_4	NO_2	KNO_3 in excess H_2SO_4	90 : 10	[60]
Me	HSO_4	Br	Br_2 in excess H_2SO_4	75 : 25	[32]
H	HSO_4	CH_2Cl	$(ClCH_2)_2O$ in excess H_2SO_4	67 : 33	[129]
Me	HSO_4	CH_2Cl	$(ClCH_2)_2O$ in excess H_2SO_4	80 : 20	[129]

atom make a contribution to charge delocalization in the σ complexes that develop during electrophilic attack at the 2 and 4 positions of the pyridinium ion. A different situation occurs in the case of N-oxides. It is well known that pyridine N-oxides are nitrated in the 4 position by a mixture of nitric and sulfuric acids; this is explained by an increase in the electron density in this position via a mesomeric mechanism [64, 131]. The bromination of alkylpyridine and quinoline N-oxides, which is realized by the action of bromine in acetic acid in the presence of thallium triacetate [132], also proceeds in the 4 position. At the same time, the sulfonation of pyridine N-oxide, which takes place in oleum, is directed to the 3 position. This peculiarity is explained [64, 131] by the participation in the reaction of protonated forms in which the orientation is similar to that examined above for the pyridinium ion.



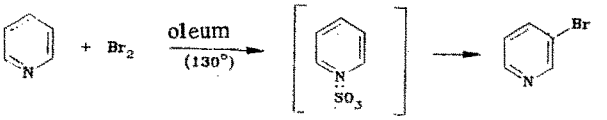
The effect of the properties of diverse compounds of the pyridine series as bases on their electrophilic substitution reactions, chiefly hydrogen isotope exchange and nitration, was studied in detail by Katritzky and co-workers, and the corresponding data were correlated in a review [64] and reflected rather fully in a monograph [3]. In this section we will focus our attention on the halogenation of pyridines, which was virtually untouched upon in a previous review [64]. The realization of such reactions is fraught with specific difficulties: The protic or aprotic acids necessary for the generation of the electrophilic particle

tie up a pyridine molecule in a complex, which is deactivated with respect to electrophilic attack to an even greater extent than the neutral molecule. Judging from the available data, the electrophilic chlorination and bromination of the pyridinium ion could not be realized at all. Thus Pearson and co-workers [133] carried out the chlorination of pyridine in excess anhydrous $AlCl_3$ without a solvent at ~100°C; however, in this case approximately half of the starting pyridine is tied up in the form of the hydrochloride and does not undergo substitution.



Bromination of pyridine under the indicated conditions does not proceed at all [133]. It might be assumed that in excess $AlCl_3$ (2.5 moles) pyridine would be completely tied up in a deactivated complex with $AlCl_3$, which can be subjected to reaction with a more active electrophilic agent ($Cl_2 + AlCl_3$) but not with a less active agent ($Br_2 + AlCl_3$). This point of view is confirmed by the successful bromination of pyridine under similar conditions but with the use of an equimolar or catalytic amount of $AlCl_3$, as well as other Lewis acids [134].

Some other unusual and by no means obvious methods for the bromination of pyridine that require clarification should be noted. The bromination of pyridine in oleum, which, in the opinion of den Hertog and co-workers [135, 136] proceeds through a complex with SO_3 during which SO_3 also participates in the generation of an electrophilic particle, has been described.



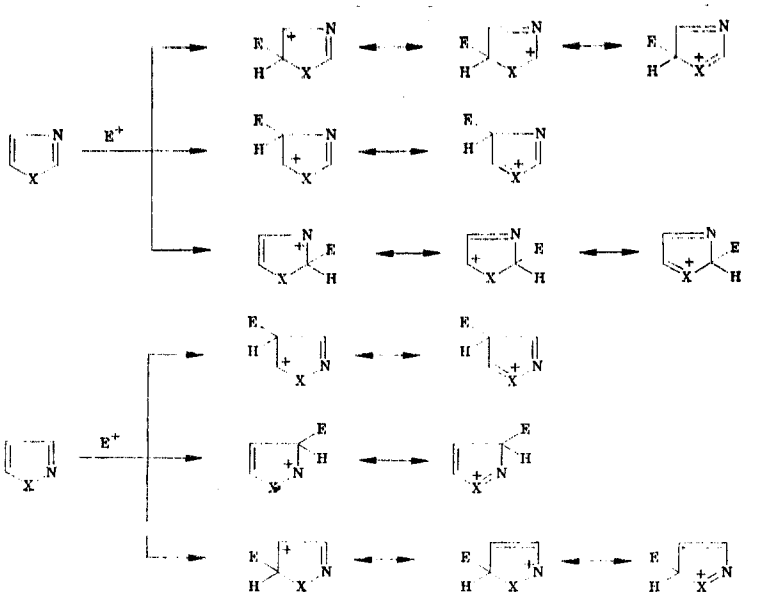
$$2\,C_5H_5N + 2\,SO_3 + Br_2 \longrightarrow 2\,C_5H_4NBr + SO_2 + H_2SO_4$$

The iodination of methylpyridines also proceeds under similar conditions; however, the halogen is partially incorporated in the methyl group [137]. Methods for the bromination of pyridine in thionyl chloride [138], as well as bromination and chlorination in phosphorus oxychloride, sulfuryl chloride, and in a monochloride medium [139], which suggest the formation of uncharged adducts of these compounds with pyridine [138], are also known.

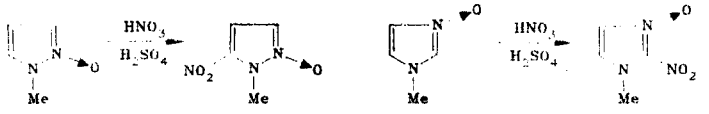
3.3. Azoles. Azoles constitute an extremely distinctive group of heteroaromatic compounds, since in them one or several "pyridine" nitrogen atoms are combined with a heteroatom of the "pyrrole" type. In this connection an examination of azoles as π-amphoteric systems [3] that are capable of manifesting both π-donor and π-acceptor properties seems extremely felicitous. At the same time, the so-called "π balance", i.e., the sum of the calculated (by the Huckel method) π charges on the carbon atoms of the heteroring, which was proposed in a book [3, p. 70] as an index of the π-donor or π-acceptor character, clearly does not suit this purpose. First of all, the magnitudes of the π charges depend substantially on the method of calculation and pertain in each case to the static state of the neutral molecule, i.e., one can, by no means, disregard either the mechanism or the conditions of the reaction. In addition, the conclusions that one might have drawn on the basis of the values under discussion contradict the experimental data in a number of cases.

Thus the idea [3] that isothiazole, isoxazole, and oxazole have lower reactivities than thiazole in electrophilic substitution reactions clearly does not correspond to the available data, particularly to the data presented in Fig. 4. Moreover, as we will demonstrate below, oxazole in the form of the free base is evidently even more active than thiazole in such reactions. The deactivating effect of "pyridine" nitrogen atoms in triazoles and tetrazole has also been clearly exaggerated.

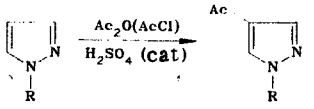
In electrophilic substitution reactions that proceed via an addition–cleavage mechanism the activities of the individual positions for 1,3-azoles change in the order 5- > 4- $\gg$ 2-, as compared with 4- $\gg$ 3- $\approx$ 5- for 1,2-azoles. The particular unfavorability of the formation of 2-substituted products in the case of 1,3-azoles and of 3- and 5-substituted products in the case of 1,2-azoles is determined by the contribution of the boundary structures with a positively charged divalent nitrogen atom to the corresponding cationic σ complexes.



As in the pyridine series, complexing with protic or aprotic acids does not change the specificity of the electrophilic substitution of azoles but markedly decreases its rate. The conversion of azoles to N-oxides makes it possible to change the specificity of substitution [140, 141].



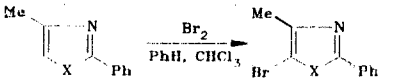
The available data on the electrophilic substitution of azoles show that imidazole and pyrazole — pyrrole analogs — are the most active compounds of this class. A comparison of diazoles with respect to activity is hindered by the fact that imidazole is a considerably stronger base than pyrazole (see Fig. 1). In particular, imidazole in the case of nitration with a mixture of nitric and sulfuric acids always undergoes the reaction in the cationic form, whereas pyrazole reacts in the cationic form only at a sulfuric acid concentration above 90% [142]. Owing to the high activities and moderate strengths of pyrazoles as bases, these compounds can even be acylated via the Friedel–Crafts reaction; under standard conditions, which require an equimolar amount of $AlCl_3$, the latter ties up pyrazole in a deactivated complex. The reaction can be carried out in the presence of a catalytic amount of sulfuric acid [143].



The "activity orders" of azoles in electrophilic substitution reactions evidently, both for 1,2- and 1,3-azoles, have the same form as for five-membered heterocycles with one heteroatom: $N \gg O > S$ (for the most active positions). Indeed, from the data for nitration (Fig. 3), one can, to counterbalance the data from hydrogen isotope exchange (Fig. 2), draw the conclusion that isothiazole derivatives are somewhat more active than their oxygen analogs.

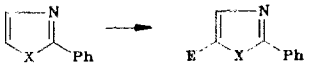
The volume of literature data on electrophilic substitution in the oxazole, isothiazole, isoxazole, and, to a lesser extent, thiazole series is relatively small. As a consequence of this, as well as the severe conditions under which the reactions under discussion are often carried out, there is an opinion that the azoles mentioned above, particularly oxazole, undergo electrophilic substitution with difficulty. In actuality, there is no basis for this opinion, and severe reaction conditions, particularly the use of protic and aprotic acids, in many cases are not only unnecessary but also simply detrimental. A number of reactions of 1,3- and 1,2-azoles that proceed under extremely mild conditions similar to those that are used for higher active π-surplus heterocycles with one heteroatom are known. Thus thiazole [144] and 4-methyl-2-phenylthiazole [145], as well as phenyloxazoles [146], are readily mercurated by the action of

mercury acetate, and all of the free positions of the heteroring are substituted. Oxazole and thiazole with both methyl and phenyl substituents are brominated without a catalyst in benzene or chloroform under conditions that differ in no way from the conditions for the bromination of their imidazole analog [147].



X=NH, O, S

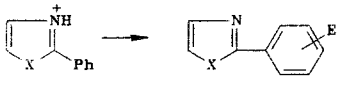
The bromination (with bromine in the presence of pyridine) and nitration with nitric acid in acetic acid have been described for a number of 4-aryl-2-chlorothiazoles, which give the corresponding 5-substituted compounds in high yields [148]. Up until recently, the only known instance of the nitration of an oxazole in the heteroring was the transformation of 2-dimethylamino-4-phenyloxazole, as a result of which a nitro group is incorporated in both the benzene and oxazole rings [149]. As we have shown, 2-phenyloxazole [150] and 2-phenylthiazole [151] are brominated smoothly by bromine in benzene and are nitrated by N-nitropicolinium tetrafluoroborate or nitric acid in acetic anhydride, and 2-phenyloxazole even undergoes Vilsmeier formylation; all of these reactions are directed to the 5 position of the heteroring.



X=O, S; E=Br, NO_2 X=O, E=CHO

Taking into account the results of competitive nitration and the fact that 2-phenylthiazole does not undergo formylation [151], it may be concluded that the oxazole ring is more active than the thiazole ring in electrophilic substitution reactions.

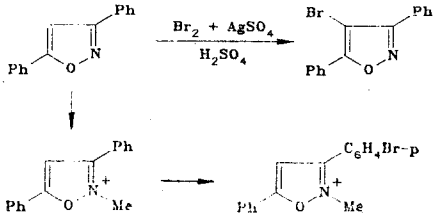
The realization of bromination and nitration in sulfuric acid, i.e., under conditions of protonation of the heterorings at the nitrogen atom, leads to substitution in the benzene ring [150, 151].



X=S; E=Br, NO_2 X=O; E=NO_2

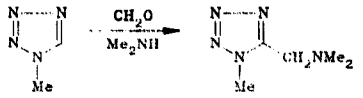
Similar effects have been described for 1-phenylpyrazole, which in sulfuric acid is nitrated in the benzene ring [152], whereas it is nitrated in the heteroring in acetic anhydride [153, 154].

If the substrate undergoes the reaction in the form of the free base, the reaction may be directed to the heteroring, despite the fact that it is carried out in an acidic medium. Precisely this case was described in [155] for the bromination in sulfuric acid of 3,5-diphenyloxazole, which is a very weak base (pK_a—3.24); its transformation to an N-methylisoxazolium ion leads to a product of bromination in the benzene ring.



Triazoles and tetrazoles can undergo electrophilic substitution under conditions that exclude complexing with protic and aprotic acids. Thus, 1,2,4-triazole and 1-benzyl-1,2,4-triazole undergo C hydroxymethylation under the influence of formalin [156]. The chlorination, bromination, and iodination of 1,2,3-triazole and its 1-, 2-, and 4-methyl-substituted derivatives at the carbon atoms of the heteroring, which proceed under diverse conditions [157, 158] including reactions in neutral solvents (CCl_4, $CHCl_3$), and require in the case of 2-methyl-1,2,3-triazole the presence of a catalyst (iron filings-bromination) or an oxidizing agent (HNO_3-iodination), have been described. Acetoxymercuration has been described for 1-phenyltetrazole [159]. Under very mild conditions (the action of

dimethylamine and formalin) 1-methyltetrazole undergoes aminomethylation [160].



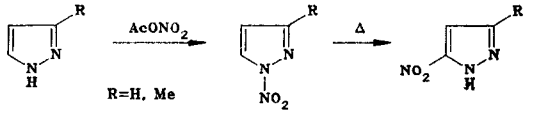
In an acidic medium, as in the case of other azoles, the triazole and tetrazole rings are deactivated with respect to electrophilic substitution, and such reactions in the case of aryl-substituted compounds are directed to the benzene ring [161-164]. The reactions of N-substituted triazoles and tetrazole are complicated by tautomeric transformations and the possibility of substitution at the nitrogen atom. The mechanisms of electrophilic substitution reactions in many cases have specific peculiarities; these will be examined in the next section.

4. CH Acidity. NH Acidity. Ylid Mechanism for the Electrophilic Substitution of Heterocycles

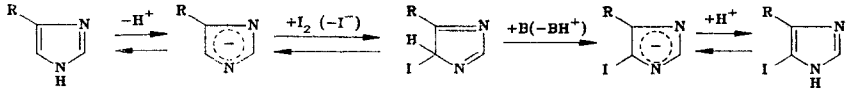
If one examines the carbanionic mechanism of electrophilic substitution proposed in [4] and depicted by Eq. (3) as applied to heteroaromatic compounds, it should be pointed out that direct metallation (chiefly lithiation) and subsequent reaction with electrophiles of the resulting carbanions or their ion pairs with metal cations are extremely characteristic for these compounds. Such reactions proceed readily for furans, thiophenes, oxazoles, thiazoles, and isothiazoles, as well as N-alkyl- and N-arylpyrroles, imidazoles, and pyrazoles. High CH acidities of the heteroaromatic systems (as compared with aromatic hydrocarbons) and the coordinating effect of the heteroatom (see [165], as well as [121, Chap. 2]) promote the occurrence of such reactions. With respect to direct metallation, within the framework of our review we will restrict ourselves to the information stated above, since this reaction is usually regarded not as electrophilic substitution but rather as a transformation of a special type — protophilic substitution. This approach is especially legitimate since the steps involving metallation and reaction with the electrophile are never realized simultaneously, as occurs in the case of the ylid mechanism examined at the end of this section.

The NH acidities may play a large role in the reactions of N-unsubstituted pyrroles, imidazoles, pyrazoles, triazoles, and tetrazoles. In many cases the reactions with electrophiles proceed through the corresponding anions; because of delocalization of the negative charge, substitution may be directed to different nitrogen atoms (in the case of diazoles, triazoles, and tetrazole), as well as to the carbon atoms. A general examination of the mechanisms of such reactions was made in a monograph [3, Section 5.2]. Here, we will restrict ourselves to some specific examples.

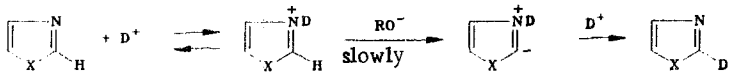
One can arrive at a judgment regarding the possibilities of electrophilic substitution at the nitrogen atom from the formation of N-nitro derivatives in the action of nitric acid in acetic anhydride (acetyl nitrate) on N-unsubstituted pyrazoles [166, 167]; when the N-nitro derivatives are heated, the nitro group migrates from the nitrogen atom to the carbon atom [167]. Similar data are also available for the nitration of imidazole [168].



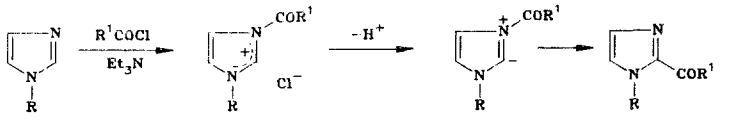
The formation of N-halo-substituted products was detected in reactions involving the halogenation of 1,2,3-triazoles in an aqueous alkaline medium [158]. Similar observations were made in the chlorination [169] and bromination [170-172] of 1,2,4-triazole and 3-methyl-1,2,4-triazole. The role of NH acidity in electrophilic substitution reactions at the carbon atom can be illustrated in the case of the well-known mechanism of the iodination of imidazole with iodine in an aqueous solution of potassium iodide [173-175]. The reaction includes a number of steps, including dissociation of imidazole to give the anion, reaction of the latter with an I_2 molecule, which leads to an uncharged intermediate (the fast step), and the rate-determining step, viz., deprotonation of this intermediate to give the iodo-substituted anion.



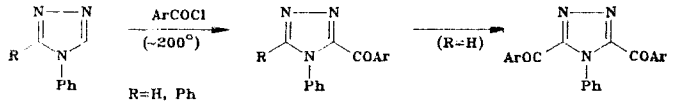
The so-called ylid mechanism of electrophilic substitution is of specific interest for the chemistry of heterocycles, particularly azoles. The principal features of this mechanism were formulated during a study of hydrogen isotope exchange in azoles. The interest in such transformations is associated with Breslow's idea [176] regarding the role of thiazolium ylids in metabolism with the participation of thiamine. The research in [176], in which the ability of thiazolium salts to undergo exchange of the hydrogen atom in the 2 position under very mild conditions was demonstrated, was followed by a number of publications devoted to the study of hydrogen isotope exchange for diverse azoles and azolium salts [177-184]. For the present review it is important that the proton in the 2 position, which should be the least active in the case of the classical addition–cleavage mechanism, turns out to be the most labile proton in 1,3-azoles over a wide range of pH values [177-180]; a marked acceleration in the rate of exchange (by several orders of magnitude) is noted on passing from the azole to the corresponding azolium salt [177]. The rates of exchange for 1,3-azolium salts are several orders of magnitude higher than for the isomeric 1,2-azolium salts [181]. These data are in agreement with the intermediate formation of azolium ylids in which the negative charge is additionally stabilized by the adjacent heteroatom of the "pyrrole" type [180].



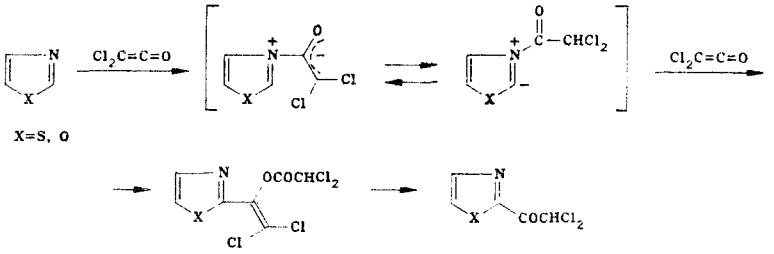
The importance of the ylid mechanism not only for hydrogen isotope exchange but also for other electrophilic substitution reactions in the azole series has become increasingly more apparent in recent years. Thus N-substituted imidazoles are acylated very readily in the presence of triethylamine; it is assumed that the reaction proceeds through an ylid [185].



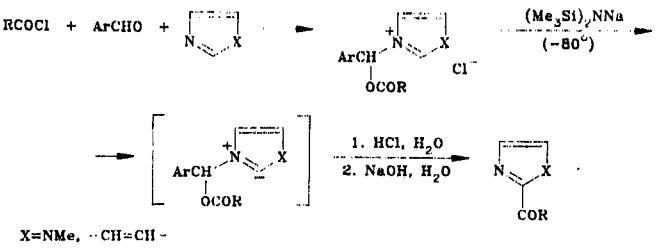
Thiazole [186], 4,5-dimethylthiazole, 1-methoxymethyl-1,2,4-triazole, and 2-phenyl-1,3,4-oxadiazole, as well as benzothiazole and benzoxazole [187], undergo a similar transformation. It might be assumed that the C acylation of 1,2,4-triazoles, which takes place in the absence of an aliphatic tertiary amine at high temperature, also preceeds through an ylid [188].



A number of transformations of thiazoles [186, 189] and oxazoles [190] under the influence of some ketenes have been described by Dondoni and co-workers. It is assumed that the ketenes activate the substrate molecule due to the intermediate formation of ylids, which then react with a second ketene molecule at the $C_{(2)}$ atom, after which transfer of the acyl residue from the N atom to the O atom and the formation of a 2-acylthiazole or 2-acyloxazole occur.



The $C_{(2)}$ acylation of 1-methylimidazole, as well as pyridine, which stipulates the production of an azolium (or, correspondingly, pyridinium) salt, its conversion to an ylid, and rearrangement of the latter, was recently described [191]. A peculiarity of this reaction is the fact that it does not require stabilization of the ylid (pyridine also undergoes this transformation) but is evidently restricted to sufficiently strong bases that are capable of forming onium salts of the type presented in the scheme given on the following page.



One cannot doubt that new possibilities of ylid substitution will be discovered in the near future, since this mechanism, which takes advantage of both the basic and acidic properties of heteroaromatic systems, makes it possible to subject deactivated compounds to the reaction and direct the entering substituent to the least active (in the case of ordinary electrophilic substitution) position.

LITERATURE CITED

1. L. S. Efros and M. V. Gorelik, The Chemistry and Technology of Intermediates [in Russian], Khimiya, Moscow (1980), Chaps. 1-6.
2. Kh. Khinei, in: General Organic Chemistry [Russian translation], Vol. 1, Khimiya, Moscow (1981), p. 314.
3. A. F. Pozharskii, Theoretical Foundations of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985).
4. M. N. Nach and J. F. Bunnett, J. Amer. Chem. Soc., 96, 936 (1974).
5. V. Calo, L. Lopez, G. Pesce, and P. E. Todesco, J. Chem. Soc., Perkin 2, No. 10, 1192 (1974).
6. D. E. Pearson and E. Buehler, Synthesis, No. 5, 455 (1971),
7. V. V. Ershov, G. A. Nikiforov, and A. A. Volod'kin, Sterically Hindered Phenols [in Russian], Khimiya, Moscow (1972).
8. P. F. Ranken and A. G. McKinie, Synthesis, No. 2, 117 (1984).
9. R. C. Cambie, P. S. Rutledge, T. Smith-Palmer, and P. D. Woodgate, J. Chem. Soc., Perkin 1, No. 11, 1161 (1976).
10. Y. Ogata, M. Kimura, Y. Kondo, H. Katoh, and Che-Fa-Ching, J. Chem. Soc., Perkin 2, No. 3, 451 (1984).
11. P. Haberfield and D. Paul, J. Amer. Chem. Soc., 87, 5502 (1965).
12. D. H. Hey, J. A. Leonard, and C. W. Rees, J. Chem. Soc., No. 11, 4579 (1962).
13. A. Guy, M. Lemaire, and J.-P. Guette, Chem. Commun., No. 1, 8 (1980).
14. A. Guy, M. Lemaire, and J.-P. Guette, Tetrahedron, 38, 2339 (1982).
15. H. Pervez, L. Rees, and C. J. Suckling, Chem. Commun., No. 8, 512 (1985).
16. B. R. Suthers, P. H. Riggins, and D. E. Pearson, J. Org. Chem., 27, 447 (1962).
17. J. H. Gorvin, J. Chem. Soc., No. 4, 1237 (1953).
18. Organic Syntheses [Russian translation], Vol. 4, Izd. Inostr. Lit., Moscow (1953), p. 374.
19. Z. Vrba and Z. J. Allan, Tetrahedron Lett., No. 43, 4507 (1968).
20. B. M. Lynch, C. M. Chen, and Y. Y. Wigfield, Can. J. Chem., 46, 1141 (1968).
21. P. H. Griffiths, W. A. Walkey, and H. B. Watson, J. Chem. Soc., No. 5, 631 (1934).
22. K. Halvarsson and L. Melander, Arkiv Kemi, 11, 77 (1957).
23. R. O. C. Norman and G. H. Radda, J. Chem. Soc., No. 7, 3030 (1961).
24. R. O. C. Norman and G. H. Radda, Proc. Chem. Soc., No. 12, 423 (1960).
25. Organic Syntheses [Russian translation], Vol. 2, Izd. Inostr. Lit., Moscow (1949), p. 116.
26. L. I. Belen'kii, Yu. B. Vol'kenshtein, and I. B. Karmanova, Usp. Khim., 46, 1698 (1977).
27. Organic Syntheses [Russian translation], Vol. 1, Izd. Inostr. Lit., Moscow (1949), p. 475.
28. D. E. Pearson and H. W. Pope, J. Org. Chem., 21, 381 (1956).
29. D. E. Pearson, H. W. Pope, W. N. Hargrowe, and W. E. Stamper, J. Org. Chem., 23, 1412 (1958).
30. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 951 (1971).
31. D. H. Derbishire and W. A. Waters, J. Chem. Soc., No. 2, 564 (1950).
32. Ya. L. Gol'dfarb, É. I. Novikova, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2822 (1971).
33. Ya. L. Gol'dfarb and Yu. B. Vol'kenshtein, Zh. Obshch. Khim., 31, 616 (1961).
34. L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, Zh. Org. Khim., 9, 1514 (1973).

35. Ya. L. Gol'dfarb, I. B. Karmanova, Yu. B. Vol'kenshtein, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 11, 1474 (1978).
36. J.-P. Gesson, J.-C. Jacquesy, M.-P. Jouannetaud, and G. Morellet, Tetrahedron Lett., 24, 3095 (1983).
37. V. N. Belov, L. A. Kheifits, and S. I. Virezub, Reactions and Methods for the Investigation of Organic Compounds [in Russian], Book 10, Goskhimizdat, Moscow (1961), p. 7.
38. B. P. Susz and J. Cook, Helv, Chim. Acta, 37, 1273 (1954).
39. K. B. Starowiejski, S. Pasynkiewicz, A. Sporzynski, and A. Chowojnowski, J. Organomet. Chem., 94, 361 (1975).
40. L. I. Belen'kii, E. N. Gur'yanova, V. Knoppova, E. D. Lubuzh, I. P. Romm, and R. R. Shifrina, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 48 (1980).
41. L. I. Belen'kii, I. B. Karmanova, G. P. Gromova, É. I. Novikova, Ya. L. Gol'dfarb, V. S. Bogdanov, and L. V. Shmelev, Zh. Org. Khim., 9, 1499 (1973).
42. L. I. Belen'kii, V. S. Bogdanov, and I. B. Karmanova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1735 (1979).
43. I. P. Romm, L. I. Belen'kii, E. N. Gur'yanova, and Yu. K. Tovbin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 11, 2478 (1979).
44. J.-C. Jacquesi, M.-P. Jounnetaud, and S. Makani, Chem. Commun., No. 3, 110 (1980).
45. J. M. Brittain, P. B. D. de la Mare, and P. A. Newman, Tetrahedron Lett., No. 21, 4111 (1980).
46. F. Effenberger and P. Menzel, Angew. Chem., 83, 535 (1971).
47. G. A. Olah, J. A. Olah, and T. Ohyama, J. Amer. Chem. Soc., 106, 5284 (1984).
48. E. Ochiai, J. Pharm. Soc. Japan, 60, 164 (1940); Chem. Abstr., 34, 5450 (1940).
49. German Patent No. 433100; Beilstein, 26, Suppl. 2, 16 (1954).
50. A. E. A. Porter, in: General Organic Chemistry [Russian translation], Vol. 8, Khimiya, Moscow (1985), p. 190.
51. A. K. Sheinkman, S. I. Suminov, and A. N. Kost, Usp. Khim., 42, 1415 (1973).
52. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, p. 3 (1974).
53. M. Hamana, Khim. Geterotsikl. Soedin., No. 9, 1155 (1973).
54. W. P. K. Girke, Tetrahedron Lett., No. 39, 3537 (1976).
55. W. P. K. Girke, Chem. Ber., 112, 1 (1979).
56. W. P. K. Girke, Chem. Ber., 112, 1348 (1979).
57. A. Kreutzberger, Angew. Chem., 79, 978 (1967).
58. S. V. Krivun, Dokl. Akad. Nauk SSSR, 180, 615 (1968).
59. F. Krönnke and K. Dicnore, Chem. Ber., 92, 46 (1959).
60. R. Wizinger and H. Angeliner, Helv. Chim. Acta, 49, 2046 (1966).
61. M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, Tetrahedron, 32, 1767 (1976).
62. Ya. L. Gol'dfarb, É. I. Novikova, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6 1233 (1971).
63. A. Albert, in: Physical Methods in the Chemistry of Heterocyclic Compounds [Russian translation], Khimiya, Moscow–Leningrad (1966), pp. 15-124.
64. A. R. Katritzky and C. D. Johnson, Angew. Chem., 79, 629 (1967).
65. S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, J. Chem. Soc., Perkin 2, No. 4, 399 (1974).
66. A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin 2, No. 7, 1065 (1973).
67. S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin 2, No. 12, 1675 (1973).
68. A. R. Katritzky, B. Terem, E. V. Scriver, S. Clementi, and H. O. Tarhan, J. Chem. Soc., Perkin 2, No. 14, 1600 (1975).
69. A. R. Katritzky, S. Clementi, and H. O. Tarhan, J. Chem. Soc., Perkin 2, No. 14, 1624 (1975).
70. A. R. Katritzky, C. Ogretir, H. O. Tarhan, H. M. Dou, and J. V. Metzger, J. Chem. Soc., Perkin 2, No. 14, 1614 (1975).
71. A. R. Katritzky, H. O. Tarhan, and B. Terem, J. Chem. Soc., Perkin 2, No. 14, 1620 (1975).
72. A. R. Katritzky, S. Clementi, G. Milletti, and G. V. Sebastiani, J. Chem. Soc., Perkin 2, No. 6, 613 (1978).
73. D. S. Noyce, J. A. Virgilio, and B. Bartman, J. Org. Chem., 38, 2657 (1973).
74. D. S. Noyce and S. A. Fike, J. Org. Chem., 38, 3316 (1973).
75. D. S. Noyce and G. T. Stowe, J. Org. Chem., 38, 3762 (1973).
76. D. S. Noyce and B. B. Sandel, J. Org. Chem., 40, 3762 (1975).
77. D. S. Noyce and G. V. Kaiser, J. Org. Chem., 34, 1008 (1969).

78. D. S. Noyce and H. J. Pavez, J. Org. Chem., 37, 2620, 2623 (1972).
79. D. S. Noyce, C. A. Lipinski, and R. W. Nichols, J. Org. Chem., 37, 2615 (1972).
80. D. S. Noyce, C. A. Lipinski, and G. M. Loudon, J. Org. Chem., 35, 1718 (1970).
81. D. S. Noyce and B. B. Sandel, J. Org. Chem., 41, 3640 (1976).
82. E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, J. Amer. Chem. Soc., 91, 7381 (1969).
83. T. J. Broxton, G. L. Butt, L. W. Deady, S. H. Toh, R. D. Topsom, A. Fischer, and M. W. Morgan, Can. J. Chem., 51, 1620 (1973).
84. G. T. Bruce, A. R. Cooksey, and K. J. Morgan, J. Chem. Soc., Perkin 2, No. 6, 551 (1975).
85. R. J. Abraham, E. Bullock and S. S. Mitra, Can. J. Chem., 37, 1859 (1959).
86. E. B. Whipple, Y. Chiang, and R. L. Hinman, J. Amer. Chem. Soc., 85, 26 (1963).
87. Y. Chiang and E. B. Whipple, J. Amer. Chem. Soc., 85, 2763 (1963).
88. R. Kassner, E. Krumtholz, and F. W. Stenber, Ann., No. 5, 789 (1981).
89. H. Hogeween, Rec. Trav. Chim., 85, 1072 (1966).
90. H. Hogeween, R. M. Kellogg, and K. A. Kuindersma, Tetrahedron Lett., No. 40, 3929 (1973).
91. L. I. Belen'kii, A. P. Yakubov, and Ya. L. Gol'dfarb, Zh. Org. Khim., 11, 424 (1975).
92. A. P. Yakubov, N. V. Grigor'eva, and L. I. Belen'skii, Zh. Org. Khim., 14, 641 (1978).
93. Ya. L. Gol'dfarb, M. A. Kalik, N. A. Shul'ts, and L. I. Belen'kii, Zh. Org. Khim., 15, 1289 (1979).
94. L. I. Belen'kii and A. P. Yakubov, Tetrahedron, 40, 2471 (1984).
95. L. I. Belen'kii and A. P. Yakubov, Tetrahedron, 42, 759 (1986).
96. U. E. Wiersum and H. Wynberg, Tetrahedron Lett., No. 31, 2951 (1967).
97. D. M. Brower and J. A. van Doorn, Rec. Trav. Chim., 89, 553 (1970).
98. D. M. Brower, J. A. van Doorn, and A. A. Kiffen, Rec. Trav. Chim., 91, 1359 (1972).
99. V. G. Kul'nevich and Yu. M. Shapiro, Khim. Geterotsikl. Soedin., No. 12, 1594 (1972).
100. L. I. Belen'kii, Khim. Geterotsikl, Soedin., No. 12, 1587 (1980).
101. V. Veinmayr, J. Amer. Chem. Soc., 72, 918 (1950).
102. L. I. Belen'kii, A. P. Yakubov, and I. A. Bessonova, Zh. Org. Khim., 13, 364 (1977).
103. L. I. Belen'kii and N. V. Grigor'eva, in: Topics in the Chemistry of Heterocyclic Compounds, edited by J. Kovac, Bratislava (1981), p. 121.
104. Ya. L. Gol'dfarb, A. A. Dudinov, and V. P. Litvinov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 1323 (1982).
105. Y. Yokoyama, Y. Yamashita, K. Takahashi, and T. Sone, Chem. Lett., No. 6, 813 (1981).
106. Y. Yokoyama, Y. Yamashita, K. Takahashi, and T. Sone, Bull. Chem. Soc. Japan, 56, 2208 (1983).
107. Y. Yamashita, A. Yoshino, K. Takahashi, and T. Sone, The 46th National Meeting of the Chemical Society of Japan, Niigata, Oct. 1982, Abstr. 4P15; Y. Yamashita, H. Kobayashi, A. Yoshino, K. Takahashi, and T. Sone, Bull. Chem. Soc. Japan, 57, 1312 (1984).
108. G. G. Furin and G. G. Yakobson, Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, Vol. 1, No. 2, 109 (1977).
109. M. Eckert-Maksic, J. Org. Chem., 45, 3355 (1980).
110. G. V. Boyd and K. Heatherington, J. Chem. Soc., Perkin 1, No. 21, 2523 (1973).
111. C. T. Wie, S. Sunder, and C. D. Bolaniou, Tetrahedron Lett., No. 44, 4605 (1968).
112. G. A. Olah, K. Dunne, D. P. Kelly, and Y. K. Mo, J. Amer. Chem. Soc., 94, 7438 (1972).
113. H. J. Chen, L. E. Hakka, R. L. Hinman, A. J. Kresge, and E. B. Whipple, J. Amer. Chem. Soc., 93, 5102 (1971).
114. T. Yamaoka, H. Hosoya, and S. Nagakura, Tetrahedron, 24, 6203 (1968).
115. F. Effenberger and R. Niess, Angew, Chem., 79, 1100 (1967).
116. A. P. Yakubov, L. I. Belen'kii, and Ya. L. Gol'dfarb, Zh. Org. Khim., 7, 525 (1971).
117. T. A. Melent'eva, T. M. Filippova, L. V. Kazanskaya, I. M. Kustanovich, and V. M. Berezovskii, Zh. Obshch. Khim., 41, 179 (1971).
118. M. I. Struchkova, G. G. Dvoryantseva, N. P. Kostyuchenko, Yu. N. Sheinker, Yu. E. Sklyar, and R. P. Evstigneeva, Khim. Geterotsikl. Soedin., No. 3, 336 (1972).
119. Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein (Volkenstein), and L. I. Belen'kii (Belen'kij), Angew. Chem., 80, 547 (1968).
120. L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 344 (1975).
121. Ya. L. Gol'dfarb (editor), New Directions in the Chemistry of Thiophene [in Russian], Nauka, Moscow (1976).
122. H. J. Anderson and C. E. Loader, Synthesis, No. 4, 353 (1985).
123. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1228 (1971).
124. Ya. L. Gol'dfarb, G. P. Gromova, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2275 (1974).

125. L. I. Belen'kii, Ya. L. Gol'dfarb, and G. P. Gromova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2733 (1973).
126. Ya. L. Gol'dfarb and Yu. B. Vol'kenshtein, Dokl. Akad. Nauk SSSR, 128, 536 (1959).
127. Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, Dokl. Akad. Nauk SSSR, 185, 941 (1969).
128. L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, Zh. Org. Khim., 7, 1743 (1971).
129. L. I. Belen'kii, E. I. Novikova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 9, 1353 (1971).
130. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 5, 597 (1972).
131. Zh. I. Aksel'rod and V. M. Berezovskii, Usp. Khim., 39, 1337 (1970).
132. H. Saito and M. Hamana, Heterocycles, 12, 475 (1979).
133. D. E. Pearson, W. W. Hargrowe, K. T. Judith, and B. R. Suhters, J. Org. Chem., 26, 789 (1961).
134. R. E. Lokhov, S. S. Lokhova, N. M. Gaidarova, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 9, 1236 (1981).
135. H. J. den Hertog, L. van der Does, and C. A. Landheer, Rec. Trav. Chim., 81, 864 (1962).
136. L. van der Does and H. J. den Hertog, Rec. Trav. Chim., 84, 951 (1965).
137. J. Abblard, C. Decoret, L. Cronenberg, and H. Pacheco, Bull. Soc. Chim. France, No. 6, 2466 (1972).
138. E. Gareia, J. Amer. Chem. Soc., 82, 4430 (1960).
139. T. Batkowski, D. Tomasik, and P. Tomasik, Roczn. Chem., 41, 2101 (1967).
140. I. J. Fergusson, M. R. Grimmett, and K. Schofield, Tetrahedron Lett., No. 27, 2771 (1972).
141. J. W. Barnett, I. J. Fergusson, and K. Schofield, unpublished data cited by K. Schofield, M. R. Grimmett, and B. R. T. Keene, in: Heteroatomatic Nitrogen Compounds. The Azoles, Cambridge Univ. Press (1976), p. 68.
142. M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, J. Chem. Soc., No. 2, 1051 (1965).
143. I. I. Grandberg, S. V. Tabak, N. I. Bobrova, A. N. Kost, and L. G. Vasina, Khim. Geterotsikl. Soedin., No. 3, 407 (1965).
144. G. Travagli, Gazz. Chim. Ital., 85, 926 (1955).
145. S. L. Gusinskaya, Khim. Geterotsikl. Soedin., No. 3, 345 (1970).
146. O. P. Shvaika and G. P. Klimisha, Khim. Geterotsikl. Soedin., No. 1, 19 (1966)
147. R. Gompper and H. Ruhle, Ann., 626, 83 (1959).
148. H. S. Suri, G. N. Sharma, and K. S. Narang, J. Indian Chem. Soc., 45, 409 (1968); Chem. Abstr., 69, 77146 (1968).
149. R. Gompper and O. Christman, Chem. Ber., 92, 1944 (1959).
150. L. I. Belen'kii and M. A. Cheskis, Khim. Geterotsikl. Soedin., No. 7, 881 (1984).
151. L. I. Belen'kii, G. P. Gromova, M. A. Cheskis, and Ya. L. Gol'dfarb, Chemica Scripta, 25, 295 (1985).
152. M. A. Khan, B. M. Lynch, and Y.-Y. Hung, Can. J. Chem., 41, 1540 (1963).
153. B. M. Lynch and Y.-Y. Hung, Can J. Chem., 42, 1605 (1964).
154. M. R. Grimmett, S. R. Hartshorn, K. Schofield, and J. B. Weston, J. Chem. Soc., Perkin 2, No. 11, 1654 (1972).
155. S. D. Sokolov and I. M. Yudintseva, Zh. Org. Khim., 7, 1765 (1971).
156. R. G. Jones and C. Ainsworth, J. Amer. Chem. Soc., 77, 1538 (1955).
157. R. Hüttel and A. Gebhardt, Ann., 558, 43 (1947).
158. R. Hüttel and G. Welzel, Ann. 593, 207 (1955).
159. R. Stolle and F. Henke-Stark, J. Prakt. Chem., 124, 261 (1930).
160. V. P. Karavai and P. N. Gaponik, Khim. Geterotsikl. Soedin., No. 4, 564 (1985).
161. B. M. Lynch, Can. J. Chem., 41, 2380 (1963).
162. B. M. Lynch and T. Chan, Can. J. Chem., 41, 274 (1963).
163. H. El-Khaden, H. A. R. Mansour, and M. H. Meshreki, J. Chem. Soc. (C), No. 11, 1329 (1968).
164. E. Lippmann and A. Könnecke, Z. Chem., 15, 226 (1975).
165. H. W. Gschwend and H. R. Rodriguez, Organic Reactions, Vol. 26, Wiley & Sons, New York (1979), p. 1.
166. R. Hüttel and F. Buehele, Chem. Ber., 88, 1586 (1955).
167. J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse, and C. L. Habraken, J. Org. Chem., 38, 1777 (1973).
168. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, V. V. Sevast'yanova, and L. V. Epishina, Khim. Geterotsikl. Soedin., No. 4, 503 (1970).
169. R. Miethchen and C.-F. Kroger, Z. Chem., 7, 184 (1967).

170. C.-F. Kroger and H. Frank, Angew. Chem., 77, 425 (1965).
171. C.-F. Kroger and H. Frank, Angew. Chem., 77, 928 (1965).
172. C.-F. Kroger and R. Miethchen, Chem. Ber., 100, 2250 (1967).
173. J. H. Ridd, J. Chem. Soc., No. 4, 1238 (1955).
174. A. Grimison and J. H. Ridd, J. Chem. Soc., Nos. 9/10, 3019 (1959).
175. L. Schutte, P. P. Kluit, and E. Havinga, Tetrahedron, Suppl. No. 7, 295 (1966).
176. R. Breslow, J. Amer. Chem., Soc., 79, 1762 (1957).
177. H. A. Staab, H.-Th. Wu, A. Mannschreck, and G. Schwalbach, Tetrahedron Lett., No. 15, 845 (1964).
178. P. Haake, L. P. Bausher, and W. B. Miller, J. Amer. Chem. Soc., 91, 1113 (1969).
179. J. D. Vaughan, Z. Mughrabi, and E. C. Wu. J. Org. Chem., 35, 1141 (1970).
180. R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, Tetrahedron, 26, 685 (1970).
181. R. A. Olofson, W. R. Thompson, and J. S. Michelman, J. Amer. Chem. Soc., 86, 1865 (1964).
182. R. A. Olofson and J. M. Landesberg, J. Amer. Chem. Soc., 88, 4263 (1966).
183. E. C. Wu and J. D. Vaughan, J. Org. Chem., 35, 1146 (1970).
184. H. Kohn, S. J. Benkovic, and R. A. Olofson, J. Amer. Chem. Soc., 94, 5759 (1972).
185. E. Regel and K.-H. Buchel, Ann., No. 1, 145 (1977).
186. A. Medici, G. Fantin, M. Fogagnolo, P. Pedrini, A. Dondoni, and G. D. Andreetti, J. Org. Chem., 49, 590 (1984).
187. E. Regel, Ann., No. 1, 159 (1977).
188. R. Fusco, F. D'Ado, and A. Masserini, Gazz. Chim. Ital., 96, 1084 (1966).
189. A. Medici, M. Fogagnolo, P. Pedrini, and A. Dondoni, J. Org. Chem., 47, 3844 (1982).
190. A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, and P. Pedrini, J. Org. Chem., 49, 3478 (1984).
191. E. Anders, H.-G. Boldt, R. Fuchs, and T. Gassner, Tetrahedron Lett., 25, 1715 (1984).

CONDENSED HETEROCYCLES.

45.* SYNTHESIS AND STRUCTURES OF IMINES OF 2-SELENOLO-3-BENZO[b]FURANALDEHYDE AND 3-SELENOLO-2-BENZO[b]FURANALDEHYDE AND THEIR DERIVATIVES

V. P. Litvinov, V. A. Petukhov, V. Yu. Mortikov, and A. F. Vaisburg

UDC 547.728.2:542.945.24:543.422.25:548.737

A number of new selenolaldimines of benzo[b]furan were synthesized. It was established that they exist in dipolar form with delocalized multiple bonds.

In a previous paper we described the synthesis of imines of 2-mercapto-3-benzo[b]furanaldehyde and 3-mercapto-2-benzo[b]furanaldehyde [1]. It was shown that a thione–enamine tautomeric form with the contribution of a dipolar structure, as in the case of their benzo[b]-thiophene analogs [2], was characteristic for them. In order to study the effect of the nature of the exocyclic heteroatom on the structures and properties of aldimines of this type we synthesized a number of isomeric selenolaldimines of benzo[b]furan.

Thus the reaction of 2-bromo-3-benzo[b]furanaldehyde (I) [3] or 3-chloro-2-benzo[b]furanaldehyde (II) [4] with sodium hydroselenide and the subsequent action of salts of primary amines lead to the formation of 2-selenolo-3-benzo[b]furylideneamines III and 3-selenolo-2-benzo[b]furylideneamines IV in high yields (Table 1).

Like their sulfur analogs, selenolaldimines III are stable readily crystallized substances, in contrast to selenolaldimines IV, which are unstable in solutions and therefore cannot be purified by recrystallization and were characterized analytically. We established

*See [1] for communication 44.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 774-778, June, 1986. Original article submitted July 5, 1985.

 0009-3122/86/2206-0608$12.50