ACTIVITY AND SELECTIVITY IN THE ELECTROPHILIC SUBSTITUTION OF FIVE-MEMBERED HETERORINGS (REVIEW)

L. I. Belen'kii

UDC 541.124:547.72.73.74

Data on the activity and selectivity in reactions involving the electrophilic substitution of five-membered heteroaromatic compounds with one heteroatom are discussed. Chief attention is directed to the reactions of pyrrole, furan, thiophene, and their substituted derivatives. The inconsistency in the change in the activity (reaction rate) — N>O>S — and in the positional selectivity (the α:β ratio) — N<S<O — that exists for all electrophilic substitution reactions in these systems is interpreted with allowance for the mechanisms of the reactions and the nature of the heteroatom.

The problem of the relationship between the reactivities of various compounds the selectivity of their reactions, including the establishment of the nature of the so-called anomalous relationship between the activity and selectivity, has attracted the attention of many researchers in recent years (for example, see [1-4]). The concept that the selectivity decreases as the reaction rate increases in the case of electrophilic substitution reactions in the aromatic series has been thoroughly substantiated, as is well known, in the research of Brown and co-workers [5, 6], who proposed quantitative criteria relative to the relationship between the activity and selectivity that are intimately associated with the principle of linearity of the free energies.

Similar relationships between the activity and selectivity are also satisfied rather well for heteroaromatic compounds. In particular, such data were obtained and correlated for thiophene, furan, and pyrrole in studies by Marino (for example, see review [7]), in which the existence of a linear correlation between the activity (the logarithm of the partial rate factor) and selectivity (the logarithm of the α:β ratio or the ρ constant for a given reaction) was demonstrated.

It should be emphasized that the linear correlation mentioned above is observed in the case of examination of the change in the selectivity of reactions of the same substrate as a function of the activity of the electrophilic reagent. However, considering the arbitrary character of the concepts "substrate" and "reagent," it is completely legitimate to compare the selectivity of the same reactions and the activities of various heteroaromatic substrates. Precisely this sort of examination is also the aim of this paper; it shows that inconsistency in the change in the activity (reaction rate) — pyrrole>furan>thiophene — and the positional selectivity (the α:β ratio) — furan>thiophene>pyrrole — occurs for any electrophilic substitution reaction.

The effect of the nature of the heteroatom on the activities of various five-membered heterorings and the selectivities of their reactions will be examined below on the basis of the currently available concepts regarding the mechanisms of electrophilic substitution reactions. This analysis will of necessity be limited to thiophene, furan, pyrrole, and their substituted derivatives. As regards selenophene and tellurophene, considerably less study has been devoted to them, and quantitative data on the positional selectivity for these heterorings are almost unavailable, as a consequence of which these compounds will be considered only in individual cases in the subsequent exposition. Pyrrole analogs — phosphole and arsole — will not be discussed at all, since they do not display a tendency to undergo substitution reactions at the carbon atoms and are evidently devoid of aromatic properties [8-11].

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1587-1605, December, 1980. Original article submitted November 12, 1979.

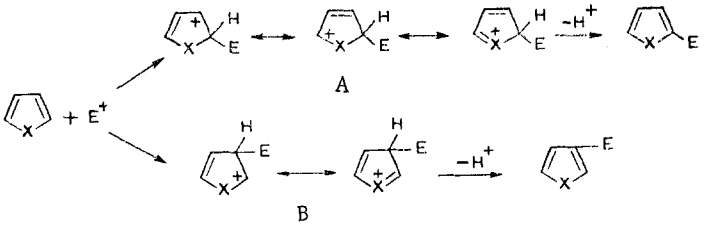
0009-3122/80/1612-1195$07.50

1. Principal Factors That Determine the Relative Activities of Five-Membered Heteroaromatic Compounds in Electrophilic Substitution Reactions

The examination of the mechanism of electrophilic aromatic substitution is usually carried out by invoking two types of intermediate particles, viz., a π complex (a Dewar intermediate) and a σ complex (a Wheland intermediate). However, whereas the former can be regarded more as a possible model of the transition state, the latter is a real intermediate, the formation of which has been established for many aromatic and heteroaromatic compounds. The concept of the formation of a π complex as the rate-determining step has been used to explain deviations from the "norm" in the relationship between the activity and selectivity of some electrophilic substitution reactions in the aromatic series [12]; however, these anomalies can also be interpreted on the basis of an examination of the formation of a σ complex as the rate-determining step [13]. Other attempts to indirectly prove the role of π complexes, particularly by establishment of a correlation between the reactivities of five-membered heterorings in the case of their electrophilic substitution and their ionization potentials, the change in which may constitute evidence for their ability to form a charge transfer complex or a π complex [14], have also been unsuccessful. In fact, the ionization potentials change in the order Te<S<O<Se [15], which is difficult to somehow link with the reactivities. At the same time, an examination of the relative stabilities of the σ complexes usually makes it possible to explain the changes in the reactivities of five-membered heterorings [16].

Nevertheless, it is most proper to also take into account the possibility of the formation of a π complex in quantitative estimates of the reactivities; this makes it possible to estimate the activation energies more accurately by means of the available computational methods. Precisely this sort of approach, which takes into account the localization energy as a quantum-chemical characteristic of the rate-determining step (the formation of a σ complex) and the ionization potential, which determines the preceding step involving the formation of a π complex or a charge-transfer complex, made it possible for the first time to quantitatively interpret the rate of acid-catalyzed isotope exchange of hydrogen in furan, thiophene, and pyrrole [17]. The same approach has also proved to be effective in the quantitative examination of the isotope exchange of hydrogen in selenophene [18].

Nevertheless, if we are dealing with a qualitative comparison of the reactivities of a number of structurally related compounds, we can, as we have already mentioned, restrict ourselves to an examination of the step involving the formation of the σ complex. A characteristic feature of this step is disruption of the aromatic character of the system:



It may be assumed that the disruption of the aromatic character due to the formation of a heteroarenium ion occurs more readily, the lower the degree of aromatic character of the starting system. To verify the validity of this assumption, one should deal with the problem of the criteria of aromatic character. A detailed discussion of these criteria does not enter into our problem, since special studies have been devoted to it (for example, see [11, 9]). Let us note only that all of the quantitative criteria of aromatic character in use today are essentially physical, viz., the resonance energies and various electronic and magnetic characteristics of compounds [11, 20, 21].

It is diffucult to establish a direct relationship between the aromatic character and the reactivity. In any case, the increased activity of the heteroaromatic systems under consideration in substitution reactions, which has provided Gilman in his time with a basis for the introduction of the concept of their "superaromatic character" [22], today cannot serve as an index of the higher degree of aromatic character of these compounds as compared with benzene. On the contrary, there are sufficient examples of a reverse relationship between the aromatic character (defined in accordance with the physical criteria mentioned above) and the reaction rate. In particular, in the case of electrophilic substitution of five-membered

heterorings that include group VI elements as the heteroatoms the reactivities decrease in the order O>Te>Se>S, whereas the aromatic character increases in the same order, viz., O<Te<Se<S [23].

The data presented above are in agreement with the assumption drawn above regarding the character of the relationship between the aromatic character and the reactivity. Unfortunately, the examination of a more extensive series of compounds that includes, for example, pyrrole does not make it possible to establish any distinct dependence of the reactivity on the aromatic character. This dependence is usually expressed purely qualitatively: aromatic compounds are more inclined to undergo substitution reactions than addition reactions. An interesting attempt to make a quantitative comparison of the ability of a compound to undergo substitution and addition was made in [24, 25], in which the KK index, which expresses the magnitude of the π-electron energy (calculated by the Hückel method) that the molecule loses as a result of addition with a change in the hybridization of two adjacent atoms from sp^2 to sp^3 as compared with substitution, in which the hybridization changes only for one atom, was proposed. Despite the insufficient degree of development of this approach, which, in particular, does not make it possible to distinctly evaluate the differences between systems such as benzene and pyridine [24] and thiophene and pyrrole [25], an examination of the relationship between the reactivity and the aromatic character in close connection with the mechanism of the reaction is undoubtedly valuable.

In speaking of the relationship between the aromatic character and the reactivity, one should emphasize that the quantitative criteria of aromatic character, except for the KK indexes mentioned above [24, 25], pertain to molecules that do not participate in the chemical reaction, whereas the difference in the energies between the starting molecule and the transition state or the intermediate is of definite value for estimating the reaction rate. This characteristic is obtained from quantum-chemical calculations in the form of the localization energy, which is defined as the difference between the total energies of the starting molecule and the product of its C protonation. In essence, the same approach on the basis of experimental rather than calculated data was first proposed by Brown and Brady, who observed the existence of a linear relationship between the relative rates of halogenation of aromatic compounds and the stabilities of the σ complexes that are formed in the reaction of arenes with HF and BF_3 [26].

According to the experimental data [7, 14], with which the results of calculation of the localization energies are also in agreement [16], the activity of pyrrole considerably exceeds (by five to seven orders of magnitude) that of furan in electrophilic substitution reactions, while the activity of thiophene is inferior to that of furan to a lesser extent (by one to three orders of magnitude). Such high activity of pyrrole can be explained by the increased ability of the nitrogen atom to delocalize the positive charge in the cationic σ complexes as compared with other heteroatoms, particularly the oxygen atom. This ability is ensured by the favorable conditions for overlapping of the unshared 2p pair of the nitrogen atom with the vacant 2p orbital of the adjacent carbon atom; it is important that the electronegativity of the nitrogen atom is lower than that of the oxygen atom, which also has an unshared 2p pair (see [27]). The peculiarities due to the nature of the heteroatom are displayed even in the neutral pyrrole molecule, in which the positive end of the dipole is localized on the heteroatom [28], while the heteroatoms in furan and thiophene [28], as well as in selenophene and tellurophene [29], are negatively polarized. In other words, in the case of pyrrole the heteroatom has at least the same activating mesomeric effect as in the case of furan and a substantially smaller deactivating inductive effect [28]. For the comparison of thiophene with other heterorings it is important to bear in mind the poorer conditions for overlapping of the unshared 3p pair of electrons of sulfur with the 2p orbital of carbon, which should reduce the activating + M effect of the heteroatom and, at the same time, the approximate equality of the effective electronegativities of S and NH [30]. Let us also point out that the stabilizing effect of the heteroatom on the adjacent cationic center in a system of the $\overset{+}{C}H_2XR$ type (X = O, S) is greater in the case of sulfur, while the overall π stabilization in compounds of the CH_2=CHXR, CH≡CXR, and C_6H_5XR type, in which the heteroatom is adjacent to an unsaturated system, is greater for oxygen [31, 32]. Apparently as a result of the combination of heteroatom effects that act in opposite directions and are manifested in both the starting compounds and the heteroarenium ions, the difference in activity between furan and thiophene is considerably smaller than between furan and pyrrole.

TABLE 1. α:β Ratios in the Reactions of Furan, Thiophene, and Pyrrole [14, 33]

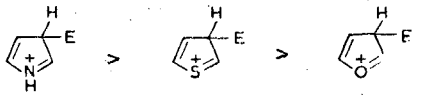
Reactions	Furan	Thiophene	Pyrrole
Acetylation with $Ac_2O/SnCl_4$	6808,5	200	—
Acetylation with $AcOCOCF_3$	6000	71,4	6
Benzoylation with $Bz_2O/SnCl_4$	250	65,6	—
Protodedeuteration	—	1940	2,4
Protodesilylation	141,6	43,5	—

2. Nature of the Heteroatom and Positional Selectivity

The electrophilic substitution of heteroaromatic compounds is distinguished by high positional selectivity due to the effect of the heteroatom, which can be regarded as an "internal function." In particular, extremely high relative reactivity of the α positions, which in the case of furan and thiophene in electrophilic substitution reactions are several orders of magnitude more active than the β positions, is characteristic for five-membered heterorings; these differences are substantially smaller for pyrrole (Table 1).

The differences in positional selectivity observed for different reactions of the same heteroring and associated with differences in the activities of electrophilic agents (to which different values of reactivity constants ρ correspond) will not be discussed further, since these questions have been examined in detail by Marino [7, 14]. Questions as to the reasons for the high positional selectivity in general and the factors that determine the differences in the α:β ratios for furan, thiophene, and pyrole are of extreme importance for this review. The increased activity of the α positions is explained most simply by the better possibilities of charge delocalization in σ complexes of the A type corresponding to a α substitution (three carbon atoms and the heteroatom participate in delocalization) as compared with σ complexes of the B type corresponding to β substitution (one α-C atom and the heteroatom participate in delocalization). Nevertheless, the positional selectivity in the case of various heterorings is in poor agreement with their activity in electrophilic substitution reactions. Thus furan turns out to be more selective than the less active thiophene. At the same time, the most active compound, viz., pyrrole, in conformity with the concepts regarding the ratio of the activity and selectivity, is the least selective.

We examined the reasons for the above-indicated disparity between the orders in which the activities (N>O>S) and positional selectivities (O>S>N) for five-membered heterorings change as a function of the nature of the heteroatom in [34]. It is natural to assume that the differences between the heterorings in their ability to form β-substituted compounds are determined by the different relative thermodynamic stabilities of σ complexes of the B type that develop in the preparation of β-substituted compounds as compared with the σ complexes of the A type corresponding to α substitution. The assumption that the stability of ions of the B type depends to a greater extent on the effect of the heteroatom than in the case of ions of the A type, in which all of the ring atoms except the carbon atom of the geminal node participate in delocalization of the positive charge is important in this case. It is postulated [34] that the change in the relative stability of ions of the B type as a function of the nature of the heteroatom should be similar to the corresponding changes known (for example, see [35]) for onium compounds: $R_4N^+ > R_3S^+ > R_3O^+$. If this assumption is correct, the stability of ions of the B type (as compared with the corresponding A ions) should change in the order



This dependence of the relative thermodynamic stabilities of σ complexes B on the nature of the heteroatom may explain the decrease in the formation of β-substituted compounds on passing from pyrrole to thiophene and then to furan.

The character of the factors that are responsible for the order presented above can be seen from a number of independent experimental and calculated data. Let us note first of all that the highest stability of the ion of the B type for pyrrole is in agreement with what we stated above relative to the stabilizing effect of various heteroatoms on the adjacent ca-

tionic center. A similar sequence of the stabilization energies of $\overset{+}{C}H_2XR$ cations (X = NR, S, O; R = H, CH_3) was obtained on the basis of data from the mass spectrometry of CH_3XR [36]:

$$CH_2{=}\overset{+}{N}R_2 > CH_2{=}\overset{+}{S}R > CH_2{=}\overset{+}{O}R.$$

Data on the higher stability of the methylthiomethyl cation as compared with the methoxymethyl cation were also obtained during a study of the mass spectra with chemical ionization of compounds of the CH_3XCH_2COR type [37, 38].

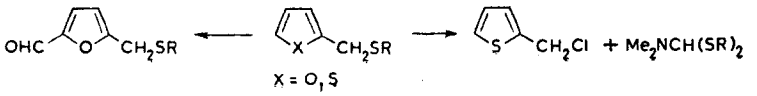
As we have already mentioned above, nonempirical quantum-chemical calculations [32, 39] provide evidence for the higher stabilizing effect of the sulfur atom on the adjacent cationic center for $\overset{+}{C}H_2XR \leftrightarrow CH_2{=}\overset{+}{X}R$ ions. This model corresponds quite well to a σ complex structure of the B type. At the same time, a σ complex of the A type with the charge delocalized over four centers is closer in a certain sense to a model of the neutral CH_2=CHXR compound [39], for which π stabilization is higher when X = O. Our analysis of the distribution of the π charges in σ complexes corresponding to pyrrole, thiophene, and furan (the calculations were made within the valence approximation by the semiempirical CNDO/2 method) shows [40] that the part of the total π charge localized on the heteroatom and the differences that depend on the nature of the latter are greater for ions of the B type (50-70% of the total π charge) than for ions of the A type (30-40%); in σ complexes of the B type the fraction of the π charge on the heteroatom decreases in the order N>S>O, as compared with N>O>S in ions of the A type. Let us point out that the selectivity of electrophilic substitution measured by the difference between the localization energies corresponding to α and β substitution [40] changes in conformity with the order experimentally established for the α:β ratio, viz., N<S<O.

3. Reactivities and Positional Selectivities and Substituted Pyrroles, Furans, and Thiophenes

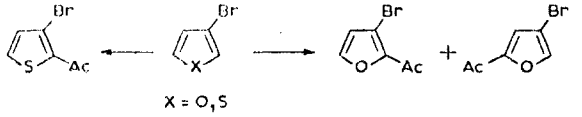
The analogy in the reactions of pyrrole, furan, and thiophene with electrophilic agents is generally known. Many of the peculiarities characteristic of each of the examined systems are due to the great differences in their activity and positional selectivity, as well as to some specific differences in transmission of the effects of the substituents through the heterorings. It is expedient to compare the properties of pyrrole, furan, and thiophene compounds separately for activated (heterorings without substituents and those bearing orienting groups of the I sort) and deactivated systems substituted by groupings that are orienting groups of the II sort.

3.1. Activated Compounds. The analogy between the heterocyclic systems under discussion is manifested in the orientation of the electrophilic substitution, which for activated compounds is generally directed primarily or exclusively to the free α position. The closeness of the activities of the α and β positions that is characteristic for pyrrole may lead to the formation of significant amounts of the β-substituted compounds, which sometimes may even turn out to be the chief reaction products if attack on the α positions is hindered. For example, steric shielding of the α positions in N-substituted pyrroles is manifested, according to the data in [41], as sharp increase in the formation of 3-formyl derivatives in the case of Vilsmeier formylaton: only the 2-formyl compound is formed in the case of N-methylpyrrole, but the α:β ratio decreases in the order 11.5:1, 1.9:1, 1:14 for N-ethyl-, N-isopropyl-, and N-tert-butylpyrrole. A similar phenomenon was also observed in the nitration of N-alkylpyrroles [42].

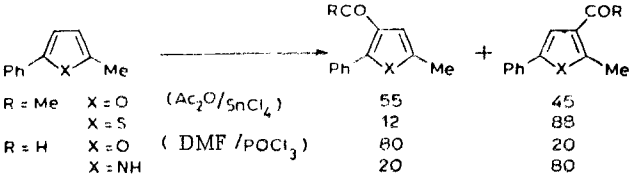
As a result of its exceptionally high reactivity, pyrrole can undergo reaction under considerably milder conditions than furan and thiophene. Thus pyrrole is acetylated by acetic anhydride in the absence of a catalyst [43,44], whereas the acetylation of both furan and thiophene requires the use of catalysts. The differences in the behavior of the corresponding furan and thiophene compounds are also most often determined by the higher activity of the former. In some cases furan and thiophene compounds may undergo conversions of different types even under the same conditions. For example, compounds of the benzyl ether, benzyl sulfide, and benzylamine type may undergo reactions with acylating agents of both the aromatic substitution types and with cleavage of the C–X bond (X = O, S, N) in the side chain; the latter reaction pathway usually predominates. Thus cleavage was observed in an attemt to formylate alkyl 2-thienyl sulfides by the action of dimethylformamide (DMF) and $POCl_3$ [45], while the furan analogs, which have a more active heteroaromatic ring, give the corresponding aldehydes smoothly under the same conditions [46]:



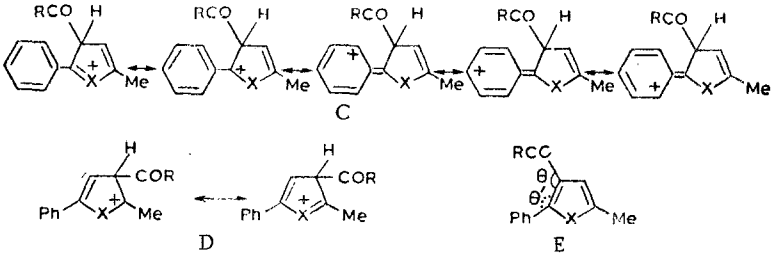
A number of differences are also observed in the substitution of furan and thiophene analogs in the ring. If the molecule contains two free α positions, the primary reaction pathway is determined by the orienting effect of the available substituent. In particular, the acylation of 3-bromothiophene takes place virtually exclusively in the 2 position [47]. However, 3-bromofuran, because of the greater activity of the α positions, gives mixtures of 2- and 5-acyl-substituted compounds containing 20-25% of the latter [48].



Interesting data pertaining to the relative activity of the β positions in 2-aryl-5-methyl-substituted furans, thiophenes, and pyrroles were obtained by a group of French researchers [49], who observed the formation of isomers with markedly different ratios for the analogs:



Dana and co-workers [49] validly consider two groups of factors that affect the specificity of the reaction and operate inconsistently in the cases under consideration, viz., electronic factors, which favor substitution in the 3 position owing to the possibility of charge delocalization in the σ complex (C) with the participation of the aryl substituent, and steric factors, which promote substitution in the 4 position, i.e., adjacent to the less bulky methyl substituent when the reaction proceeds through cation D.

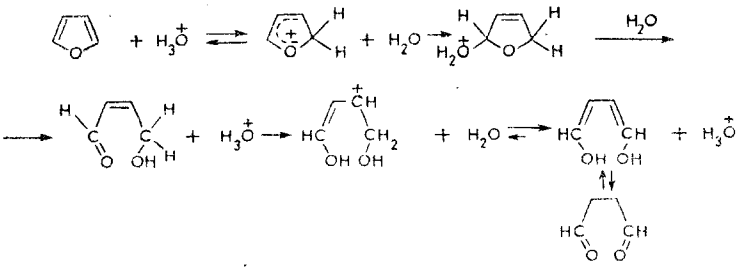


However, one cannot fully agree with this interpretation. Thus in explaining the formation of a substantially larger amount of the 3-acetyl-substituted compound in the case of the furan compound than in the case of the thiophene compound Dana and co-workers [49] assume that it is due to the larger values of the exterior bond angles θ and θ' when X = O (see structure E). In view of the closeness of the geometries of furan [50] and thiophene [51] this explanation does not seem too convincing. We assume that the already-noted differences between the heteroatoms and their abilities to exist in the onium state are manifested here. This ability is lower for the oxygen atom than for the sulfur atom, so that charge delocalization with the participation of the aryl substituent (ion C) has greater significance for the furan compound. However, in the case of the thiophene analog the sterically less hindered σ complex (D), in which the charge is distributed between one carbon atom and the heteroatom, turns out to be quite favorable.

In order to explain the markedly different ratios of the isomeric aldehydes formed in the formylation of 2-phenyl-5-methyl-substituted furan and pyrrole (the thiophene compound does not react under the conditions used) Dana and co-workers [49] attempted to invoke the concept of an "earlier" transition state (of the π-complex type) for the pyrrole analog and a "later" transition state (of the σ-complex type) for the furan analog; however, this point of view was not, of course, confirmed in any way, whereas these differences become understandable when one takes into account the greater ability of the nitrogen atom as compared

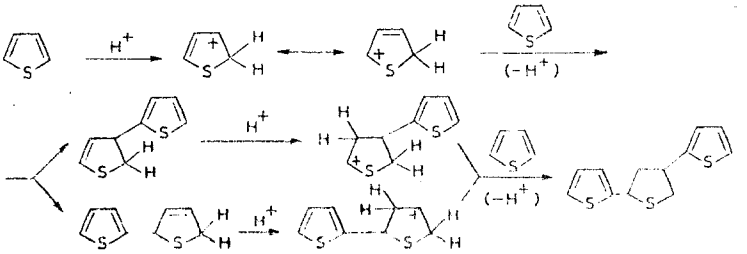
with the oxygen atom to stabilize the adjacent cationic center in the intermediately formed σ complexes of the C and D type.

The quantitative evaluation of the reactivities of furan, pyrrole, and derivatives of these compounds that bear activating substituents is frequently complicated by their acidophobic character, which is manifested in the formation of products of "resinification" or ring opening under electrophilic substitution conditions. Thiophene compounds are considerably more resistant to the action of acids. For example, acid-catalyzed hydrogen-isotope exchange is widely used to evaluate the reactivities of various positions of thiophene and substituted thiophenes (for example, see [52-54]). However, in the case of furan, for example, one can accurately measure only the "lability" of the α-H atoms, since at H_2SO_4 concentrations above 30% by weight, in which solutions the protons in the β positions undergo exchange at a sufficient rate, one simultaneously observes hydrolytic cleavage of the furan ring [55], which has been found to commence with protonation of the α position of the furan ring [56, 57]:

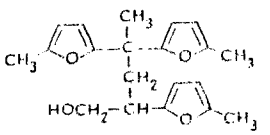


α-C Protonation of the furan ring also occurs in the hydrolysis of homologs and derivatives of furan, including 2,5-disubstituted compounds [56]. The opinion of Aaltonen and coworkers that hydrolysis commences with β-C protonation in the case of 2,5-dimethylfuran [58] and 2-methoxyfuran [59] was not confirmed by them and, as established in [60], was based on an inaccurate determination of the structures of the products of hydrolysis of 2-methoxyfuran. Ring cleavage is not characteristic for thiophene compounds under electrophilic substitution conditions, except for the specific case of 2,5-dimethoxythiophene [61], which is converted to dimethyl monothionosuccinate by the action of HCl in ether.

It is well known that so-called resinification of five-membered heterorings also takes place readily under the influence of protic and aprotic acids. Structures have been established for some of the resinification products. These structures make it possible to assume that the first step in this process is C protonation, generally in the α position, which is accompanied by reaction of the resulting cation with the neutral molecule via an electrophilic substitution scheme. Protonation of the resulting "dimer" may similarly lead to the production of a "trimer" etc. A mechanism for such electrophilic oligomerization for thiophene was proposed in 1950 [62], and the structure of the "trimer" was later confirmed by means of x-ray diffraction analysis [63]:

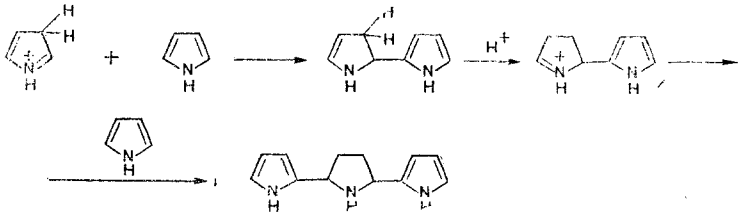


Oligomerization of furan compounds also proceeds similarly. Facile cleavage of the saturated heteroring in the oligomer is peculiar to this process; this can be illustrated by the structure of the 2-methylfuran "tetramer" [64]:

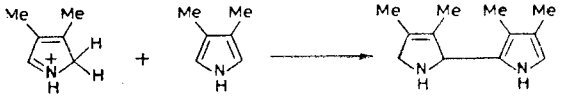


As a consequence of the high activity of pyrrole, hydrogen-isotope exchange in the latter can be studied at such low acid concentrations that "resinification" can be disregarded [55,

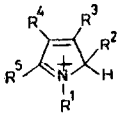
65-68]. For example, H-D exchange in the case of pyrrole proceeds at a high rate in 10% solutions of CH_3COOD in a mixture of dioxane and D_2O [66] or in an aqueous methanol medium in the presence of 0.5% by weight H_2SO_4 [65]. An increase in the concentration of the mineral acid leads to oligomerization of pyrrole and many substituted pyrroles [69]. Thus pyrrole is converted to a "trimer" in a few seconds by the action of 6 N HCl. The mechanism of this oligomerization is similar to the mechanism examined above for compounds of the thiophene and furan series. A peculiarity of this process in the case of pyrrole is the fact that the β-C-protonation product proves to be an active electrophile and is present in rather high concentration [70]:



In other cases self-condensation may proceed through α-C protonation. For example, 3,4-dimethylpyrrole gives a dimer in 6 N HCl [71]:

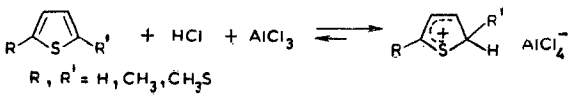


Some alkylpyrroles do not undergo oligomerization but give salts under the influence of acids; these salts can sometimes be isolated in the crystalline state [69]. Similar salts are also formed when pyrrole and its homologs are dissolved in concentrated mineral acids such as 12 M H_2SO_4. A study of solutions of the salts by PMR spectroscopy [72-74] showed that they are σ complexes, viz., products of C protonation of the pyrrole ring; the heteroarenium ions that are produced by protonation of the α position are the more stable forms, which generally are also observed in the spectra:



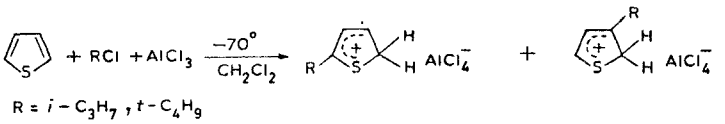
(R^1,R^2,R^3,R^4 = Me; the remaining R = H)

The heteroarenium ions that are formed in the α-C protonation of furan, thiophene, and particularly substituted furans and thiophenes that bear activating substituents have been studied thoroughly recently, mainly by NMR spectroscopy. Thiophenium ions are distinguished by the particular ease of their formation and their high stabilities. They were first observed by PMR spectroscopy in excess strong acid [75, 76]. It is interesting to note that we were able to obtain thiophenium ions in inert solvents ($ClCH_2CH_2Cl$ and CH_2Cl_2) by the action of an approximately equimolar amount of HCl in the presence of $AlCl_3$; some of them were found to be so stable that they remained unchanged at room temperature for several weeks and even months [77]:



R, R' = H, CH_3, CH_3S

Complexes of a similar sort that are stable at room temperature are also formed in the alkylation of thiophene in the presence of an equivalent amount of $AlCl_3$ [78].



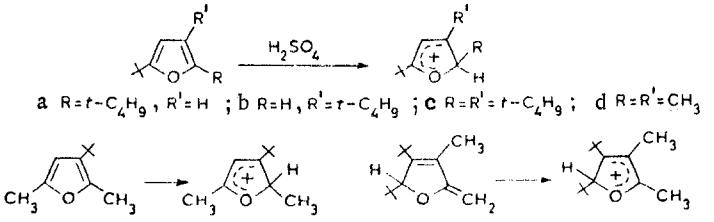
R = i-C_3H_7, t-C_4H_9

Stable thiophenium ions can be formed under the conditions of electrophilic substitution reactions; part of the starting thiophene compound is deactivated under these conditions. For example, in the case of acylation of 2,5-dimethylthiophene in dichloroethane in the presence of $AlCl_3$ up to half of the starting compound is tied up (by the HCl evolved during acylation) in the form of an α-C-protonation product; the ratio of the latter and the ketone

(of course, in the form of a complex with $AlCl_3$) changes only slightly when the mixture is allowed to stand for a long time [77].

If the structure of the thiophene compound is particularly favorable for charge delocalization, as in the case of 2,4-bis(alkylmercapto)thiophenes, virtually complete protonation is observed in trifluoroacetic acid [79] or in the HCl—$SnCl_4$ system [80].

The most important condition that makes it possible to avoid resinification in the preparation of thiophenium ions in the presence of $AlCl_3$ is realization of protonation or alkylation at reduced temperatures (below —50°C), which prevents the reaction of the resulting ions with the neutral molecules that have not yet undergone protonation or alkylation. Attempts to obtain furanium ions under the same conditions lead to resinification, whereas, as we have demonstrated by mass spectrometry with chemical ionization, furan and its homologs, as well as alkyl α-furyl sulfides, in the gas phase are close to the corresponding thiophene analogs [81]. The difficulties involved in the preparation of furanium ions in the liquid phase are evidently not due to their "intrinsic" instability but rather to the high reactivities of the free furan compounds that exist in equilibrium with the σ complexes. This is in agreement with the literature data on the production of stable furanium ions from tert-butylfurans, in the case of which one observes additional stabilization of the cation by the tert-butyl group; steric shielding hinders an intermolecular reaction in this case [82]:



a R=t-C4H9, R'=H ; b R=H, R'=t-C4H9 ; c R=R'=t-C4H9 ; d R=R'=CH3

2,5-Dimethylfuran undergoes complete resinification under the same conditions [82]. α-C-Protonated forms corresponding to it and other methylfurans were obtained either by an indirect method, viz., by the action of strong protic acids on unsaturated aliphatic ketones [83, 84], or by extraction of furans (2-methyl- and 2,5-dimethylfurans) from solutions in CCl_3F with FSO_3H—SbF_5 at —78°C [83]. Heteroarenium ions obtained by protonation of furan and 2-methylfuran at room temperature could be observed by means of the UV spectra [85]. However, these ions existed for several minutes in concentrated H_2SO_4 only under high-dilution conditions (10^{-5}-10^{-6} mole/liter), which lowered the probability of intermolecular reaction of the furanium ion with the neutral molecule.

In the case of pyrrole compounds this sort of reaction of the heteroarenium ions with the neutral molecules does not play such a substantial role. This is due to the considerably lower (under comparable conditions) concentration of the neutral molecules, which "compensates" for the higher activity of pyrroles in electrophilic substitution reactions and is due to their relatively high basicity. For example, the pK_a value for 2,5-dimethylpyrrole (for α-C protonation in H_2SO_4) reaches —1.0, while it is nine orders of magnitude lower (—10.01 and —10.16, respectively) for 2,5-dimethylfuran and 2,5-dimethylthiophene [86]. Thus, with respect to their strengths as bases, alkylpyrroles are close to carboxylic acid amides and considerably surpass esters, aldehydes, and ketones (pK_a values from —6 to —7.5) [87]. The latter circumstance is important for an understanding of the fact that polyalkylated carbonyl compounds of the pyrrole series are protonated at the ring α-carbon atom rather than at the oxygen atom [88, 89].

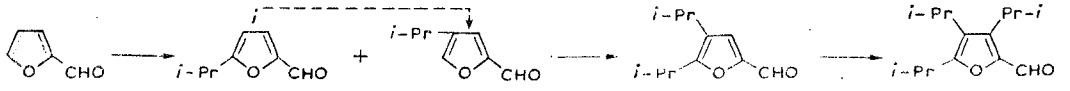
3.2. Deactivated Compounds. The differences between the heteroaromatic systems under discussion with respect to positional selectivity and transmission of the effect of substituents are of particular significance for the interpretation of the behavior of deactivated compounds. In the case of compounds that bear a substituent of the II sort in the 3 position, as a result of coincidence of the orienting effects of the substituent and the heteroatom, attack of the electrophilic agent is directed primarily (and sometimes exclusively) in the 5 position. When an electron-acceptor substituent is present in the α position of the ring, one observes competition between the α-orienting effect of the heteroatom and the meta-orienting effect of the substituent; in this case none of the ordinary orienting groups of the II sort is able to completely overcome the effect of the heteroatom.

The character of the difference between furan, thiophene, and pyrrole compounds that bear deactivating substituents can be illustrated by data on bromination in acetic acid in

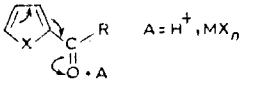
the presence of LiBr of methyl esters of the corresponding 2-carboxylic acids [90]. Under the indicated conditions furan and thiophene esters give only 5-bromo substituted compounds, while a mixture of isomeric 4- and 5-bromides in a ratio of 76.8:23.2 is formed in the case of pyrrole-2-carboxylic acid ester (see also [91, 92]). Let us note that the rates of bromination of esters (in the 5 position) are arranged in the S:O:N order $1:1.2\cdot10^2:5.9\cdot10^8$ [90]. In the case of stronger meta-orienting groups than the $COOCH_3$ group the formation of 4-substituted compounds is also observed in the thiophene series. Thus the bromination of furfural without a catalyst leads only to 5-bromofurfural [93]; in the case of 2-formylthiophene the ratio of the 4- and 5-bromo compounds is 3:97 [94]. An especially large number of 4-substituted compounds are formed in the nitration of thiophene and pyrrole compounds that bear orienting groups of the II sort in the 2 position. In particular, the ratios of 4- and 5-nitro-substituted compounds under conditions that exclude modification of the substituent already present reach 52:48 (for acetothienone [95]), 57:43 (for 2-nitrothiophene [96]), and even 65:35 (for dimethyl-2-thienylsulfonium perchlorate [97]). However, the low degree of selectivity of nitration does not make it possible to detect differences with pyrrole analogs such as 2-acylpyrroles [98].

As a rule, furan compounds give exclusively 2,5-disubstituted compounds [48]. Until recently, only two reports that contradict the information stated above were available. In one of them [99] it was asserted that a mixture of 4- and 5-acyl-substituted compounds is obtained in the caproylation of methyl 2-furoate; however, we have demonstrated [47] that these results were based on an incorrect interpretation on the PMR spectra of the reaction products.

The second report [100] deals with the isolation of 10% 4-isopropylfurfural from the products of the reaction of furfural with isopropyl chloride in the presence of $AlCl_3$, in which the 5-alkyl-substituted compound was not detected. The 4-isopropylfurfural structure was proved distinctly in [100] and does not raise any doubts. Recently we [101] and Valenta and Koubek [102] obtained data that show that 4-isopropylfurfural is not the only product of this reaction. Considerable amounts of products of further alkylation, viz., 4,5-diisopropyl- and 3,4,5-triisopropylfurfurals, are formed; up to 40% of the starting furfural does not react at all. A small amount of 5-isopropylfurfural is also detected. Thus the reaction does not stop at the monosubstitution step, and 5-isopropylfurfural possibly undergoes further alkylation more rapidly than the 5-isopropyl isomer. One also cannot exclude the possibility of isomerization of the 5-alkyl-substituted compound to 4-isopropylfurfural under the reaction conditions (see [103]).



Nevertheless, the fact of the formation of a small amount of 4-isopropylfurfural is absolutely certain and is probably due to the formation of complexes with $AlCl_3$ at the carbonyl group. This transformation of carbonyl compounds makes it possible to markedly intensify the electron-acceptor capacity of the substituent; owing to the effect of conjugation, the 5 position is deactivated to a much greater extent than the 4 position (see [47, 104] for a more detailed discussion). Protonation of the CO group also has a similar effect [47, 105]:



We estimated the quantitative intensification of the electron-acceptor capacity of the substituent as a consequence of complexing by means of the ^{13}C NMR spectra of the corresponding benzene compounds and characterized it by means of the σ_p^+ values (Table 2) [106].

The above-noted intensification of the electron-acceptor capacity of a substituent makes it possible in the case of complexes of 2-acylthiophenes with $AlCl_3$ to obtain the corresponding 2,4-disubstituted compounds with high selectivity [47]. The admixing of the 2,5-disubstituted isomer in the case of bromination [107-109] and chloromethylation [110, 111] does not exceed 1%. Close results are also obtained when complexes of carbonyl compounds with strong protic acids are used. In particular, the admixing of the 2,5-disubstituted compound for 2-formylthiophene and 2-acetothienone amounts to 2 and 4% in the bromination products [109] and 6 and 11% in the nitration products [112] when the reactions are carried out in an inert solvent (1,2-dichloroethane) with complexes of the $RR'CO\cdot HSbCl_6$ type. Nitration [113],

TABLE 2. σ_p^+ Constants of Some Substituents (Y), Including Those Modified by Complexing with MX_n

Y	MeO	CN	COOMe	PhCO	MeCO	CHO	NO_2
σ_p^+ (Y)	−0,7	0,6	0,6	0,6	0,6	0,8	0,8
σ_p^+ (Y · AlX_3)	0,1	1,2	1,2	1,3	1,5	1,9	1,6
X = Cl, Br							
Substituents:	MeCO	MeCO · $SbCl_5$		MeCO · $AlCl_3$		MeCO · BCl_3	
σ_p^+	0,6	0,9		1,5		1,6	

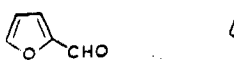
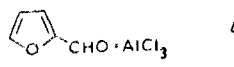
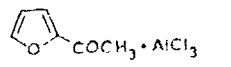
bromination [114], and chloromethylation [115] of the same carbonyl compounds in concentrated H_2SO_4 lead to the greater formation of 5-substituted compounds; however, in these cases also 2,4-disubstituted compounds constitute from 70 to 90% of the reaction products.

Protonation at the carbonyl group cannot be used in the furan series because of resinification in strong protic acid media. Complexing with $AlCl_3$ makes it possible in some cases to change the specificity of electrophilic substitution for 2-acylfurans; however, the formation of 2,5-disubstituted compounds also predominates, as a rule, for the complexes. The special case of isopropylation of furfural that has already been discussed does not refute the conclusion drawn above. Let us also note that 4- and 5-isopropyl- and 4,5-diisopropyl-substituted compounds in a ratio of 2:3:2 were obtained in the isopropylation of methyl 2-furoate; the ratio of the 4- and 5-substituted compounds increased when the temperature was raised, and this provided a basis for the assumption of the possibility of isomerization of the 5-substituted isomer to the 4-substituted isomer [103]. The chloromethylation of 2-acylfurans by the action of bis(chloromethyl) ether in the presence of $AlCl_3$ gives the products in low yields; the 5-substituted isomer predominates in the resulting mixture of chloromethyl-substituted products [116]. The most illustrative results were obtained in the bromination of the complex of furfural with $AlCl_3$. In particular, the conditions (0°C in $CHCl_3$) under which 4-bromofurfural is the principal reaction product were found [117]. However, in the case of 2-acetylfuran both isomers are formed in approximately equal amounts [109]. The formation of a 4-bromo-substituted compound cannot be detected at all in the bromination of methyl 2-furoate in the presence of excess $AlCl_3$ [118]. Thus complexing with $AlCl_3$ at the carbonyl group does not make it possible to suppress the activity of the 5-position in 2-acylfurans and does not make it possible to obtain virtually individual 2,4-disubstituted compounds as in the case of the thiophene analogs. This can be explained primarily by the large differences in the activities of the α and β positions of furan, which are also retained in the case of substituted furans.

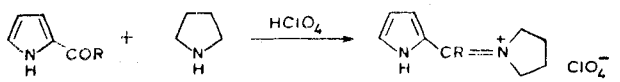
Considering the fact that, as compared with its analogs, unsubstituted pyrrole has the lowest α:β ratio, one need not be surprised at the capacity for selective conversion to 2,4-disubstituted compounds that is characteristic for pyrrole compounds that bear deactivating substituents when electrophilic substitution reactions are carried out in the presence of excess Lewis acid, i.e., when these compounds undergo the reaction in the form of a complex. 2,4-Disubstituted compounds that bear bromo [119], acyl [120-124] (including formyl [121-123] and alkylthiocarbonyl [123]), and alkyl [103, 125-127] groups in the 4 position were obtained in high yields by this method from complexes of 2-acyl, 2-alkoxycarbonyl-, 2-alkylthiocarbonyl-, and 2-cyanopyrroles with $AlCl_3$, as well as with $AlBr_3$ and $GaCl_3$, although isomerization with the formation of 5-alkyl-substituted compounds is often observed in the latter case under the reaction conditions.

As an example that demonstrates simultaneously the high activity of compounds of the pyrrole series and the possibility of a change in the specificity of substitution owing to complexing, let us point out the preparation of formyl-substituted compounds from 2-ethoxycarbonyl- and 2-ethylthiocarbonylpyrrole [122]. Mixtures of 4- and 5-substituted compounds that contain ∿70% of the latter are obtained by the action of DMF and $POCl_3$ in both cases; however, the percentages of the 4-substituted compounds reached 98 and 94%, respectively, when dichloromethyl methyl ether and excess $AlCl_3$ were used. The use of thioesters is extremely attractive, since treatment of the 2,4-disubstituted compounds obtained from them with Raney nickel leads to desulfuration and the simultaneous decarbonylation to give the corresponding 3-monosubstituted pyrroles [121].

TABLE 3. Competitive Bromination of Equimolar Mixtures of Carbonyl Compounds of the Thiophene and Furan Series or Their Complexes with $AlCl_3$

Starting compounds (1:1)	Molar ratios (A:B) of the unchanged compounds in the reaction products
	32 : 68
	73 : 27
	77 : 23

The tertiary immonium salts formed from 2-acylpyrroles and pyrrolidine in the presence of perchloric acid constitute an interesting type of deactivated compounds of the pyrrole series:



Bromination [128, 129], chlorination [129], iodination [129, 130], acylation [128, 129], and formylation (by the action of Cl_2CHOCH_3) [129] of these salts lead almost exclusively to 4-substituted compounds, by hydrolysis of which the corresponding carbonyl compounds can be obtained. The synthetic possibilities created by tertiary immonium salts are restricted to compounds of the pyrrole series: the furan ring in the analogous salt obtained from furfural and pyrrolidine is so deactivated that bromination does not take place [129].

Thus deactivated compounds of the thiophene and pyrrole series, on the one hand, and deactivated compounds of the furan series, on the other, differ markedly with respect to the specificity of electrophilic substitution reactions. The substantial differences in the α:β ratios of unsubstituted heterorings already mentioned above do not, however, constitute the only reason for the above-noted peculiarities of the furan compounds. Differences in the transmission of the effect of the substituent through the pyrrole, thiophene, and furan rings also play an important role.

3.3. Transmission of the Effect of a Substituent Through the Heteroring. During a study of the reactions of complexes of carbonyl compounds with electrophilic reagents it was observed that the furan ring is deactivated to a greater extent than the thiophene ring as a result of complexing with $AlCl_3$. For example, as we have already mentioned, 2-acetylfuran and furfural are chloromethylated to give mixtures of chloromethyl-substituted compounds in yields of only a few percent; the bulk of the starting compound is recovered [116]. On the other hand, 2-formylthiophene and 2-acetylthiophene under the same conditions give 4-chloromethyl-substituted compounds in up to 50% yields based on the starting compounds and up to 80% yields based on the converted carbonyl compound [134]. In an attempt to acetylate 2-acetylfuran it was recovered unchanged [101], although under the same conditions (~100°C in the presence of excess $AlCl_3$ without a solvent) 2-acetylthiophene is converted to 2,4-diacetylthiophene with admixed 2,5-disubstituted isomer in up to 25% yield on the basis of the starting compound and up to 70% yield on the basis of the converted ketone [132]. The acetylation of 5-methyl-2-acetylfuran can be carried out; however, more severe conditions than in the case of its thiophene analog are required for this [101]. Finally, competitive bromination shows that complexes of carbonyl compounds of the furan series are less active than their thiophene analogs, although the opposite is true for the free carbonyl compounds [109] (Table 3).

Nevertheless, even bromination of the furfural complex, which gives the greatest relative amount of the 4-substituted compound, takes place in the 4 position only primarily, whereas bromination of the corresponding 2-formylthiophene complex takes place virtually exclusively in the 4 position.

To ascertain the reasons for the above-noted differences in the behavior of the complexes of carbonyl compounds of the furan and thiophene series with $AlCl_3$ in electrophilic substitution reactions we studied the ^{13}C NMR spectra of such complexes [133, 134]. These spectra, in agreement with the results of quantum-chemical calculations by the CNDO/2 method

[105], show that the changes in the electron density in the various position on passing from the free carbonyl compound to the complex are qualitatively close for the thiophene and furan compounds. In particular, a pronounced decrease in the electron density in the 5 and 3 positions is observed, whereas it decreases to a considerably smaller extent in the 4 position. However, during an attempt to make a quantitative correlation it becomes apparent that the character of transmission of the effect of the substituent in the furan ring differs from that in the thiophene ring. That is to say, the changes in the chemical shifts as compared with the unsubstituted heterorings that characterize the transmission of the effect of the substituent to the α positions are greater for thiophene compounds, whereas the corresponding values and, consequently, the degree of transmission of the effect of the substituent to the β positions are greater for the furan compounds. A similar correlation turns out to be valid for an extensive set of compounds with substituents of various types in both the 2 and 3 positions [134].

The above-noted differences in the transmission of the effect of substituents to the α and β positions make it possible to understand the differences in the effect of complexing with $AlCl_3$ on the selectivity of electrophilic substitution of carbonyl derivatives of furan and thiophene. First of all, the stronger and more determining effect of the more electronegative heteroatom, viz., the oxygen atom, on the adjacent α positions is apparent. In addition, it seems likely that the relatively smaller (as compared with the thiophene analogs) effect of the substituent on the 5 position and the relatively greater effect on the 4 position in the case of furan compounds lead to more pronounced deactivation of the 4 position and incomplete suppression of the activity of the 5 position. In the case of thiophene compounds the activity of the 4 position decreases to a lesser extent, whereas the 5 position is virtually completely deactivated with respect to electrophilic attack.

An examination of the peculiarities of transmission of the effect of substituents through the pyrrole ring on the basis of data from the ^{13}C NMR spectra is difficult because of the scantiness of the appropriate data. Let us note only that the greater effect of substituents on the α positions than in the case of furan compounds is clearly seen from the increments presented in [135]. The experimental data on the relative ease of production of 2,4-disubstituted pyrroles presented above are in complete agreement with this.

Thus the differences in the behavior of furan, thiophene, and pyrrole compounds in electrophilic substitution reactions can be explained with allowance for the relative reactivities of these compounds, the positional selectivity characteristic of the first members of the series, and the specific conditions for transmission of the effect of a substituent through the heteroring. The indicated factors probably also play a substantial role for other heterorings, particularly the selenophene and tellurophene rings. However, the lack of quantitative data pertaining primarily to β-substituted compounds makes it impossible at the present time to compare then with furan, thiophene, and pyrrole. One can only state that selenophene is evidently closer to thiophene than to furan with respect to its chemical behavior and, in particular, with respect to its positional selectivity. This is evidenced by the formation of β-substituted compounds observed in individual cases [136] and the great similarity in the ^{13}C NMR spectra of selenophene and thiophene compounds [137]. As regards tellurophene, its study is now in its initial stages. In particular, it would be interesting to ascertain the α:β ratios for series of reactions; however, the formation of β-substituted compounds in the tellurophene series has not yet been described at all [23]. The transmission of the effects of substituents to various positions of the tellurophene ring, insofar as one can judge from the available limited ^{13}C NMR data [23], for compounds of the tellurophene series differs markedly from the transmission observed for both the furan and thiophene analogs.

The author is grateful to Professors Ya. L. Gol'dfarb and N. S. Zefirov and I. A. Abronin, V. A. Budylin, and A. P. Yakubov for their useful discussion of a number of the problems examined in this review. The author recalls with sincere gratitude the valuable advice he obtained from the prematurely deceased A. N. Kost in the preparation of this paper.

LITERATURE CITED

1. D. Farkasiu, J. Chem. Ed., 52, 76 (1975).
2. C. D. Johnson, Chem. Rev., 75, 755 (1975).
3. C. D. Johnson, The Hammett Equation, Cambridge University Press (1973).
4. D. J. McLennan, Tetrahedron, 34, 2331 (1978).
5. H. C. Brown and K. Nelson, J. Am. Chem. Soc., 75, 6292 (1953).

6. H. C. Brown and L. M. Stock, J. Am. Chem. Soc., 84, 3298 (1962).
7. G. Marino, Khim. Geterotsikl. Soedin., No. 5, 579 (1973).
8. A. N. Hughes and C. Srivanavit, J. Heterocycl. Chem., 7, 1 (1970).
9. W. Schäfer, A. Schweig, G. Märul, H. Hauptman, and F. Mathey, Angew. Chem., 85, 140 (1973).
10. N. D. Epiotis and W. Cherry, J. Am. Chem. Soc., 98, 4365 (1976).
11. M. J. Cook, A. R. Katritzky, and P. Linda, Adv. Heterocycl. Chem., 17, 255 (1974).
12. G. Olah, Acc. Chem. Res., 4, 240 (1971).
13. P. Rys, P. Skrabal, and H. Zollinger, Angew. Chem. Int. Ed., 11, 874 (1972).
14. G. Marino, Adv. Heterocycl. Chem., 13, 235 (1971).
15. F. Fringuelli, G. Marino, A. Taticchi, G. Distefano, F.-P. Colonna, and S. Pignataro, J. Chem. Soc., Perkin II, No. 3, 276 (1976).
16. I. A. Abronin and G. M. Zhidomirov, Khim. Geterotsikl. Soedin., No. 1, 3 (1977).
17. I. A. Abronin, G. M. Zhidomirov, and Ya. L. Gol'dfarb, Dokl. Akad. Nauk SSSR, 218, 363 (1974).
18. I. A. Abronin, L. I. Belen'kii, and Y. L. Gol'dfarb, New Trends in Heterocyclic Chemistry, Elsevier, Amsterdam (1979), p. 154.
19. M. E. Vol'pin, Usp. Khim., 29, 298 (1960).
20. J. Devanneaux and J.-F. Labarre, J. Chim. Phys., 66, 1780 (1969).
21. F. Fringuelli, G. Marino, A. Taticchi, and G. Grandolini, J. Chem. Soc., Perkin II, No. 4, 332 (1974).
22. H. Gilman and G. F. Wright, Chem. Rev., 11, 323 (1932).
23. F. Fringuelli, G. Marino, and A. Taticchi, Adv. Heterocycl. Chem., 21, 120 (1977).
24. J. Kruszewski and T. M. Krygowski, Tetrahedron Lett., No. 4, 319 (1970).
25. T. M. Krygowski, Tetrahedron Lett., No. 16, 1311 (1970).
26. H. C. Brown and J. D. Brady, J. Am. Chem. Soc., 74, 3570 (1952).
27. A. N. Kost and V. A. Budylin, Zh. Vses. Khim. Ova., 22, 315 (1977).
28. G. Marino, J. Heterocycl. Chem., 9, 817 (1972).
29. F. Fringuelli, S. Gronowitz, and A.-B. Hörnfeldt, J. Heterocycl. Chem., 11, 827 (1974).
30. R. Gleiter, M. Kobayashi, J. Spanget-Larsen, S. Gronowitz, A. Konar, and M. Farmier, J. Org. Chem., 42, 2230 (1977).
31. G. Modena, G. Scorrano, and P. Venturello, J. Chem. Soc., Perkin II, No. 1, 1 (1979).
32. F. Bernardi, A. Mangini, N. D. Epiotis, J. R. Larson, and S. Shaik, J. Am. Chem. Soc., 99, 7465 (1977).
33. G. Ciranni and S. Clementi, Tetrahedron Lett., No. 41, 3833 (1971).
34. L. I. Belen'kii, Third International Symposium of Furan Chemistry, Collection of Lectures, Smolenice, Czechoslovakia (1979), p. 4.
35. H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, J. Prakt. Chem., 147, 257 (1937).
36. R. W. Taft, R. H. Martin, and F. W. Lampe, J. Am. Chem. Soc., 87, 2490 (1965).
37. F. H. Field and D. P. Weeks, J. Am. Chem. Soc., 92, 6521 (1970).
38. D. P. Weeks and F. H. Field, J. Am. Chem. Soc., 92, 1600 (1970).
39. F. Bernardi, I. G. Csizmadia, H. B. Schlegel, and S. Wolfe, Can. J. Chem., 53, 1144 (1975).
40. L. I. Belen'kii and I. A. Abronin, Zh. Org. Khim., 17, No. 5 (1981).
41. C. F. Candy, R. A. Jones, and P. H. Wright, J. Chem. Soc., C, No. 18, 2563 (1970).
42. G. Doddi, R. Mencarelli, A. Razzini, and F. Stegel, J. Org. Chem., 44, 2321 (1979).
43. R. Schiff, Chem. Ber., 10, 1500 (1877).
44. G. L. Ciamician and M. Dennstedt, Gazz. Chem. Ital., 13, 455 (1883).
45. B. P. Fedorov and F. M. Stoyanovich, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 10, 1828 (1960).
46. Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1281 (1965).
47. L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 344 (1975).
48. Ya. L. Gol'dfarb, M. A. Marakatkina, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 1, 132 (1970).
49. G. Dana, P. Scribe, and J.-P. Girault, Compt. Rend., C275, 49 (1972).
50. B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, R. Anderson, and M. Schottlander, J. Mol. Spectrosc., 9, 124 (1962).
51. B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Andersen, J. Mol. Spectrosc., 7, 58 (1961).

52. A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Yu. I. Ranneva, and E. N. Zvyagintseva, Dokl. Akad. Nauk SSSR, 168, 364 (1966).
53. E. N. Zvyagintseva, T. A. Yakushina, and A. I. Shatenshtein, Zh. Obshch. Khim., 39, 1993 (1968).
54. A. I. Shatenshtein, Ya. L. Gol'dfarb, I. O. Shapiro, E. N. Zvyagintseva, and L. I. Belen'kii, Dokl. Akad. Nauk SSSR, 180, 1379 (1968).
55. K. Schwetlick and K. Unverferth, J. Prakt. Chem., 314, 603 (1972).
56. E. J. Stamhuis, W. Drendt, and H. van den Berg. Rec. Trav. Chim., 83, 167 (1964).
57. K. Unverferth and K. Schwetlick, J. Prakt. Chem., 312, 882 (1970).
58. P. Salomaa, A. Kankaanperá, E. Nikanden, K. Kaipainen, and R. Aaltonen, Acta Chem. Scand., 27, 153 (1973).
59. A. Kankaanperá and R. Aaltonen, Acta Chem. Scand., 26, 2537 (1972).
60. I. E. Garst and G. L. Schmir, J. Org. Chem., 39, 2920 (1974).
61. J. M. Barker, P. D. Huddleston, and S. W. Schutler, J. Chem. Soc., Perkin I, No. 23, 2483 (1975).
62. S. I. Meisel, G. C. Johnson, and H. D. Hartough, J. Am. Chem. Soc., 72, 1910 (1950).
63. R. F. Curtis, D. M. Jones, G. Ferguson, D. M. Hawley, J. G. Sime, K. U. Cheung, and G. Germain, Chem. Commun., No. 4, 165 (1969).
64. A. Ichigaki and T. Shono, Bull. Chem. Soc. Jpn., 17, 1467 (1974).
65. K. Schwetlick, K. Unverferth, and R. Mayer, Z. Chem., 7, 58 (1967).
66. G. P. Bean, Chem. Commun., No. 9, 421 (1971).
67. G. P. Bean and T. J. Wilkinson, J. Chem. Soc., Perkin II, No. 1, 72 (1978).
68. D. M. Muir and M. C. Whiting, J. Chem. Soc., Perkin II, No. 4, 388 (1976).
69. G. F. Smith, Adv. Heterocycl. Chem., 2, 287 (1963).
70. H. A. Potts and G. F. Smith, J. Chem. Soc., No. 9, 4018 (1957).
71. C. O. Bender and R. Bonnett, J. Chem. Soc., C, No. 20, 2526 (1968).
72. R. J. Abraham, E. Bullock, and S. S. Mitra, Can. J. Chem., 37, 1859 (1959).
73. E. B. Whipple, Y. Chiang, and R. L. Hinman, J. Am. Chem. Soc., 85, 26 (1963).
74. Y. Chiang and E. B. Whipple, J. Am. Chem. Soc., 85, 2763 (1963).
75. H. Hogeveen, Rec. Trav. Chim., 85, 1072 (1966).
76. H. Hogeveen, R. M. Kellogg, and K. A. Kuindersma, Tetrahedron Lett., No. 40, 3929 (1973).
77. L. I. Belen'kii, A. P. Yakubov, and Ya. L. Gol'dfarb, Zh. Org. Khim., 11, 424 (1975).
78. L. I. Belen'kii, A. P. Yakubov, and I. A. Bessonova, Zh. Org. Khim., 13, 364 (1977).
79. A. P. Yakubov, N. V. Grigor'eva, and L. I. Belen'kii, Zh. Org. Khim., 14, 641 (1978).
80. Ya. L. Gol'dfarb, M. A. Kalik, N. A. Shul'ts, and L. I. Belen'kii, Zh. Org. Khim., 15, 1289 (1979).
81. L. I. Belen'kii, V. I. Kadentsev, V. D. Sokovykh, and O. S. Chizhov, Fifteenth Session on the Chemistry and Technology of Organic Sulfur Compounds and Sulfurous Petroleum Oils (Summaries of Papers) [in Russian], Ufa (1979), p. 88.
82. U. E. Wiersum and H. Wynberg, Tetrahedron Lett., No. 31, 2951 (1967).
83. D. M. Brower and J. A. van Doorn, Rec. Trav. Chim., 89, 553 (1970).
84. D. M. Brower, J. A. van Doorn, and A. A. Kiffen, Rec. Trav. Chim., 91, 1359 (1972).
85. V. G. Kul'nevich and Yu. M. Shapiro, Khim. Geterotsikl. Soedin., No. 12, 1594 (1972).
86. M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, Tetrahedron, 32, 1767 (1976).
87. A. M. Arnett, Modern Problems of Physical Organic Chemistry [Russian translation], Mir, Moscow (1967), p. 276.
88. T. A. Melent'eva, T. M. Filippova, L. V. Kazanskaya, I. M. Kustanovich, and V. M. Berezovskii, Zh. Obshch. Khim., 41, 179 (1971).
89. 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).
90. P. Linda and G. Marino, J. Chem. Soc., B, No. 4, 392 (1968).
91. P. Hodge and R. W. Rishards, J. Chem. Soc., No. 1, 459 (1965).
92. H. J. Anderson and S.-F. Lee, Can. J. Chem., 43, 409 (1965).
93. Z. N. Nazarova, Zh. Obshch. Khim., 24, 575 (1954).
94. Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and B. V. Lopatin, Zh. Obshch. Khim., 34, 969 (1964).
95. L. I. Belen'kii, É. I. Novikova, I. A. D'yachenko, and Ya. L. Gol'dfarb, Zh. Org. Khim., 7, 1736 (1971).
96. B. Ostman, Acta Chem. Scand., 22, 2754 (1968).
97. L. I. Belen'kii, N. S. Ksenzhek, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 3, 310 (1972).

98. K. J. Morgan and D. P. Morrey, Tetrahedron, 27, 245 (1971).
99. G. C. Robinson, J. Org. Chem., 31, 4252 (1966).
100. H. Cilman, M. McCorkle, and N. O. Calloway, J. Am. Chem. Soc., 55, 745 (1934).
101. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 5, 591 (1972).
102. M. Valenta and J. Koubek, Collect. Czech. Chem. Commun., 41, 78 (1976).
103. H. J. Anderson and C. W. Huang, Can. J. Chem., 48, 1550 (1970).
104. Ya. L. Gol'dfarb (Goldfarb), Yu. B. Vol'kenshtein (Volkenstein), and L. I. Belen'kii (Belenkij), Angew. Chem., 80, 547 (1968).
105. Ya. L. Gol'dfarb, G. M. Zhidomirov, N. D. Chuvylkin, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 2, 155 (1972).
106. L. I. Belen'kii, V. S. Bogdanov, and I. B. Karmanova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1735 (1979).
107. Ya. L. Gol'dfarb and Yu. B. Vol'kenshtein, Dokl. Akad. Nauk SSSR, 128, 536 (1959).
108. S. G. Mairanovskii, N. V. Barashkova, and Yu. B. Vol'kenshtein, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1539 (1965).
109. L. I. Belen'kii, Ya. L. Gol'dfarb, and G. P. Gromova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2733 (1973).
110. L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, Zh. Org. Khim., 7, 1743 (1971).
111. Ya. L. Gol'dfarb, I. B. Karmanova, Yu. B. Vol'kenshtein, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 11, 1474 (1978).
112. 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, 1799 (1973).
113. Ya. L. Gol'dfarb, É. I. Novikova, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1233 (1971).
114. Ya. L. Gol'dfarb, É. I. Novikova, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2822 (1971).
115. L. I. Belen'kii, É. I. Novikova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 10, 1353 (1971).
116. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 3, 306 (1978).
117. L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., No. 5, 597 (1972).
118. D. J. Chadwick, J. Chambers, G. D. Meekins, and R. L. Snowden, J. Chem. Soc., Perkin I, No. 16, 1766 (1973).
119. C. Jaureguiberry, M. C. Fournier-Zaluski, J.-P. Chevallier, and B. Roques, Compt. Rend., 273, 276 (1971).
120. H. J. Anderson and C. W. Huang, Can. J. Chem., 45, 897 (1967).
121. C. E. Loader and H. J. Anderson, Tetrahedron, 25, 3879 (1969).
122. P. Fournari, M. Farnier, and C. Fournier, Bull. Soc. Chim. Fr., No. 1, 283 (1972).
123. H. J. Anderson, C. R. Ricke, T. G. Costello, C. E. Loader, and G. H. Barnett, Can. J. Chem., 56, 654 (1978).
124. P. Barker, P. Gendler, and H. Rapoport, J. Org. Chem., 43, 4849 (1978).
125. H. J. Anderson and L. C. Hopkins, Can. J. Chem., 42, 1279 (1964).
126. H. J. Anderson and L. C. Hopkins, Can. J. Chem., 44, 1831 (1966).
127. J. K. Groves, H. J. Anderson, and H. Nagy, Can. J. Chem., 49, 2427 (1971).
128. P. E. Sonnet, J. Org. Chem., 36, 1005 (1971).
129. P. E. Sonnet, J. Org. Chem., 37, 925 (1972).
130. P. E. Sonnet, J. Heterocycl. Chem., 10, 113 (1973).
131. L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, Zh. Org. Khim., 9, 1514 (1973).
132. Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, Dokl. Akad. Nauk SSSR, 185, 941 (1969).
133. L. I. Belen'kii, I. B. Karmanova, Yu. B. Vol'kenshtein, P. V. Petrovskii, L. A. Fedorov, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1725 (1974).
134. L. I. Belen'kii, I. B. Karmanova, and S. V. Rykov, Chem. Scr., 10, 201 (1976).
135. R. J. Abraham, R. D. Lapper, K. M. Smith, and J. F. Unsworth, J. Chem. Soc., Perkin II, No. 9, 1004 (1974).
136. N. N. Magdesieva, Adv. Heterocycl. Chem., 12, 1 (1970).
137. S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, Chem. Scr., 7, 111 (1975).