SYNTHESIS, REACTIONS, AND PROPERTIES OF SOME SELENIDES OF THE THIOPHENE, FURAN, AND SELENOPHENE SERIES (REVIEW)

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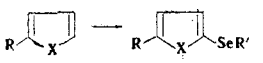
The review is devoted to the authors' research on the synthesis and study of the reactivities of selenides of the thiophene series, and, to a lesser extent, of selenides of the furan and selenophene series. The properties of the indicated compounds – their capacity for reaction with electrophilic agents and organolithium compounds – and their spectral characteristics are examined in order to compare them with the properties of the corresponding sulfides and alkoxy derivatives.

Interest in aromatic and heteroaromatic derivatives bearing a sulfide function as one of the substituents as potential physiologically active and complexing compounds, as various types of additives, etc., has grown in recent years. One of the directions of the chemistry of such sulfides includes the field of sulfides of the thiophene series. In the light of the data obtained in the course of the development of this field, it was of interest to study the methods used to prepare alkyl thienyl selenides and their chemical behavior and physical properties. In fact, it seemed possible, by carrying out this sort of study with the idea of comparing them with the corresponding sulfides, to detect not only the similar characteristics that are a consequence of the affiliation of sulfur and selenium with the same group but also the differences caused by the differences in their atomic radii and electronegativities. In this connection, it is necessary to note that we find ourselves only at the very beginning of research in this division of thiophene chemistry, since it has apparently been reflected only in the studies undertaken in our laboratory [1-13].

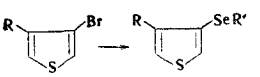
Synthesis of Selenides of the Thiophene, Furan, and Selenophene Series

We have developed a method for the introduction of a selenide function into thiophene, furan, and selenophene. The method consists in the reaction of the appropriate heterocyclic compound with a metallating agent (n-C_4H_9Li), elementary selenium, and a halogen-containing compound (an alkyl halide or a haloacetate ester) [1, 9].



X = O, S, Se; R = H, Alk; R' = Alk

A number of β-(alkylseleno)thiophenes [6] were obtained by the action of n-C_4H_9Li, selenium, and an alkyl halide on 3-bromo- and 3,4-dibromothiophene (or by the action of a dialkyl selenide on 3-thienyllithium).



R = H, Br; R' = Alk

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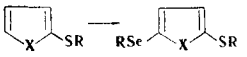
The corresponding 2-alkylmercapto-5-alkylseleno derivatives [9, 10] are similarly obtained by the action of the above-indicated reagents on 2-alkylmercaptofurans or 2-alkylmercaptothiophenes.



X = O, S; R = Alk

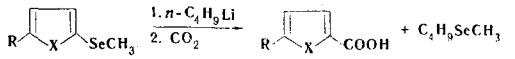
In 1966, Niwa and co-workers [14] synthesized several selenides of the furan series using a method similar to our previously described method [1] with the only difference being that phenyllithium was used as the metallating agent.

Within the plan of the formulated problem, it seemed expedient to investigate some reactions of the selenides of the thiophene series in comparison with the analogous previously described transformations of the corresponding sulfides in the case of nucleophilic and electrophilic substitution reactions.

Action of n-Butyllithium on Alkyl Hetaryl Selenides

The capacity of thiophene for metallation in the α position by the action of n-C_4H_9Li [15] has opened up broad possibilities for the synthesis of diverse thiophene derivatives. In this connection, it seemed of interest to expand the number of facts that pertain to the problem of the effect of the nature and position of substituents in the thiophene ring on the specificity of the metallation process. It is known that both thiophene itself [15] and 2-alkyl- [16-19], 2-methoxy- [19, 20], and 2-alkylmercaptothiophenes [17] are metallated in the free α position by butyllithium. We found that a metallation of 2-methylmercaptoselenophene also proceeds similarly.

Proceeding from the considerations of the formal analogy between 2-alkylmercapto- and 2-alkylselenothiophenes, it might have been expected that 2-alkylselenothiophene would also react similarly with n-C_4H_9Li. However, as we observed in [2, 3], 2-alkylselenothiophenes react completely differently with n-C_4H_9Li: under comparable conditions, the alkylseleno group is displaced, and 2-thienyllithium and a dialkyl selenide are formed. Selenides of the furan and selenophene series behave similarly; the corresponding carboxylic acids are formed in high yields as a result of metallation and carbonation [2, 3, 12].



X = O, S, Se; R = H, Alk

When two equivalents of n-C_4H_9Li react with 2-alkylselenothiophenes, the metal enters both α positions, owing to which thiophene-2,5-dicarboxylic acids are obtained when the products are carbonated [2].

The alkylseleno group is also displaced in other cases, for example, in the reaction of n-C_4H_9Li with 2-methylmercapto-5-methylselenothiophene to form 5-methylmercapto-2-thienyllithium [3]. The specificity of the action of n-C_4H_9Li on the alkylseleno group is also confirmed by the fact that the reaction of one equivalent of n-C_4H_9Li with an equimolar mixture of 2-methylmercaptothiophene and 2-methylselenothiophene and subsequent carbonation gives thiophene-2-carboxylic acid (in yields above 66%) and methyl butyl selenide, and the starting 2-methylmercaptothiophene is recovered unchanged [5]. It is interesting to note that the displacement of the alkylseleno group occurs even at −70°C, while unsubstituted thiophene is not metallated under these conditions.

In order to compare the behavior of aromatic and heteroaromatic alkyl selenides under the conditions of metallation with butyllithium, we studied the behavior of selenoanisole toward the latter under similar conditions. We found that the alkylseleno group is not cleaved under mild conditions [12]. We note, however, that the C_6H_5–Se bond in selenoanisole [21] and also in diphenyl selenide [22] is nevertheless cleaved, although to a lesser degree, under more severe conditions. The cleavage of the C–S bond in alkyl phenyl sulfides in the reaction with n-C_4H_9Li in refluxing ether has also been reported [21, 23].

It is known that when both α positions of the thiophene ring are blocked, the metallation depends on the nature of the substituents. For example, 2,5-dimethylthiophene is not metallated, but 5-methoxy-2-methylthiophene reacts with n-C_4H_9Li to give a 3-lithio derivative in 50% yield [20]. Similarly, anisole is metallated in the ortho position [22, 24, 25]. 5-Methylmercapto-2-methylthiophene is similarly metallated, although the yield is low [17]. We recall here that thioanisole is metallated in the side chain [21, 26]. In contrast to this, as should have been expected on the basis of the data presented above, 5-methylseleno-2-methylthiophene behaves differently – in this case, the methylseleno group is eliminated, and a lithium atom enters the α position of the thiophene ring [3].

The indicated observations take on even greater significance when it is considered that the hydrogen in the free α position of the thiophene ring is substituted rather than the chlorine atom in the attack of 2-chlorothiophene by butyllithium [27]; however, when the second α position is occupied by an activating sulfide function, the lability of the chlorine atom increases sharply. In fact, the action of n-C_4H_9Li on 5-chloro-2-methylmercaptothiophene and subsequent carbonation give 5-methylmercaptothiophene-2-carboxylic acid in 70% yield [3]. In this connection, it was of interest to study the action of n-C_4H_9Li on 5-bromo-2-methylselenothiophene. As might have been supposed, the bromine atom is replaced in the reaction of one equivalent of n-C_4H_9Li to give 5-methylselenothiophene-2-carboxylic acid in 68% yield, while thiophene-2,5-dicarboxylic acid is obtained in yields up to 93% as a result of the action of two equivalents of n-C_4H_9Li and subsequent carbonation [3].

Thus it may be noted that the substituents in the α positions of the thiophene ring can be arranged in the following order with respect to the ease of exchange by lithium on reaction with n-C_4H_9Li: Br > SeR > H > Cl > ... SR. The presence of an SR group in this series is arbitrary, since in practice it cannot be displaced in the indicated manner.

Of considerable interest in connection with what has been stated above is the fact that the C–Se bond is cleaved with retention of a bromine atom in the molecule, even at −70°, if there is a bromine atom in the β position of 2,5-disubstituted thiophenes [5]. We note that, in the absence of a selenide function, a bromine atom in the β position of the thiophene ring is readily exchanged by a lithium atom (for example, see [28]).

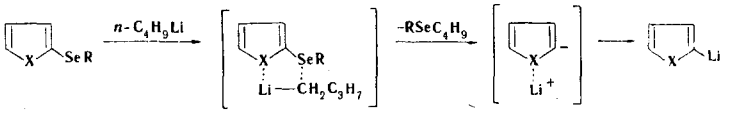
The sharp difference in the behavior of 2-alkylselenothiophenes and the corresponding sulfides and alkoxy derivatives of the thiophene series with respect to n-C_4H_9Li compelled us to investigate the behavior of 3-alkylselenothiophenes in this direction. The observations made in the process should have provided material for the elucidation of both the mechanism of the action of n-C_4H_9Li on the selenides of the thiophene series and the orienting effect of the alkylseleno group.

The representation of the mechanism of the metallation of heteroaromatic compounds and aromatic compounds with functional groups containing a heteroatom, which includes as a primary act coordination of the metallating agent through the unshared pair of electrons of the heteroatom (for example, see [29-32]) with the formation of a cyclic transition state, has been widely propagated. This sort of coordination was recently confirmed by the results of PMR spectroscopy [33-35]. The positive charge that develops on the donor heteroatom during complexing, thereby raising its inductive effect, causes an increase in the polarization of the adjacent C–H bond and thereby facilitates removal of a proton by the incipient carbanion of the coordinated metallating agent (coordination also leads to weakening of the metal–carbon bond in the metallating agent). The importance of the inductive effect of the substituent during the metallation of substituted benzenes has been noted by Wittig [36]. The principal factor that determines the position of the lithium atom that enters into the metallation is the relative acidity of the ring hydrogen atoms as a consequence of the influence of the inductive effect of the substituent [24, 25, 37, 38]. At the same time, the ease of metallation of different compounds cannot be associated, as has been sometimes done [39], only with the magnitude of the inductive effect of the ring or exocyclic heteroatom with neglect of the effect of its conjugation with the π-electron system of the aromatic or heteroaromatic ring. The data on the competitive metallation of thiophene and furan [40] completely refute the assumption [39] that the metallation of furan will proceed more readily than in the case of thiophene because of the high electronegativity of oxygen as compared with sulfur. A study of the kinetics of deuterium exchange of furan, thiophene, and selenophene demonstrated that the α-deuterium atoms in thiophene and selenophene are exchanged more rapidly (by a factor of 2.5 orders of magnitude) than in furan, although the inductive effect of the oxygen is considerably greater than the effects for sulfur and selenium. This was explained by the participation of the d orbitals of the sulfur and selenium atoms in stabilization of the carbanions of thiophene and selenophene in the transition state [41]. It was also noted that the effect of conjugation of the sulfur in the thiophene ring is greater than that of oxygen in furan, since the sulfur atom can manifest not only electron-donor properties but also electron-acceptor properties because of the presence of vacant d orbitals [42]. At first glance, the data on the competitive metallation of dibenzofuran and dibenzothiophene [43, 44] contradict, as it were, what has been set forth above, since the former is metallated more readily than the latter. However, the contradiction vanishes if one assumes that the hydrogen being replaced in these systems is similar in activity to the β-hydrogen of a five-membered heterocycle rather than the α-hydrogen, and the inductive effect of the heteroatom rather than the conjugation effect may predominate in this case. A similar rationale explains the metallation of phenoxthin [43] in the ortho position relative to oxygen.

The problem of the center of coordination of the metallating agent becomes more complex in those compounds of the thiophene, furan, and selenophene series that have a heteroatom as a substituent; in this case,

coordination may occur at both the ring heteroatom and at the heteroatom of the functional group. The fact that metallation of 2-methoxythiophene proceeds in the free α position of the thiophene ring [20] has served as a basis for the assumption that, in this case, coordination at the ring sulfur atom predominates over coordination at the oxygen of the methoxy group [45]. The metallation of 2-methylmercaptothiophene proceeds similarly – the lithium atom also enters the free α position, and the sulfide function has an activating effect on the substitution of hydrogen by the metal [17].

On the basis of what has been advanced above, the following scheme of the reaction mechanism, which includes a five-membered cyclic transition state, can be proposed for the metallation of 2-alkylseleno-substituted five-membered heterocycles.



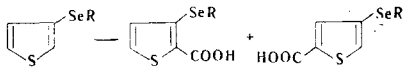
The elimination of an alkyl selenide function is facilitated by both a high degree of polarization of the hetaryl–selenium bond (as compared with the C–H bond) and by the capacity of the selenium atom to display not only electron-donor properties but also electron-acceptor properties, which promotes the formation of a cyclic transition state. The proposed scheme differs from the mechanism of the elimination of an alkylmercapto group in alkyl phenyl sulfides [23] by the fact that, in the latter case, metallation of the α-carbon atom of the side chain occurs initially, a four-membered cyclic transition state then develops, and the C_6H_5–S bond is cleaved.

Turning now to an examination of the metallation of 3-alkylselenothiophenes, we note that there is a limited amount of data on the orienting effect of substituents in the 3 position of the thiophene ring. The metallation of 3-methylthiophene and carbonation of the product give 4-methylthiophene-2-carboxylic acid (61-68%) and 3-methylthiophene-2-carboxylic acid (19%) [46], while it was previously assumed [29, 47] that the metallation of 3-methylthiophene occurs only in the 5 position.

The orienting effect of –I, +M substituents [OCH_3, $OC(CH_3)_3$, SCH_3, and $SeCH_3$] is of particular interest. The metal enters the 2 position of the thiophene ring in the metallation of 3-methoxy- [30] and 3-methylmercaptothiophene [48]. In contrast to 3-methylmercaptothiophene, the metallation of its sulfone proceeds in the side chain [48], which attests to the great activating effect of the sulfone group as compared with the sulfur atom of the thiophene ring. The introduction of a bulky tert-butoxy group into the 3 position of the thiophene ring does not change the direction of metallation: in this case, the lithium atom enters the 2 position [49]. The metallation is little sensitive to steric hindrance caused by a bulky substituent in both the compound undergoing metallation and in the metallating agent itself [50]. The entry of a lithium atom into the 2 position (phenyl is considered to be a weak electron-acceptor group) might therefore have been expected in the metallation of 3-phenylthiophene. However, in this case, a mixture (~1 : 1) of 2- and 5-isomers is formed, on the basis of which it was concluded that the orientation observed in this case is not in agreement with a protophilic mechanism for the metallation reaction [51]. An assumption was recently stated to the effect that metallation can proceed via a multistep mechanism including the intermediate formation of radical anions, in which the steps that determine the orientation and rate of removal of a ring hydrogen are separate [50]. At the same time, in addition to the above-indicated examples of o-metallation relative to the substituent and the decisive role of the relative acidity of the ring hydrogens of the compound undergoing metallation, a confirmation of the protophilic character of the reaction is the existence of an isotope effect (for example, see [52, 53]). In concluding our review of data on the metallation of 3-substituted thiophenes, we note the studies of the metallation of 2,3-dithienyl (in the 2 and 5 positions) [54], 3-cyanothiophene (in the 2 position) [55], and 3,3'-dithienyl sulfide and its sulfone (in the 2 position) [56].

If the proposed scheme of the mechanism of metallation of 2-hetaryl selenides is correct, the entry of a lithium atom into one of the free α positions rather than substitution of an alkylseleno group might have been expected in the case of the reaction of n-C_4H_9Li with 3-alkylselenothiophene. In fact, when one equivalent of n-C_4H_9Li reacts with 3-butylselenothiophene under conditions similar to those in the reaction of 2-alkylselenothiophene, the metal atom replaces an α-hydrogen atom of the thiophene ring to give (after carbonation) a (butylseleno)thiophenecarboxylic acid [6]. Proceeding from the fact that, according to the data in [48], 3-methylmercaptothiophene is metallated exclusively in the 2 position, it might have been assumed that the acid obtained is 3-butylselenothiophene-2-carboxylic acid. However, an analysis of the product of esterification of the acid by gas-liquid chromatography (GLC) demonstrated that it is a mixture of two esters – esters of 3-butylselenothiophene-2-carboxylic acid (~60%) and 4-butylselenothiophene-2-carboxylic

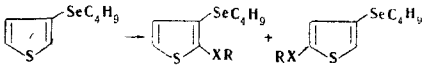
acid (~40%). Calculations on the basis of the data of PMR and IR spectroscopy [8] (analysis of the product before esterification) led to satisfactorily agreeable results: 71-73% of the 3,2-isomer and 27-29% of the 4,3-isomer.



R = CH_3, C_4H_9

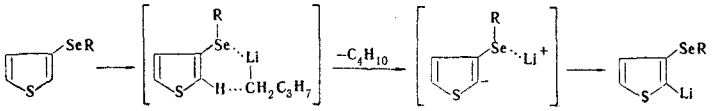
We also obtained similar results in the metallation and subsequent carbonation of 3-methylselenothiophene. Consequently, the formation of two acids rather than one, as in the case of 3-methoxythiophene [30] and 3-methylmercaptothiophene [48] (which requires refinement in the light of later data), is due chiefly to the nature of the heteroatom in the substituent and of the substituent as a whole and not to the steric hindrance associated with the long side chain.

A similar pattern is also observed in the production of bisselenides and selenidosulfides from 3-butylselenothiophene by the action of n-C_4H_9Li, selenium, or sulfur, respectively, and alkyl halides [6].



X = S, Se; R = Alk

It is necessary to note that if metallation of 3-alkylselenothiophene were to proceed through a step involving the coordination of the metallating agent at the selenium atom of the alkylseleno group, one should have observed either substitution of the selenide function (via the mechanism proposed for the splitting out of an ethylmercapto group during the reaction of thiophenetole with n-C_4H_9Li and including a four-center transition state [23]), or a lithium atom would have entered exclusively the α position adjacent to the alkylseleno group, i.e., the 2 position, through a six-membered transition state:



Since displacement of the alkylseleno group is not observed in the case of 3-alkylselenothiophenes, and lithium enters not only the 2 position but also the 5 position, we prefer a mechanism that includes coordination of the lithium atom of the metallating agent at the ring sulfur atom rather than at the selenium atom of the alkylseleno group.

Above we have demonstrated that displacement of the alkylseleno function with retention of bromine in the thiophene ring is observed in the reaction of 4-bromo-2-methylseleno-5-methylthiophene with n-C_4H_9Li, even at −70°. It was of interest to follow the direction of the attack of n-C_4H_9Li on 4-bromo-3-methylselenothiophene and to ascertain whether metallation occurs in one of the free α positions of the ring, or the bromine atom is exchanged for a metal atom, as in the case of 4-bromo-3-methylmercaptothiophene [18]. It turned out that, in this case also, the action of n-C_4H_9Li is directed to the bromine atom, and neither the hydrogen atom of the thiophene ring nor the alkylseleno group are involved [6]; this established the prerequisites for the synthesis of a new heteroaromatic system — selenopheno[2,3-c]thiophene [11].

In concluding our examination of the metallation of alkyl thienylselenides, we note that by the reaction of 3-bromothiophene with n-C_4H_9Li and subsequent action of selenium and methyl iodide on the resulting 3-thienyllithium we obtained a difficult-to-separate mixture of 3-methylselenothiophene and 3-butylselenothiophene (in a ratio of 3:1) [6]. The formation of the latter apparently occurs as a consequence of the alkylation of the lithium salt of thiophene-3-selenol with the butyl bromide formed during the metallation of 3-bromothiophene. We also observed a similar pattern in the production of selenopheno[3,2-b]thiophene [4]: when 3-bromothiophene is treated with butyllithium and the product is subjected to the action of selenium and methyl chloroacetate, 3-butylselenothiophene is obtained (in 66% yield) instead of the expected methyl (3-thienylseleno)acetate. Gronowitz [48] made similar observations in the preparation of 3-methylmercaptothiophene.

Since the elimination of an alkylseleno group can potentially be used for the synthesis of the difficult-to-obtain 3,4- and 2,4-derivatives of thiophene and possibly other five-membered heterocycles, we attempted to find a different method for cleaving the hetaryl—selenium bond, since, in the case of alkylseleno-substituted heterocycles additionally bearing functional groups of the OH, CHO, COR, etc. types, attack of the butyllithium can be directed primarily to these groups. Our first attempts [12], for example, reduction with hy-

drogen in the presence of palladium on carbon, the action of lithium metal in ether–benzene solution at room temperature or in refluxing dioxane, did not give the desired result – the starting selenide was recovered, and practically no elimination occurred. We detected another type of cleavage of the C–Se bond during an investigation of the electrophilic substitution of 2-alkylselenothiophenes.

Electrophilic Substitution in the Alkyl Thienyl Selenide Series

Without dwelling on the details of the effect of various substituents in the thiophene ring on the specificity of electrophilic substitution, which was quite fully reflected in review [28] and goes beyond the limits of the present paper, we note that –I, –M substituents in the 2 position, by deactivating the 3 and 5 positions, direct the electrophilic substitution to the 4 position. Nevertheless, owing to the effect of the ring heteroatom, substitution usually occurs primarily in the 5 position; moreover, depending on the type of electrophilic agent, a certain amount of 4-isomer is also formed. If there is a –I, –M substituent in the 3 position, the 2 position is deactivated, and substitution occurs in the 5 position.

When there is a weak –I, +M substituent in the 2 position of the thiophene ring, the α-orienting effect of the ring sulfur predominates, and substitution occurs in the 5 position. In the case of stronger –I, +M substituents (OCH_3, SCH_3), the 3 position is also strongly activated, and, despite the orienting effect of the ring sulfur atom, substitution proceeds not only in the 5 position but also in the 3 position of the thiophene ring. Thus 2-methoxythiophene is nitrated and acylated to give a mixture of 3- and 5-isomers [20]. As we have recently demonstrated in our laboratory, 2-methylmercaptothiophene is similarly nitrated [57]. It is necessary to note that the nature of the electrophilic reagent has a pronounced effect on the isomer distribution: formylation [58] and bromination with N-bromosuccinimide [20] of 2-methoxythiophene proceed in the 5 position; 2-methylmercaptothiophene is similarly iodinated [19], formylated [59], and acylated [60]. We have established that 15% 2-acetothienone and 48% 5-methylmercapto-2-acetothienone [60] are formed in the competitive acetylation of thiophene and 2-methylmercaptothiophene. This illustrates the activating role of an alkylmercapto group in electrophilic substitution (see [17]). The formylation of 2-ethylmercaptothiophene [61] and 2-(p-methoxyphenylmercapto)thiophene [62] proceeds similarly – the formyl group enters the 5 position of the thiophene ring.

Deuterium exchange with acids demonstrated that electrophilic substitution in 3-methoxythiophene [41] and 3-methylmercaptothiophene [63] proceeds in the 2 position, and in the latter case the rate of substitution in the 2 position is four orders of magnitude higher than in the 5 position. The formylation of 3-ethylmercaptothiophene gives 3-ethylmercapto-2-formylthiophene in 82% yield [64]. The methyl esters of (3-thienylmercapto)- and (3-thienylseleno)acetic acids are also similarly formylated, and we used this for the synthesis of thieno[3,2-b]thiophene [65] and selenopheno[3,2-b]thiophene [4].

In contrast to what occurs in the case of the reaction with n-C_4H_9Li, there is, according to our observations, a parallelism in the behavior of sulfides and selenides of the thiophene series in electrophilic substitution reactions. When there is a free α position, as in the corresponding 2-alkylmercaptothiophenes, the formyl and acetyl groups enter this position. A confirmation of this is the fact that oxidation of formyl and acetyl derivatives of 2-methylselenothiophene converts them to 5-methylselenothiophene-2-carboxylic acid, which is identical to the acid obtained by metallation of 5-bromo-2-methylselenothiophene with an equimolar amount of n-C_4H_9Li and subsequent carbonation [5]. It is necessary to note that, while 5-methylseleno-2-formylthiophene is formed exclusively in the Vilsmeier formylation of 2-methylselenothiophene, acetylation of the indicated selenide via the Friedel–Crafts reaction (CH_3COCl and $SnCl_4$) gives 5-methylseleno-2-acetothienone containing (according to GLC) up to 15% of an impurity, which is apparently 2-methylseleno-3-acetothienone [5]. We detected a similar impurity in about the same quantity in the product of the acetylation of 2-methylmercaptothiophene. However, in the case of a selenide in which the second α position is occupied by a methyl group, the formyl and acetyl groups predominantly replace a hydrogen atom in the ortho position relative to the alkylseleno group, i.e., in the 3 position. The fact of the entry of the acyl group into this position is confirmed by the synthesis of the corresponding derivatives by an independent path [5].

We obtained some data on the relative reactivities of sulfides and selenides of the thiophene series by using the method of competitive reactions under the conditions that we previously described in [60]. A mixture (1 : 1.6) of 5-methylseleno-2-acetothienone and 5-methylmercapto-2-acetothienone and unchanged selenide (62%) and sulfide (27%) is formed in the reaction of one equivalent of acetyl chloride with an equimolar mixture of 2-methylmercaptothiophene and 2-methylselenothiophene in chlorobenzene in the presence of stannic chloride [5]. Similarly, the formylation and acetylation of selenides with the second α position occupied

by an alkyl group proceed in the 3 position with lower yields than in the case of the analogous sulfide [16, 66, 67]. However, the acetylation of 2-methylselenothiophene itself gives 5-methylseleno-2-acetothienone in good yield [5], while the yield of 5-methylmercapto-2-acetothienone does not exceed 40%, and the reaction is accompanied by copious resinification [16, 67].

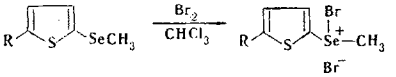
A complete analogy is observed in the electrophilic substitution of 3-alkylselenothiophenes and 3-alkylmercaptothiophenes – the acyl group enters the α position of the ring adjacent to the alkylseleno group. In particular, pure 3-butylseleno-2-formylthiophene and 3-butylseleno-2-acetothienone, respectively, were obtained in high yields in the formylation and acetylation of 3-butylselenothiophene.

The results of the oxidation of formyl and acetyl derivatives to the acid, which proved to be identical to the 3-butylselenothiophene-2-carboxylic acid obtained by an independent path, may serve as a confirmation of the fact of the entry of an acyl group in the 2 position. Thus substitution of the sulfide group by a selenide group does not bring about a sharp change in the reactivity of the thiophene ring with respect to such electrophilic reagents as dimethylformamide in the presence of phosphorus oxychloride and acetyl chloride in the presence of stannic chloride, although a certain difference in the yields of the acylation products was also noted.

Different ratios are observed in the bromination of the corresponding sulfides and selenides. Recently in our laboratory it was found that 2-methylmercaptothiophene on reaction with a bromide–bromate mixture in the amount necessary for the liberation of 1 mole of bromine gives 5-bromo-2-methylmercaptothiophene in 47% yield, while 2 moles of bromine in chloroform gives 77% 3,5-dibromo-2-methylmercaptothiophene [57]. Bromination with a bromide–bromate mixture of a sulfide in which the second α position is occupied by an alkyl group – 2-ethylmercapto-5-ethylthiophene – leads to 3-bromo-2-ethylmercapto-5-ethylthiophene in 84% yield. The action of bromine water on 2,5-bis(alkylmercapto)thiophenes gives good yields of the corresponding 3,4-dibromo derivatives [68].

Proceeding from the noted analogy in the behavior of the sulfides and selenides of the thiophene series in electrophilic substitution reactions, it might have been expected that bromine would enter the free α position of the thiophene ring in the bromination of 2-methylselenothiophene. We obtained 5-bromo-2-methylselenothiophene in 40-45% yield by the action of a bromide–bromate solution in the quantity necessary for the liberation of 1 mole of bromine; however, according to GLC, the product contained up to 10% 2,5-dibromothiophene, the formation of which was not noted in the bromination of 2-methylmercaptothiophene (see [57]).

Moreover, direct attack of the α position is not observed in the reaction of bromine in chloroform (at −40 to −5°) with 2-methylselenothiophene, while a product of the addition of bromine to the selenium atom is formed in quantitative yield. 5-Methylseleno-2-methylthiophene behaves similarly [12].

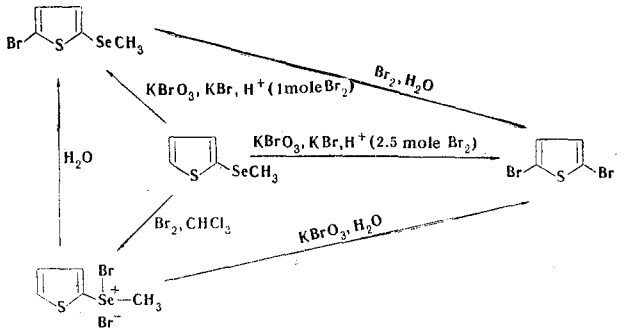


R = H, CH_3

We note that the ability of dialkyl selenides and alkyl aryl selenides to form dihalides on reaction with halogens in inert solvents at low temperatures is well-known and is used to characterize selenides (for example, see [69, 70]). Dialkyl, diaryl, and alkyl aryl sulfides also form similar dihalides (for example, see [71-75]).

The dibromides obtained apparently contain ionogenic bromine, since the isolated compounds are titrated potentiometrically. The ionogenic character of bromine in the dibromides of selenides of the aromatic series has been reported [70, 76], and, in addition, the data on the poor conductivity of a solution of 4-methylselenoacetophenone dichloride have served as a basis for the assumption of covalent character of the halogen–selenium bond in such compounds [77].

The alkylseleno group is displaced in the reaction of an aqueous solution of potassium bromate with 2-methylselenothiophene dibromide for 15-20 min, and 2,5-dibromothiophene is formed. On contact with water, the dibromide is slowly converted to 5-bromo-2-methylselenothiophene. As already noted above, the bromine atom also enters the free α position of the ring in the reaction of 2-methylselenothiophene with a bromide–bromate solution (1 mole of bromine). 2-Methylselenothiophene reacts with a bromide–bromate solution in the quantity necessary for the liberation of 2.5 moles of bromine with cleavage of the alkylseleno group to give 2,5-dibromothiophene. The latter is also formed as a result of the action of bromine water on 5-bromo-2-methylselenothiophene [12].



The data that we obtained make it possible to interpret the bromination of 2-methylselenothiophene in the following manner: two bromine atoms initially add to the selenium atom of the alkylseleno group. This process is apparently reversible, as a consequence of which the newly generated selenide and bromine react to form 5-bromo-2-methylselenothiophene. Where there is excess bromine in solution, cleavage of the hetaryl–selenium bond with entry of a second bromine atom into the position previously occupied by the alkylseleno group occurs along with attack of the free α position.

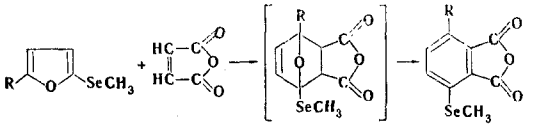
We note that the dihalides of diphenyl selenide and its substituted derivatives dissociate in solution with liberation of free halogen (for example, see [72, 78-80]). Data on the preparation of p-bromophenyl methyl sulfide from methyl phenyl sulfide have also been presented [81]. In addition, the dibromides of dimethyl sulfide [71], diphenyl sulfide [72], substituted alkyl phenyl sulfides [73-75], methyl phenyl selenide [70], and diphenyl selenide [82] hydrolyze to give the corresponding sulfoxide or selenoxide with HBr evolution.

In the light of the data presented, the elucidation of the mechanism of the cleavage of the hetaryl–selenium bond and the bromination of 2-alkylselenothiophenes in the free α position under the influence of bromine requires additional thorough investigation.

Diene Synthesis in the Alkyl Furyl Selenide Series

Continuing our study of the properties of alkyl hetaryl selenides in comparison with the properties of the analogous sulfides, we investigated the diene synthesis of selenides of the furan series with maleic anhydride. Previously in our laboratory it was shown that sulfides of the furan series react with maleic anhydride to form adducts that readily split out a molecule of water to give phthalic anhydrides containing a sulfide function [83].

The corresponding selenides also behave similarly. Thus the reaction of maleic anhydride with 2-methylselenofuran and 5-methylseleno-2-methylfuran gives good yields of 3-methylselenophthalic and 6-methylseleno-3-methylphthalic anhydrides [12].



R = H, CH_3

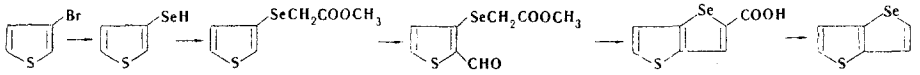
Thus the diene synthesis opens up the possibility of transition from selenides of the furan series to selenides of the benzene series.

Synthesis of New Heteroaromatic Systems – Selenophenothiophenes from Selenides of the Thiophene Series

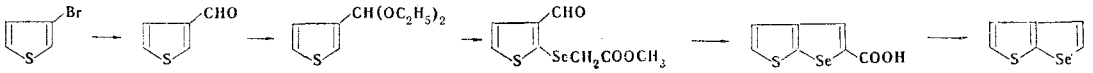
Our investigation of the behavior of selenides of the thiophene series in nucleophilic and electrophilic substitution reactions made it possible to make a transition to the synthesis of new condensed heteroaromatic systems – selenophenothiophenes. In the development of our research on the chemistry of condensed systems, it was of interest to obtain compounds with condensed thiophene and selenophene rings and to compare their properties with those of thienothiophenes – compounds that contain two condensed thiophene rings.

We have accomplished the synthesis of this sort of system – selenopheno[3,2-b]thiophene [4] – via the following scheme. Methyl 3-thienylselenoacetate was synthesized by the reaction of methyl monobromoace-

tate with thiophene-3-selenol, which was obtained from 3-thienyllithium. Formylation of methyl 3-thienylselenoacetate via the Vilsmeier reaction gave methyl (2-formyl-3-thienylseleno)acetate, the cyclization of which with sodium alkoxide gave selenopheno[3,2-b]thiophene-5-carboxylic acid in 76% yield. Selenopheno-[3,2-b]thiophene was obtained in 98% yield by decarboxylation of the acid in quinoline.



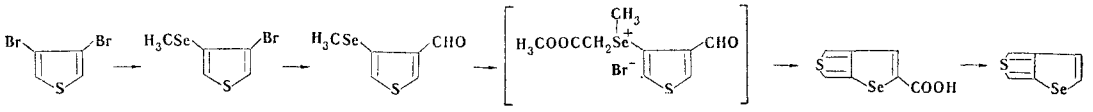
Selenopheno[2,3-b]thiophene was similarly synthesized.



Bugge [84] also synthesized selenopheno[2,3-b]thiophene using our method but without isolation of methyl (3-formyl-2-thienylseleno)acetate.

Our attempt to obtain a third isomer – seleno[2,3-c]thiophene – by the method previously used in the synthesis of thieno[3,4-b]thiophene [85] proved to be unsuccessful: only resinification products were obtained in the metallation of 4-bromo-3-formylthiophene and subsequent treatment of the product with selenium and methyl bromoacetate (with intermediate isolation of 3-formylthiophene-4-selenol).

Another path to the synthesis of selenopheno[2,3-c]thiophene was therefore projected and realized. It consists in the reaction of 4-methylseleno-3-formylthiophene with methyl bromoacetate and subsequent heating of the selenonium salt with acetic anhydride and pyridine to give selenopheno[2,3-c]thiophene-4-carboxylic acid, the decarboxylation of which gave selenopheno[2,3-c]thiophene.



Some Spectral Properties of Alkyl Hetaryl Selenides

Within the plan of our investigation involving a comparison of the properties of sulfides and selenides of heterocyclic compounds, it seemed of interest to compare the spectral characteristics of these compounds with recourse, in some cases, to the corresponding alkoxy derivatives. Since the functional groupings in these compounds are formed by related elements, similarities in the spectra might have been expected, but only within certain limits, since oxygen, sulfur, and selenium have substantially different atomic parameters.

Our comparison [7] of the UV spectra of alkoxy, alkylthio, and alkylseleno derivatives of the thiophene series made it possible to observe that the spectra of the S and Se derivatives are close in character to one another but differ substantially from the spectra of the O derivatives. The effect of a substituent on the spectrum is manifested in an increase in the bathochromic effect in the order OR < SR < SeR, in conformity with the spacing of the energy levels of the unshared pairs of the heteroatom of the substituent. In addition, the intensity of the long-wave band of the selenides is lower than the intensity of the long-wave band of the corresponding sulfides, which may attest to less overlapping of the electron clouds of the ring with the selenide function.

The spin–spin coupling constants in selenides of the thiophene series that bear electron-acceptor groups (COOH, $COCH_3$, and CHO) [8] differ little from the constants of the corresponding sulfides. In contrast to the sulfides, in the spectra of selenides one observes spin–spin coupling between the selenium atom and the protons of the methyl group bonded to it, which is caused by the presence of Se^{77}.

In order to study the behavior of selenides of the furan, thiophene, and selenophene series under electron impact in comparison with the behavior of the analogous sulfides, we made a mass-spectroscopic investigation of a number of alkoxy, alkylthio, and alkylseleno derivatives of the indicated heterocycles [9]. It was observed that the mass spectra of 2-methylmercaptothiophene and 2-methylselenoselenophene are similar. The most intense peaks in the spectra of both compounds are the molecular ion peaks (M^+). Correspondingly, the principal process in their disintegration consists in splitting out of a CH_3 radical with subsequent loss of CS or CSe, while the ions formed split out an acetylene molecule.

The mass spectrum of a compound with different heteroatoms in the ring and side chain, namely, 2-methylmercaptofuran, differs considerably from the spectra considered above. Here, competition between cleavage of CO and CS is observed after elimination of a methyl radical, and both processes occur to an al-

most equal extent. A similar fragmentation pattern is observed in the mass spectrum of 2-methylselenofuran. However, there are differences in the case of the latter compounds: in 2-methylmercaptofuran the cleavage of CO and CS occurs to an almost identical extent, while the cleavage of CO in 2-methylselenofuran prevails considerably over cleavage of CSe.

A complete analogy in the order of fragmentation is observed in the case of 2-methylselenothiophene, 3-methylselenothiophene, and 2-methylmercaptoselenophene. After the loss of CH_3, CS and CSe are cleaved simultaneously. In this case, cleavage of CS predominates by a factor of 1.6 over cleavage of CSe in 2-methylselenothiophene; this predominance is somewhat less (a factor of 1.4) in 3-methylselenothiophene, and, finally, an equal ratio of disintegration products is observed in 2-methylmercaptoselenophene. On the basis of this, it can be concluded that the loss of a heteroatom as CX is easier the lower the atomic number of element X and, correspondingly, the higher its electronegativity.

Predominant cleavage of a CX group with a more electronegative heteroatom X (X = O or S, respectively) is observed for 5-methoxy-2-methylthiophene and its 5-methylseleno-2-methylthiophene analog to an even greater degree than for the compounds examined above.

Thus it can be concluded that the chief fragmentation process in the examined compounds is cleavage of a CH_3 radical with subsequent rearrangement of the $[M-15]^+$ ion, which makes cleavage of any of the two heteroatoms as CX possible, but the more electronegative heteroatom is primarily eliminated.

To ascertain the relative ease of cleavage of the R–S and R–Se bonds, we studied the mass spectra of compounds simultaneously containing both alkylmercapto and alkylseleno groups. On the basis of an examination of the mass spectra of 2-methylmercapto-5-methylselenothiophene, its 5-d_3 analog, 2-propylmercapto-5-methylselenothiophene, and 2-methylmercapto-5-propylselenothiophene, it was concluded that the R–Se bond in these disubstituted compounds is not as strong as the R–S bond.

Thus alkoxy, alkylthio, and alkylseleno derivatives of furan, thiophene, and selenophene are characterized by initial cleavage of an alkyl group with subsequent rearrangement of the resulting $[M-R]^+$ ion followed by loss of one heteroatom as CX. This process is observed most distinctly in the case of monosubstituted compounds; more complex transformations are characteristic for disubstituted compounds.

LITERATURE CITED

1. Ya. L. Gol'dfarb and V. P. Litvinov, Izv. Akad. Nauk SSSR, Ser. Khim., 2088 (1964).
2. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, Izv. Akad. Nauk SSSR, Ser. Khim., 2585 (1967).
3. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, Dokl. Akad. Nauk SSSR, 182, 340 (1968).
4. Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin', Izv. Akad. Nauk SSSR, Ser. Khim., 1419 (1968).
5. A. N. Sukiasyan, V. P. Litvinov, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 1345 (1970).
6. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, Izv. Akad. Nauk SSSR, Ser. Khim., 1296 (1971).
7. V. A. Petukhov, V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 1700 (1971).
8. V. S. Bogdanov, V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, Zh. Organ. Khim., 7, 1257 (1971).
9. O. S. Chizhov, B. M. Zolotarev, A. N. Sukiasyan (Sukiasian), V. P. Litvinov, and Ya. L. Gol'dfarb, Org. Mass Spectr., 3, 1379 (1970).
10. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, USSR Author's Certificate No. 235,045 (1967); Byull. Izobr., No. 5, 17 (1969).
11. V. P. Litvinov, A. N. Sukiasyan, Ya. L. Gol'dfarb, and L. V. Bogacheva, Izv. Akad. Nauk SSSR, Ser. Khim., 1595 (1971).
12. V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., 466 (1972).
13. B. P. Fedorov and F. M. Stoyanovich, USSR Author's Certificate No. 165,752 (1963); Byull. Izobr., No. 20, 20 (1964).
14. E. Niwa, H. Aoki, H. Tanaka, K. Munakata, and M. Namiki, Ber., 99, 3215 (1966).
15. H. Gilman and D. A. Shirley, J. Am. Chem. Soc., 71, 1870 (1949).
16. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Zh. Obshch. Khim., 29, 2034 (1959).
17. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Zh. Obshch. Khim., 29, 3631 (1959).
18. S. Gronowitz and B. Gestblom, Arkiv Kemi, 18, 513 (1962).
19. S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Hakansson, Arkiv Kemi, 17, 165 (1961).
20. J. Sice, J. Am. Chem. Soc., 75, 3697 (1953).
21. H. Gilman and F. J. Webb, J. Am. Chem. Soc., 71, 4062 (1949).
22. H. Gilman and R. L. Bebb, J. Am. Chem. Soc., 61, 109 (1939).

23. D. A. Shirley and R. J. Reeves, J. Organomet. Chem., 16, 1 (1969).
24. G. Wittig, U. Pockels, and H. Dröge, Ber., 71, 1903 (1938).
25. D. A. Shirley, J. R. Jonson, and J. P. Hendrix, J. Organomet. Chem., 11, 209 (1968).
26. H. Gilman and F. J. Webb, J. Am. Chem. Soc., 62, 987 (1940).
27. G. B. Bachman and L. V. Heisey, J. Am. Chem. Soc., 70, 2378 (1948).
28. S. Gronowitz, Advances in Heterocyclic Chemistry, Vol. 1, New York–London (1963), p. 1.
29. S. Gronowitz, Arkiv Kemi, 7, 361 (1954).
30. S. Gronowitz, Arkiv Kemi, 12, 239 (1958).
31. J. D. Roberts and D. Y. Curtin, J. Am. Chem. Soc., 68, 1658 (1946).
32. F. N. Jones, M. F. Zinn, and C. R. Hauser, J. Org. Chem., 28, 663 (1963).
33. B. M. Graybill and D. A. Shirley, J. Org. Chem., 31, 1221 (1966).
34. C. S. Giam and J. L. Stout, Chem. Comm., 142 (1969).
35. Z. K. Cheema, G. W. Gibson, and J. F. Eastham, J. Am. Chem. Soc., 85, 3517 (1963).
36. G. Wittig, Angew. Chem., 66, 10 (1954).
37. H. Gilman and R. V. Young, J. Am. Chem. Soc., 56, 1415 (1934).
38. R. A. Benkeser, D. J. Foster, D. M. Sauve, and J. F. Nobis, Chem. Rev., 57, 867 (1957).
39. H. D. Hartough and S. L. Meisel, Compounds with Condensed Thiophene Rings, New York (1954), p. 14.
40. Ya. L. Gol'dfarb and Ya. L. Danyushevskii, Zh. Obshch. Khim., 31, 3654 (1961).
41. A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Yu. I. Raneeva, and E. N. Zvyagintseva, Dokl. Akad. Nauk SSSR, 168, 364 (1966).
42. C. Price and S. Oae, Sulfur Bonding, New York (1962), p. 28.
43. H. Gilman, M. W. Van Ess, H. B. Willis, and C. G. Stuckwich, J. Am. Chem. Soc., 62, 2606 (1940).
44. H. Gilman and C. G. Stuckwich, J. Am. Chem. Soc., 67, 877 (1945).
45. S. Gronowitz, Arkiv Kemi, 13, 295 (1959).
46. V. Ramanthan and R. Levine, J. Org. Chem., 27, 1667 (1962).
47. J. Sice, J. Org. Chem., 19, 70 (1954).
48. S. Gronowitz, Arkiv Kemi, 13, 269 (1958).
49. S. Gronowitz, Arkiv Kemi, 16, 363 (1960).
50. D. A. Shirley and J. P. Hendrix, J. Organomet. Chem., 11, 217 (1968).
51. N. Gjös and S. Gronowitz, Arkiv Kemi, 30, 225 (1968).
52. S. Gronowitz and K. Halvarson, Arkiv Kemi, 8, 343 (1955).
53. A. I. Shatenshtein (Shatenstein), Tetrahedron, 18, 95 (1962).
54. H. Wynberg and A. Banties, J. Am. Chem. Soc., 82, 1447 (1960).
55. S. Gronowitz and B. Eriksson, Arkiv Kemi, 21, 335 (1963).
56. F. M. Stoyanovich and B. P. Fedorov, Zh. Organ. Khim., 1, 1282 (1965).
57. L. I. Belen'kii, N. S. Ksenzhek, and Ya. L. Gol'dfarb, Khim. Geterotsikl. Soedin., 310 (1972).
58. E. Profft, Ann., 622, 196 (1959).
59. J. Cymerman-Craig and J. W. Loder, J. Chem. Soc., 237 (1954).
60. Ya. L. Gol'dfarb, V. P. Litvinov, and V. I. Shvedov, Zh. Obshch. Khim., 30, 534 (1960).
61. B. P. Fedorov and F. M. Stoyanovich, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1834 (1960).
62. B. P. Fedorov and F. M. Stoyanovich, Zh. Obshch. Khim., 31, 238 (1961).
63. E. N. Zvyagintseva, L. I. Belen'kii, T. A. Yakushina, Ya. L. Gol'dfarb, and A. I. Shatenshtein, Zh. Obshch. Khim., 38, 2004 (1968).
64. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Khim. Geterotsikl. Soedin., 62 (1967).
65. Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin', Izv. Akad. Nauk SSSR, Ser. Khim., 510 (1965).
66. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 701 (1962).
67. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Zh. Obshch. Khim., 30, 1012 (1960).
68. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Izv. Akad. Nauk SSSR, Ser. Khim., 1769 (1969).
69. H. Rheinboldt, in: Methoden der Organischen Chemie, Vol. 9, Stuttgart (1955), p. 1005.
70. O. K. Edwards, W. R. Gaytwaite, J. Kenyon, and H. Phillips, J. Chem. Soc., 2293 (1928).
71. E. Fromm and G. Raiziss, Ann., 374, 90 (1910).
72. K. Fries and W. Vogt, Ann., 381, 337 (1911).
73. T. Zincke and W. Frohneberg, Ber., 42, 2721 (1909).
74. T. Zincke and W. Frohneberg, Ber., 43, 837 (1910).
75. T. Zincke and R. Brune, Ber., 44, 185 (1911).
76. P. Spinoglio and M. De Gasperi, Gazz. Chim. Ital., 67, 318 (1937).
77. E. Hannig and H. Ziebandt, Pharmazie, 23, 552 (1968).
78. J. D. McCullough, J. Am. Chem. Soc., 64, 2672 (1942).

79. J. D. McCullough and B. A. Eckerson, J. Am. Chem. Soc., 67, 707 (1945).
80. J. D. McCullough and M. K. Barsh, J. Am. Chem. Soc., 71, 3029 (1949).
81. E. Bourgeois and A. Abraham, Rec. Trav. Chim., 30, 407 (1911).
82. F. Krafft and W. Vorster, Ber., 26, 2819 (1893).
83. Ya. L. Danyushevskii, M. A. Marakatkina, and Ya. L. Gol'dfarb, Zh. Organ. Khim., 4, 474 (1968).
84. A. Bugge, Acta Chem. Scand., 23, 1823 (1969).
85. V. P. Litvinov and G. Frenkl, Izv. Akad. Nauk SSSR, Ser. Khim., 1328 (1968).