SYNTHESIS OF BENZOTHIAZEPINES (REVIEW)

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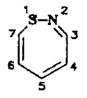
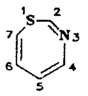
UDC 547.892.07(047)

Methods for the preparation of benzothiazepines, which are grouped with respect to their structural features (1,2-, 1,3-, and 1,4-thiazepines), are correlated. Methods for the synthesis of compounds of each type are discussed in the case of the most thoroughly studied representatives.

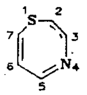
Benzothiazepines are benzo-condensed derivatives of three structural isomers of thiazepine.



1,2-thiazepine

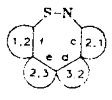


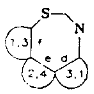
1,3-Thiazepine

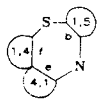


1,4-Thiazepine

On the basis of these three pincipal types of thiazepines one can, theoretically, formulate ten types of benzothiazepines and six types of dibenzothiazepines, which can be represented by the following generalizing formulas [1]:

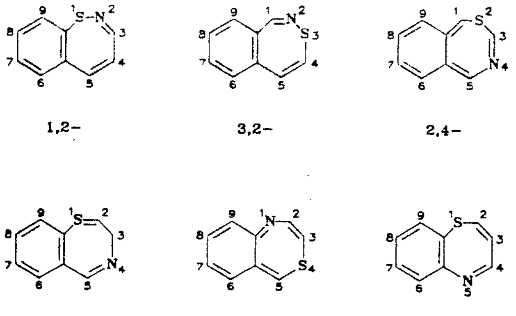






1,3-Thiazepine may be the parent compound of four benzothiazepines (1,2-, 2,3-, 3,2-, and 2,1-benzothiazepine). Of these, several 1,2- and 3,2-benzothiazepine derivatives have been described [1], whereas, of the number of possible benzologs of 1,3-thiazepine (1,3-, 2,4-, and 3,1-benzothiazepine), only 2,4-benzothiazepine derivatives are known to us [1].

Derivatives of all of the benzologs of 1,4-thiazepine (1,4-, 4,1-, and 1,5-benzothiazepine) are known in the literature. In the scheme given below we present the structures of the presently known benzothiazepines and their numbering in conformity with the IUPAC rules.



1,2- 3,2- 2,4-

1,4- 4,1- 1,5-

Benzothiazepine

Various methods for the preparation of benzothiazepines have been described (for example, see [1-5]). This is understandable if one takes into account the fact that from the

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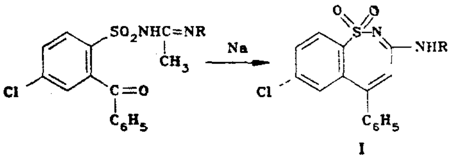
three isomeric thiazepines one can obtain nine types of benzothiazepines, the construction of which, in many cases, is realized by means of various methods. In addition, all of the synthetic methods used are characterized by a number of peculiarities, on the basis of which these methods can be arbitrarily divided into two groups. The first group includes cases in which sulfur- and nitrogen-containing seven-membered rings are constructed from the elements of open chains. The second group includes methods for the preparation of the desired benzothiazepine by means of expansion of the heterocyclic ring of a suitable starting heterocycle. In the present review methods of synthesis are presented in the order of preparation of the possible benzologs of 1,2-, 1,3-, and 1,4-thiazepines.

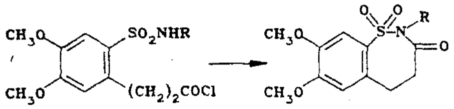
1,2-Benzothiazepines

3-Amino-substituted 5-phenyl-7-chloro-1,2-benzothiazepine 1,1-dioxides (I) were synthesized by cyclization of 2-benzoyl-4-chlorophenylsulfonylacetamidines under the influence of sodium in ethyl acetate [2].



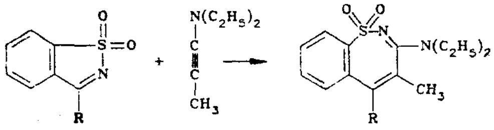
I

N-Substituted 4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepine-3-one 1,1-dioxides (II) were obtained by cyclization of carefully selected intermediates with open chains [3].



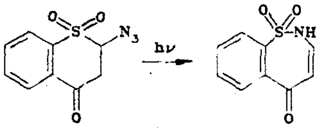
II

Methods for the preparation of 1,2-benzothiazepines that are based on ring expansion are known. Thus 5-substituted 3-diethylamino-4-methyl-1,2-benzothiazepine 1,1-dioxides (III) were obtained by [2 + 2] cycloaddition of 3-substituted 1,2-benzothiazole 1,1-dioxides to 1-diethylaminopropyne, which is accompanied by ring expansion [4].



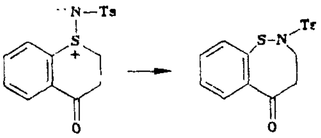
III

2H-Benzo[f]-1,2-thiazepine-5-one 1,1-dioxides (IV) are formed in the photolysis of 2-azido 1-thiochromanone 1,1-dioxide in benzene or dichloromethane [5].



IV

1,2-Benzothiazepines were also obtained from 1-thiochromanone derivatives [6, 7]. Thus, treatment of 1-thiochromanone N-tosylsulfimides with Chloramine T leads to their conversion to 2,3-dihydro-2-tosyl-1,2-benzothiazepin-5(4H)-one (V).

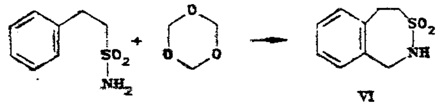


V

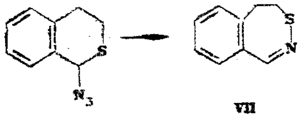
Ts=p-$CH_3C_6H_4SO_2$

3,2-Benzothiazepines

The literature contains little information regarding 3,2-benzothiazepines. It has been shown [8] that 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide (VI) is formed in the reaction of β-phenylethanesulfonamide with trioxane in a mixture of methanesulfonic and acetic acids.

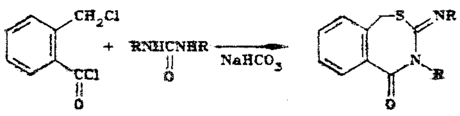

VI

It has also been found that benzothiazepines of this type can also be obtained by ring expansion. For example, the thermal conversion of isochroman-1-yl azide to 4,5-dihydro-3,2-benzothiazepine (VII) was described in [9].


VII

2,4-Benzothiazepines

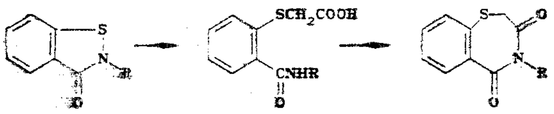
The reaction of 2-chloromethylbenzoyl chloride with 1,3-disubstituted thiocarbamides in acetone in the presence of sodium carbonate leads to 2,4-dihydro-3-alkylamino-4-alkyl-2,4-benzothiazepine-5(1H)-ones (VIII) [10].


VIII

2,4-Benzothiazepines of the VIII type were also obtained by the reaction of 2-(bromomethyl)benzyl bromide or 2-(bromomethyl)benzoyl bromide with thioamides under similar conditions [11].

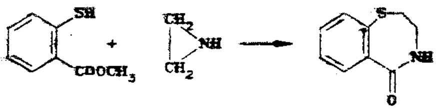
1,4-Benzothiazepines

Of the 1,4-benzothiazepine derivatives, 2,3,4,5-tetrahydro-1,4-benzothiazepine-3,5-diones were the first to be described [12]. 2-Mercaptobenzamides, which can be cyclized to 1,4-benzothiazepine derivatives (IX), were obtained by treatment of benzisothiazolones with potassium acetate.


IX

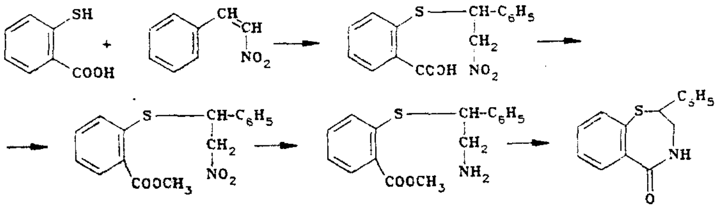
Benzothiazepines IX were later synthesized from 2-mercaptobenzamides and chloroacetic acid with subsequent cyclization [13].

The synthesis of 2,3-dihydro-1,4-benzothiazepine-5(4H)-one (X) was first accomplished by the reaction of methyl 2-mercaptobenzoate with ethyleneimine in methanol in the presence of sodium methoxide [14].

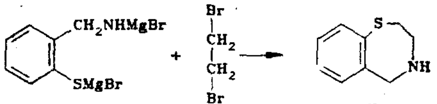

X

Halo-substituted derivatives of X were later obtained under similar conditions [15, 16].

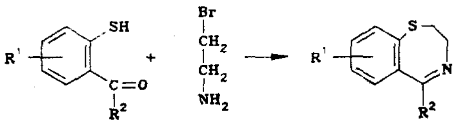
The method [17] shown in the scheme given below was developed for the synthesis of 2,3-dihydro-2-phenyl-1,4-benzothiazepin-5(4H)-one (XI) and its derivatives:


XI

2,3,4,5-Tetrahydro-1,4-benzothiazepine (XII) was obtained relatively recently [18] by the reaction of the N,S-bis(bromomagnesium) derivative of 2-mercaptobenzylamine and 1,2-dibromoethane in tetrahydrofuran (THF).


XII

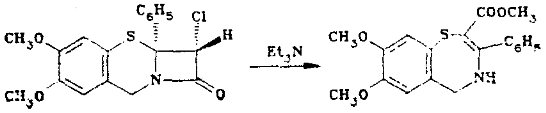
Analogs of the biologically most active 1,4-benzodiazepines, viz., 5-substituted 2,3-dihydro-1,4-benzothiazepines, were first obtained by the reaction of 2-mercapto ketones with 2-bromoethylamine [19].



Hirohashi and coworkers synthesized 2,3-dihydro-5-phenyl-7-chloro-1,4-benzothiazepines by cyclization of N-benzoyl-2-(p-chlorophenylthio)ethylamine [20].

In familiarizing oneself with methods for the synthesis of 1,2-benzothiazepines it is interesting to note synthesis based on the cycloaddition of 1,2-benzothiazoles. 1,4-Benzothiazepines have also been obtained in this way. For example, 2,3-dihydro-5-phenyl-1,4-benzothiazepines were synthesized by the photoaddition of 3-phenyl-1,2-benzisothiazoles and alkenes [21, 22].

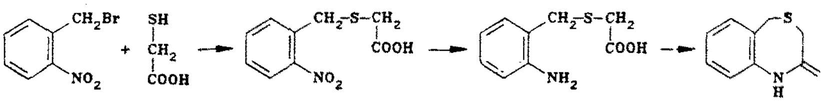
Compounds of the 4,5-dihydro-1,4-benzothiazepine type were obtained by ring expansion of β-lactam derivatives of dihydrobenzothiazepine under base-catalysis conditions [23].



1,4-Benzothiazepines can also be synthesized by ring expansion of 1-thiochromanones. Mixtures of 1,4- and 1,5-benzothiazepines are generally formed in this reaction. We will discuss this method in our description of methods for the preparation of 1,5-benzothiazepines.

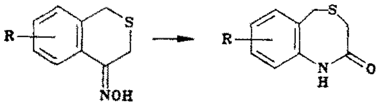
4,1-Benzothiazepines

The smallest amount of study in the field of 1,4-thiazepine derivatives has been devoted to 4,1-benzothiazepines. Only a few methods for their preparation are known. The most well-known representatives of this group of compounds are 3,5-dihydro-4,1-benzothiazepine-2(1H)-ones (XIII). They are primarily synthesized by a single method [24-26], the essential features of which are presented in the following scheme:

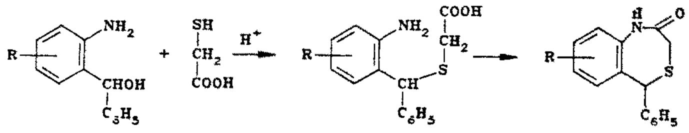


XIII

The synthesis of XIII derivatives was recently accomplished by Beckmann rearrangement of isothiochromanone oximes [27].



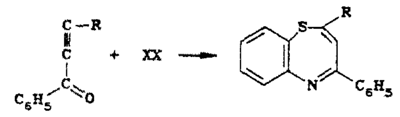
5-Phenyl-substituted benzothiazepines XIII were obtained by the reaction of 2-aminobenzhydrazole and thioglycolic acid in an acidic medium with subsequent cyclization of the resulting product [28, 29].



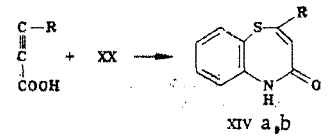
1,5-Benzothiazepines

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine. A relatively large number of methods for their preparation have been described. According to our data, 1,5-benzothiazepine itself has not yet been described, although its 2,4-disubstituted derivatives and many hydrated derivatives have been synthesized. The methods for the preparation of 1,5-benzothiazepines can also be divided into two major groups, viz., the construction of a seven-membered heteroring from the elements of open chains, and reactions involving ring expansion. The known methods will be examined precisely in this sequence.

Only one method for the preparation of 2,4-disubstituted 1,5-benzothiazepines is known; this method consists in the reaction of 2-aminothiophenol (XX) with acetylenic ketones [30].



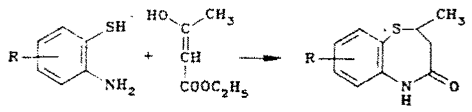
Several methods for the preparation of 1,5-benzothiazepine-4(5H)-ones (XIV) are known. For example [31], 1,5-benzothiazepine-4(5H)-one (XIVa) was obtained by the reaction of 2-aminothiophenol (XX) and propiolic acid with subsequent cyclization of the addition product in the presence of dicyclohexylcarbodiimide. 2-Phenyl-1,5-benzothiazepine-4(5H)-one (XIVb) was synthesized by the reaction of 2-aminothiophenol (XX) and phenylpropiolic acid [32].



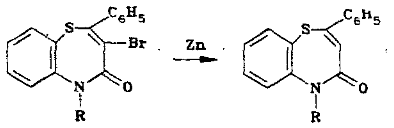
XIV a,b

XIV a R=H; b R=C_6H_5

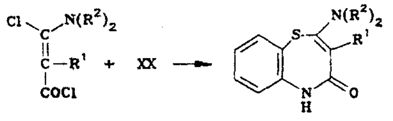
2-Methyl-1,5-benzothiazepin-4(5H)-one derivatives can be obtained by the reaction of acetoacetic ester with substituted 2-aminothiophenols [33, 34].



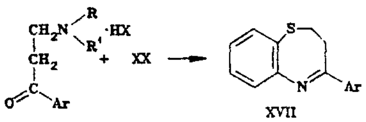
Lévai and Bata [35] obtained 1,5-benzothiazepin-4(5H)-ones (XV) by reductive dehalogenation of 2-phenyl-3-bromo-1,5-benzothiazepin-4(5H)-ones.


XV

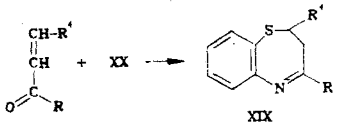
2,3-Disubstituted 1,5-benzothiazepin-4(5H)-ones (XVI) were synthesized by the reaction of α-chloro-β-chlorocarbonylenamines with 2-aminothiophenol (XX) [36].


XVI

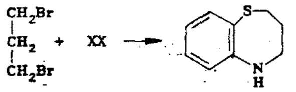
Hideg and Hankovszky [37-39] developed a method for the preparation of 2,3-dihydro-4-aryl-1,5-benzothiazepines (XVII); this method consists in heating 2-aminothiophenol (XX) with N,N-disubstituted 2-aminoethyl aryl ketones.


XVII

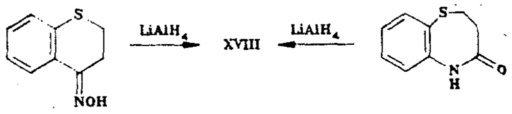
2,4-Disubstituted 2,3-dihydro-1,5-benzothiazepines (XIX) are also well known. Methods for their preparation from 2-aminothiophenol (XX) and α,β-unsaturated ketones under various reaction conditions have been studied in detail [33, 40-50].


XIX

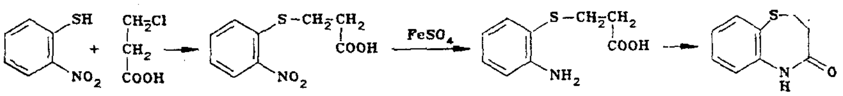
The most thoroughly studied group of 1,5-benzothiazepines consists of 2,3,4,5-tetrahydro-1,5-benzothiazepines (XVIII). Tetrahydro-1,5-benzothiazepine (XVIII) was synthesized for the first time from 2-aminothiophenol and 1,3-dibromopropane [51].


XVIII

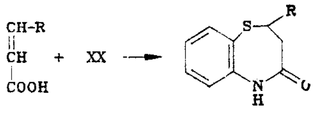
The same compound (XVIII) was obtained from 1-thiochromanone and from 2,3-dihydro-1,5-benzothiazepin-4(5H)-one by reduction with lithium aluminum hydride [52].



A method for the synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5H)-one (XXI) from nitrothiophenol and 2-chloropropionic acid with subsequent reduction of the nitro group to an amino group by the action of iron (II) sulfate and cyclization of the intermediately formed 3-(2-amino-phenylthio)propionic acid is known.


XXI

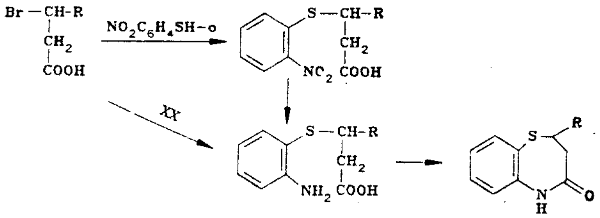
2-Substituted benzothiazepines (XXI) were first obtained by the reaction of 2-aminothiophenol (XX) with α,β-unsaturated carboxylic acids [54].



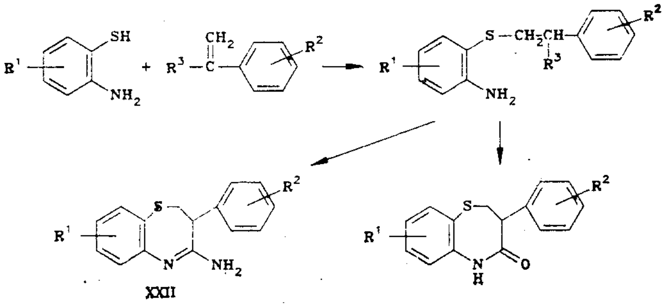
$R = CH_3, CH_2COOH, C_6H_5$

A number of 2-aryl derivatives of XXI, which are cardiovascular agents, were later synthesized by the same method [17, 32, 55, 56]. We obtained [57] 2,3-disubstituted derivatives of XXI from the corresponding acrylic acids and 2-aminothiophenol (XX).

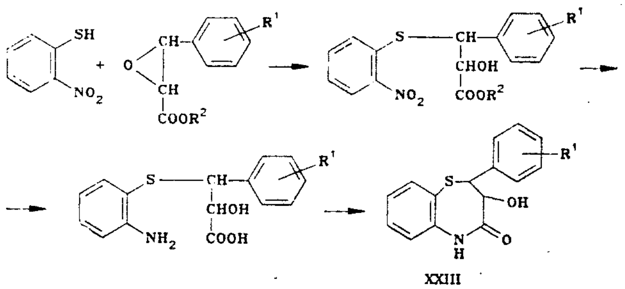
By using the reaction of 3-bromopropionic acid derivatives with 2-amino- or 2-nitrothiophenol we developed a method for the preparation of 2-substituted derivatives of XXI [58].



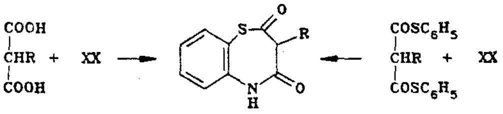
3-Substituted derivatives of XXI are also known. 2,3-Dihydro-3-methyl-1,5-benzothiazepin-4(5H)-one was obtained by the reaction of XX with the corresponding acrylic acid [59]. 2,3-Dihydro-3-phenyl-4-amino-1,5-benzothiazepines (XXII) were synthesized with the aid of atropic acid and atroponitrile [60].



Kugita and coworkers [61-63] and Miyazaki and coworkers [64] developed a general method for the synthesis of 2,3-dihydro-2-aryl-3-hydroxy-1,5-benzothiazepin-4(5H)-ones (XXIII). The reaction of cinnamic acid ester epoxides with XX or 2-nitrothiophenol gave addition products, the hydrolysis of which, in the case of 2-nitrothiophenol derivatives after reduction of the nitro group, and subsequent cyclization lead to the corresponding benzothiazepines XXIII.

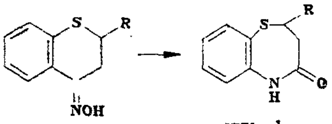


Dione derivatives of 2,3,4,5-tetrahydro-1,5-benzothiazepine of the XXIV type are also known; dione derivatives XXIV are obtained by the reaction of 2-aminothiophenol (XX) with maleic acid derivatives of S,S'-diphenyl dithiomalonates [65, 66].



XXIV

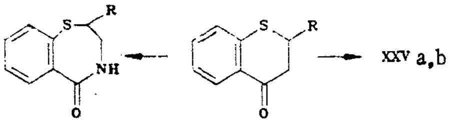
Having examined methods for the synthesis of 1,5-benzothiazepines that consist in the formation of a thiazepine ring, let us turn to an examination of methods based on ring expansion. Relatively little study has been devoted to the latter methods. We have already mentioned that 2,3,4,5-tetrahydro-1,5-benzothiazepine was obtained by reduction of 1-thiochromanone oxime with lithium aluminum hydride [52]. Zagorevskii and Dudykina [52] also isolated 2,3-dihydro-1,5-benzothiazepin-4(5H)-one from the products of Beckmann rearrangement of 1-thiochromanone oxime. We [67], in turn, synthesized 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one as a result of Beckmann rearrangement of 1-thioflavanone oxime.



XXVa,b

a R=H; b R=C_6H_5

1-Thiochromanones [68] and 1-thioflavanone [69] can be converted to benzothiazepines by the Schmidt reaction; mixtures of the corresponding 1,5- and 1,4-benzothiazepines (XXV, XXVI) are formed [68, 69].

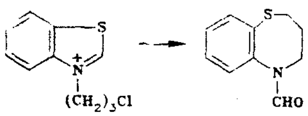


XXVI a,b

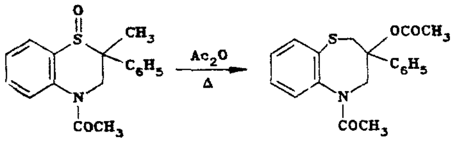
a R=H; b R=C_6H_5

New methods for the preparation of 1,5-benzothiazepines based on ring expansion, in which substances other than 1-thiochromanone derivatives are used as the starting compounds, have recently been reported.

It has been shown [70] that in alkaline-catalysis reactions quaternary salts of N-haloalkylbenzthiazole form 2,3,4,5-tetrahydro-5-formyl-1,5-benzothiazepine.



It has been observed [71] that benzothiazoline S-oxide (XXVII) is capable of undergoing ring expansion. 2,3,4,5-Tetrahydro-3-phenyl-3-acetoxy-5-acetyl-1,5-benzothiazepine (XXVIII) is formed as one of the products when 4-acetyl-2-methyl-2-phenyl-2,3-dihydro-4H-1,4-benzothiazin-1-one is refluxed in acetic anhydride.



XXVII XXVIII

Thus, in the case of the most characteristic compounds, we have examined all of the principal methods for the synthesis of derivatives of various benzothiazepines. We hope that the material presented in this review may be of use both for the synthesis of new compounds via the methods that have already been developed and for the search for new methods of synthesis.

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REACTION OF FURAN COMPOUNDS WITH HYDROGEN SULFIDE AND ASPECTS OF ITS APPLICATION

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The conversion of α-methylfuran, di- and polyalkylfurans, and ethers, esters, ketones, and other derivatives of the furan series to the corresponding substituted thiophenes was realized under acid-catalysis conditions.

The conversion of compounds of the furan series upon reaction with hydrogen sulfide and hydrogen selenide under acid-catalysis conditions to the corresponding isoelectronic analogs, viz., 2,5-disubstituted thiophenes and selenophenes, has been previously reported [1-4]. Our investigation was undertaken in order to ascertain the peculiarities of this reaction in the case of mono-, di-, and polyalkyl-substituted furans, as well as ketones, alcohols, ethers, and esters of the furan series; we also studied the effect of the degree of substitution of the furan ring by alkyl groups and the position and character of the functional substituents of the side chain on the course of the reaction. The reaction of furan compounds II-XX with hydrogen sulfide was carried out in alcohol under the influence of concentrated hydrochloric acid or hydrogen chloride at 20-50°C.

It was established that, regardless of the length and degree of branching of the hydrocarbon chain or the number of substituents, 2,5-dialkyl- (II-VII), 2,3,5-trialkyl- (VIII, IX), and 2,3,4,5-tetraalkylfurans (X) are capable of reacting with hydrogen sulfide under conditions presented above to give the corresponding alkyl substituted thiophenes (XXII-XXX). In the case of the reaction of furans II-IX with hydrogen sulfide using 2-2.5 N hydrochloric acid, in addition to thiophenes XXII-XXIX, one observes the formation of the corresponding 1,4-diketones, which, under the reaction conditions, are also converted to thiophene

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