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CYCLOTHIOMETHYLATION OF PRIMARY AMINES WITH FORMALDEHYDE AND HYDROGEN SULFIDE TO NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES (REVIEW)

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Published data and the authors' own experimental results on the synthesis of nitrogen- and sulfur-containing heterocycles based on the cyclothiomethylation of amines with formaldehyde and H_2S are reviewed. Features of the three-component condensation are discussed in relation to the nature and structure of the initial amines and also the reaction conditions.

Keywords: 1,3,5-dithiazinanes, 1,5-dithia-3,7-diazacyclooctane, 1,3,5-thiadiazinanes, 1,3-thiazetidines, N,S-containing heterocycles, cyclocondensation.

Heterocycles containing both nitrogen and sulfur atoms in the molecule – thiazetidines, thiazoles, isothiazoles, thiazolines, thiazolidines, dithiazinanes, thiadiazines, and their derivatives – are widely used in industry and in medical practise.

Preparations with antimicrobial activity, diuretics, mitodepressants, and antihistamine, antiparasitic, antiviral, and antipyretic agents [1-4] have been developed and introduced on the basis of these types of heterocycles [1-4].

Until now the development of methods for the production of nitrogen- and sulfur-containing heterocycles of specific structure with given properties has been an important task of synthetic organic chemistry. The overwhelming majority of methods for the synthesis involved [4+2] and 1,3-dipolar cycloaddition to unsaturated carbon atoms or cyclocondensation of functionally substituted monomers [5-9]. In the literature these two types of reaction are often combined under the name of "heterocyclization", where the molecule of the heterocycles is formed with the participation of two, three, and more molecules containing various heteroatoms.

In recent years great interest has been shown in saturated sulfur- and nitrogen-containing heterocycles, which on account of the unshared electron pairs on the heteroatoms have high complexing ability toward the cations of metals and toward biological systems. For example, 1,3,5-dithiazinanes are effective as ligands of organoboron and organoaluminum compounds [10, 11] and have been patented as sorbents for gold and silver [12], antagonists of pathogenic microorganisms [13], fungicides [14, 15], and food additives [16-22].

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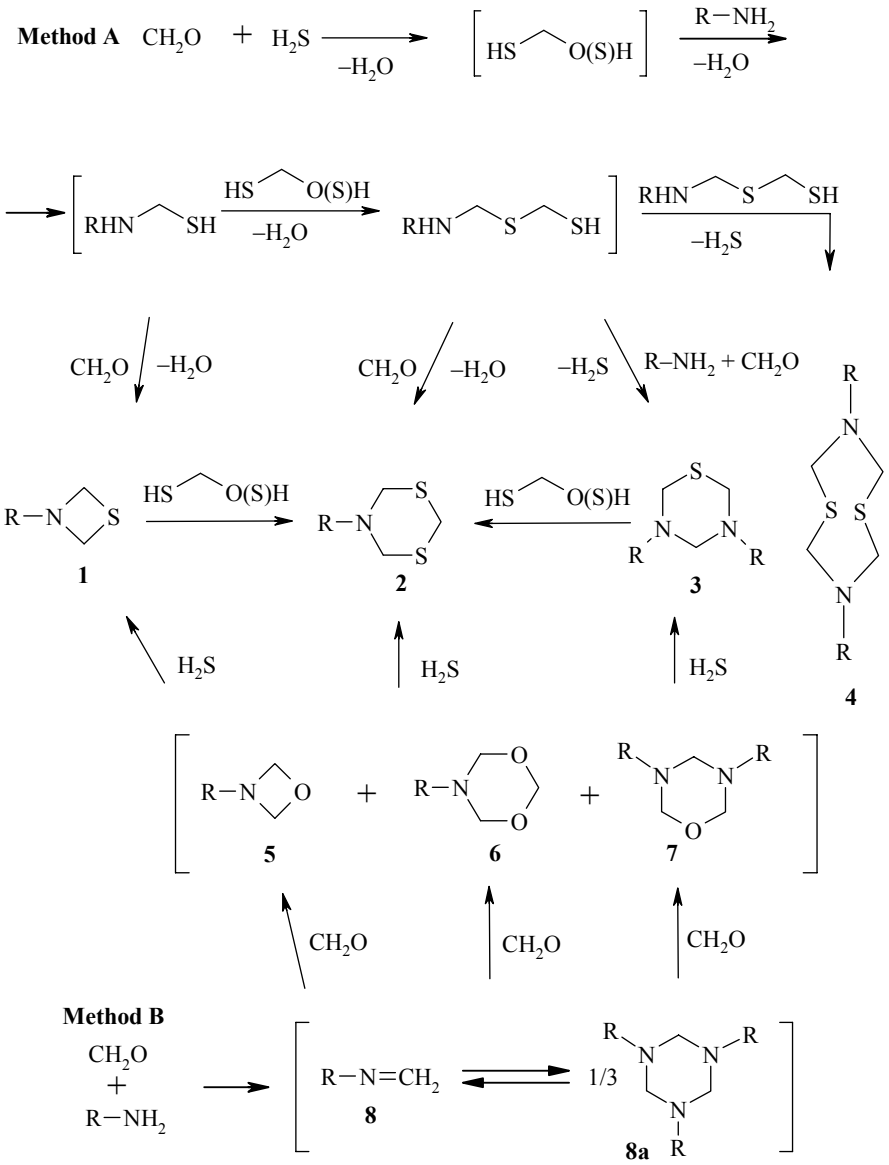
Of special interest and promise among the various methods for the production of 1,3,5-dithiazinanes [23-34] is the simple and convenient method based on the multicomponent reaction of readily obtainable amines, formaldehyde, and H_2S. This reaction, discovered by Wohl [23] more than 100 years ago, was not properly developed, and the few published data in a number of cases contain contradictory information.

In view of the practical significance of 1,3,5-dithiazinanes and the undisclosed potential of the synthetic possibilities of the above-mentioned multicomponent reaction for the production of heterocycles with various structures in this review we examine the existing published material and also the trends in the development of the cyclocondensation of formaldehyde and H_2S with aliphatic (Section 1.1) and aromatic (Section 1.2) amines, with functionally substituted amines such as aliphatic amino alcohols (Section 2.1) and aminophenols (Section 2.2), and with aliphatic amino acids (Section 3.1) and aromatic amino acids (Section 3.2) and their derivatives.

Published data over the last 15-20 years on research into the cyclothiomethylation of various primary amines with formaldehyde and H_2S are examined. In a number of cases earlier publications will also be included in order to represent the chronological development of research in this field.

Scheme 1



1. HETEROCYCLIZATION OF PRIMARY AMINES WITH FORMALDEHYDE AND H_2S

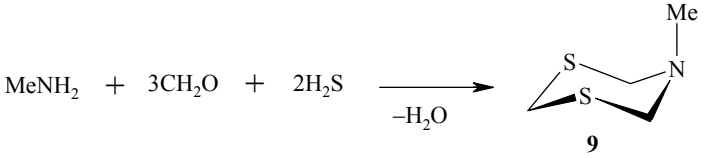
The multicomponent reaction mentioned above is described by two types of chemical transformations and leads to the production of 1,3-thiazetidines **1**, 1,3,5-dithiazinanes **2**, 1,3,5-thiadiazinanes **3**, and 1,5-dithia-3,7-diazacyclooctanes **4**. (Scheme 1). The first type of transformation is based on the condensation of amines with the thio- and semithioacetals of formaldehyde, previously prepared by bubbling H_2S into a solution of formaldehyde (method A). The second type of construction for the nitrogen- and sulfur-containing heterocyclic systems involves the reaction of H_2S with cyclic adducts **5-7** and Schiff bases **8**, previously prepared by the condensation of amines with formaldehyde (method B). It should be noted that in the case of the realization of both method A and method B with the components amine–CHO_2–H_2S in ratios of 1:3:2 the concluding stage is in most cases the formation of 1,3,5-dithiazinanes **2**. These two heterocyclization routes can be represented by the general Scheme 1.

The direction of the reactions presented above and the composition of the formed heterocycles depend to a significant degree on the stability of the N- and S-containing intermediates and also on the targeted heterocycles – 1,3-thiazetidines **1**, 1,3,5-dithiazinanes **2**, 1,3,5-thiadiazinanes **3**, 1,5-dithia-3,7-diazacyclo-octanes **4**, 1,3-oxazetidines **5**, dioxazinanes **6**, oxadiazinanes **7**, and 1,3,5-triazinanes **8a**.

Thus, the yields and the composition of the formed N- and S-containing heterocycles and also the direction of heterocyclization of the amines with H_2S and CH_2O depend on the order in which the initial components of the reaction mixture are mixed and also on the nature and structure of the initial amines, affecting the stability of the intermediate heteroatomic compounds.

1.1. Cyclothiomethylation of Aliphatic Amines

In the work of Wohl [23], who laid the foundation of research into the reaction of amines with CH_2O and H_2S, 5-methyl-1,3,5-dithiazinane **9** was first synthesized by method A [35-39].



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Somewhat later [40] the products from the condensation of CH_2O with H_2S–1,2,4-trithiolane **10** and 1,2,4,6-tetrathiepane **11** – were obtained and isolated together with compound **9** in the presence of methylamine under analogous conditions.

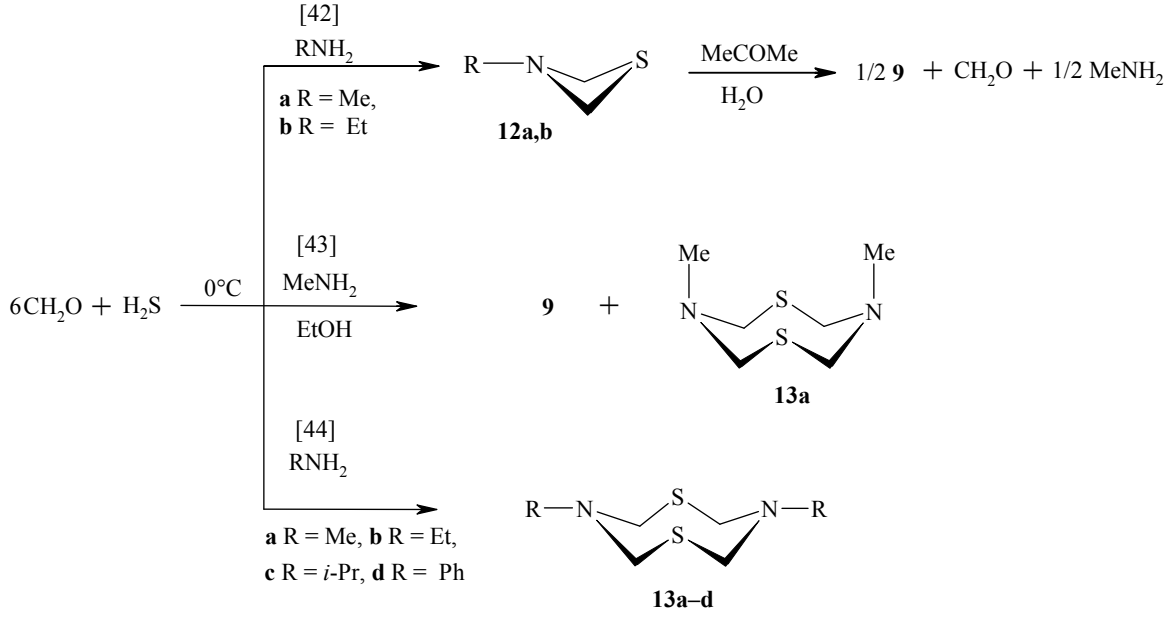
10 **11**

According to [41], if H_2S is replaced by Na_2S the selective formation of compound **9** is observed in the cyclothiomethylation of methylamine hydrochloride.

In [42] it was shown that it is not possible to direct the reaction toward the formation of compound **9** in the cyclothiomethylation of ethylamine with H_2S and CH_2O if the concentration of the latter is increased. In addition, the authors found that N-methylperhydro-1,3-thiazetidine **12a** is formed if the reaction is carried out at 0°C; this product is slowly converted into compound **9** by the action of aqueous acetone.

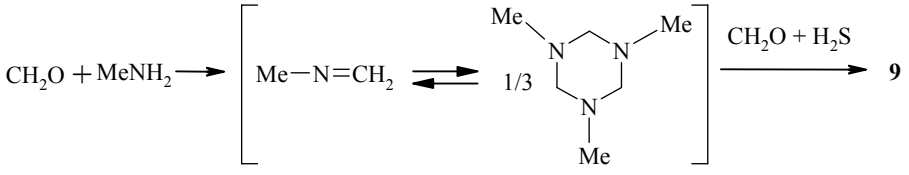
During the cyclothiomethylation of methylamine with H_2S and CH_2O under analogous conditions in ethanol 3,7-dimethyl-1,5-dithia-3,7-diazacyclooctane **13a** was obtained [43].

The use of methyl-, ethyl-, isopropyl-, and phenylamines under analogous conditions during cyclothiomethylation with CH_2O and H_2S with the initial reagents in ratios of 1:6:4 leads to the selective formation of 1,5-dithia-3,7-diazacyclooctanes. As a result N-substituted 1,5-dithia-3,7-diazacyclooctanes **13a-d**, for which the symmetrical crown (C_1) conformation was established by dynamic ^{1}H NMR spectroscopy, were obtained [44]. Unfortunately, the authors did not provide the physicochemical characteristics of the synthesized samples.

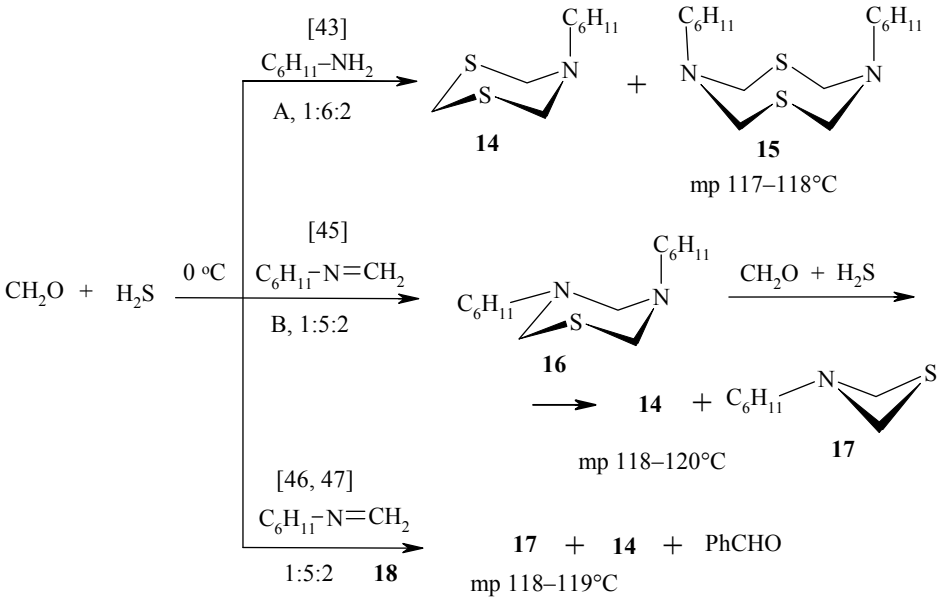


It should be mentioned that there contradictions in [43] in the results of the cyclothiomethylation of cyclohexylamine with H_2S and CH_2O. Thus, for example, 1,3,5-dithiazinane **14** and the eight-membered heterocycle **15** (mp 117-118°C) were obtained by method A at 0°C with amine–CH_2O–H_2S ratios of 1:6:2.

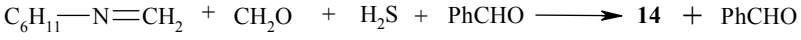
The authors of [45] describe the formation of 3,5-dicyclohexyl-1,3,5-thiadiazinane **16** during the reaction by method B under analogous conditions; in the authors' opinion compound **16** then enters into reaction with the CH_2O and H_2S with the preferential formation of the 3-substituted 1,3-thiazetidine **17** with mp 118-120°C (close to the melting point of compound **15**) and a small amount of 1,3,5-dithiazinane **14**. The authors consider that the formation of 5-methyl-1,3,5-dithiazinane (**9**) by the methods of Wohl and Le Fevre probably takes place through a stage involving the formation of methylene imine.



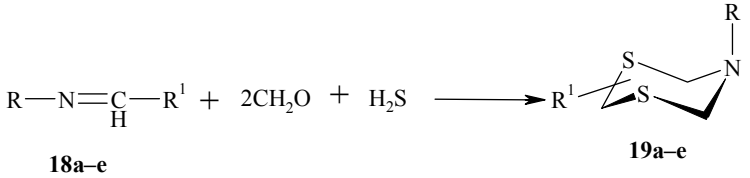
The same authors [46] synthesized compound **17**, melting at 118-119°C, by a method based on the cyclothiomethylation of N-methyleneamine **18** (cyclohexylimine **18**–CH_2O–H_2S, 1:5:2, 0°C) [47].



The experiments were later [48] carried out with the simultaneous addition of formaldehyde and benzaldehyde to the reaction mixture. Here the authors found that N-methylenecyclohexylamine with H_2S and CH_2O in the presence of benzaldehyde forms the N-cyclohexyl-1,3,5-dithiazinane (**14**) exclusively, while the mother solution contains free benzaldehyde. The authors state that it is difficult to obtain 2(or 4),5-disubstituted 1,3,5-dithiazinanes by this method.



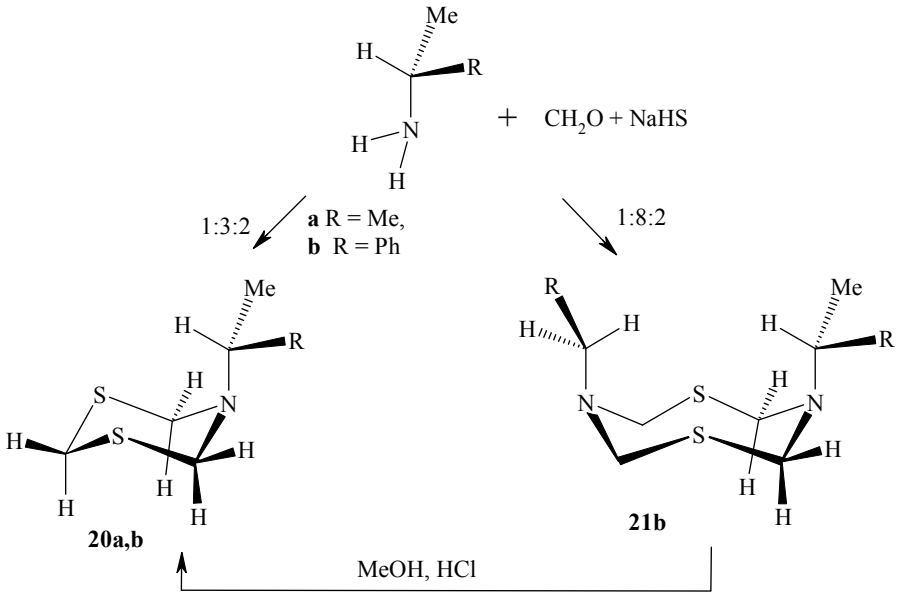
At the same time the condensation of formaldehyde and H_2S using the Schiff bases **18a-e** obtained from cyclohexyl(methyl, ethyl)amines with benzaldehyde and other aromatic aldehydes leads to 2(or 4),5-disubstituted 1,3,5-dithiazinanes **19a-e**.



8, 19 a R = C_6H_{11}, R^1 = Ph; **b** R = C_6H_{11}, R^1 = 4-MeC_6H_4;
c R = C_6H_{11}, R^1 = 4-$MeOC_6H_4$; **d** R = Me, R^1 = Ph; **e** R = Et, R^1 = Ph

It must be assumed that the different directions of the heterocyclization of the imines **18a-e** with formaldehyde and H_2S, described in [46-49], depend both on the ratio of the initial reagents and on the temperature of cyclothiomethylation.

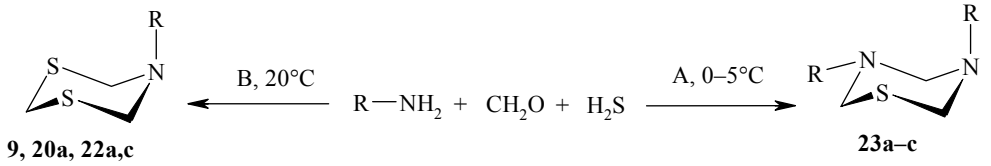
During the reaction of isopropylamine or (*R*)-(+)-1-methylbenzylamine with CH_2O and NaSH in ratios of 1:3:2 the corresponding dithiazinanes **20a** and (*R*)-**20b** are formed with yields of 64 and 63%. When the concentration of formaldehyde in the thiomethylating mixture was increased (1:8:2) the chiral 1,5-dithia-3,7-diazacyclooctane **21b** was obtained selectively from (*R*)-(+)-1-methylbenzylamine with a yield of ~70% {$[\alpha]_D$ = +134.7 (0.02, CH_2Cl_2)}; its subsequent treatment with hydrochloric acid in methanol gave 5-[(*R*)-(+)-1'-methylbenzyl]-1,3,5-dithiazinane **20b** with $[\alpha]_D$ = +72.2 (0.02, CH_2Cl_2) [50].



Thus, according to published data the preferential formation of 1,5-dithia-3,7-diazacyclooctanes is observed during the cyclothiomethylation of amines at 0°C with the initial reagents in amine–CH_2O–H_2S ratios of 1:(6-8):2, while 1,3,5-dithiazinanes are mainly formed at 20°C with reagent ratios of 1:3:2. The results described above make it possible to suppose that Le Fevre and Graymore's group probably obtained 1,5-dithia-3,7-diazacyclooctanes **13a-c** and not thiazetidines **12a**.

The ethyl- and isopropyl-1,3,5-dithiazinanes **23a** and **23b** were synthesized selectively by method B with NaHS at 20°C and were patented as effective sorbents for the isolation of silver and gold [12].

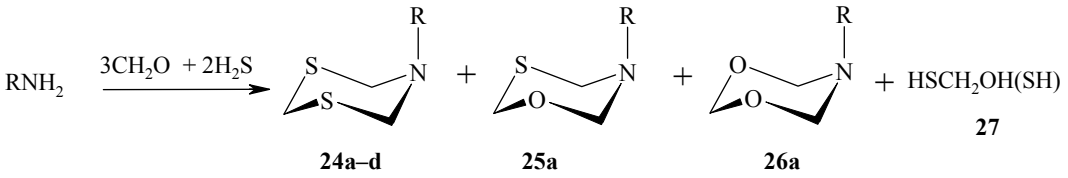
The production of the dithiazinanes **9**, **20a**, and **22a**,**c** by method B by first mixing equivalent amounts of a primary amine with formaldehyde and then bubbling H_2S into the mixture at 20°C was described in detail in [51]. Under these conditions the imine is formed initially and then undergoes heterocyclization with the H_2S. The analogous reaction by method A at 0-5°C gives the diazines **23a-c**.



9, 20a, 22a,c **23a–c**

9, **23** R = Me, **22a**, **23a** R = Et, **20a**, **23b** R = *i*-Pr, **22c**, **23c** R = *t*-Bu

The publications described above contain limited information of the effect of the structure of the initial reagents and the reaction conditions on the direction of the reaction and the product yields in the cyclothiomethylation of amines with formaldehyde and H_2S. Recently [52] a detailed investigation was made of the liquid-phase condensation of aliphatic primary amines with various structures [*n*-butyl- (**a**), *n*-hexyl- (**b**), cyclohexyl- (**c**), and *n*-nonylamine (**d**)] with formaldehyde and H_2S in an aqueous medium in order to develop effective methods for the synthesis of 5-alkyl-1,3,5-dithiazinanes. Thus, it was established for the model cyclothiomethylation of *n*-hexylamine by formaldehyde and H_2S that the dithiazinanes **24a-d** are formed more effectively by method B at 80°C.



24a–d **25a** **26a** **27**

a R = *n*-Bu; **b** R = *n*-C_6H_{13}; **c** R = C_6H_{11}; **d** R = *n*-C_9H_{19}

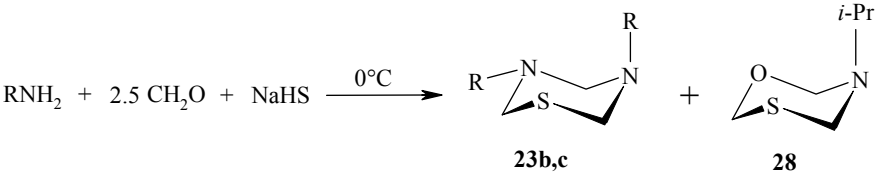
In addition to the dithiazinanes **24b** the reaction mixture contained formaldehyde thio- and semithioacetals **27**, which are intermediate products taking part in the cyclothiomethylation of the initial amines. Analogous thioacetals **27** were also obtained during the cyclothiomethylation of nonylamine.

It was established by chromato-mass spectrometry that oxathiazinane **25a** and dioxazinane **26a**, isolated in the individual form and characterized by the ^1H and ^{13}C NMR spectra, are formed from butylamine in this reaction [52].

The largest yield of the dithiazinanes can be obtained from *n*-butylamine and cyclohexylamine (33-43%). Least active in cyclothiomethylation were *n*-hexyl- and *n*-nonylamines, where the yields of the corresponding dithiazinanes were 10-36%. On the basis of the obtained data it was suggested that the yields of the dithiazinanes are affected by the mobility of the hydrogen atoms in the initial amines, i.e., the yield of the required heterocycles increases with decrease in the basicity of the amines.

The heterocyclization of *n*-cyclohexylamine with formaldehyde and NaHS by the method described above [17] also leads to the formation of the dithiazinane **24b** but with a smaller yield than with H_2S [52]. Thus, the synthesis of dithiazines in an aqueous medium based on aliphatic amines takes place successfully with a threefold molar excess of formaldehyde in relation to the initial amine at 80°C. Here it was found that the reactivity of the amines in cyclothiomethylation increases with decrease in their basicity.

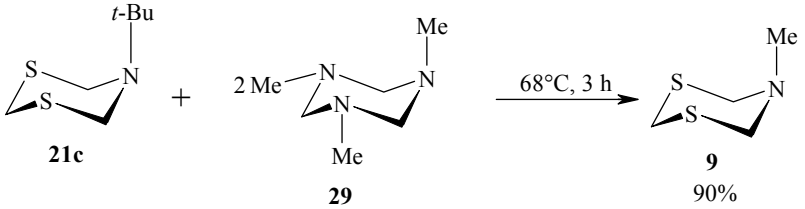
In contrast to aliphatic amines with linear structure, branched amines (*i*-$PrNH_2$, *t*-$BuNH_2$) form 1,3,5-thiadiazines **23b**,**c** with yields of 70-90% in reaction with formaldehyde and NaHS (0.8:2.5:1). In the case of *i*-$PrNH_2$ 1,3,5-oxathiazinane **28** was isolated in addition to 3,5-diisopropyl-1,3,5-thiadiazinane **23b** [53], and its content in the mixture amounted to ~20%.



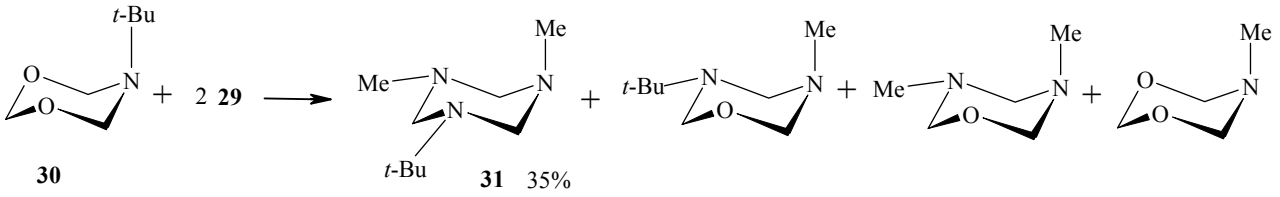
23b,c **28**

23 b R = *i*-Pr, **c** R = *t*-Bu

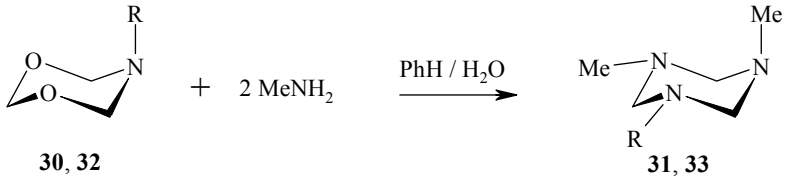
The same authors showed that the reaction of 5-*tert*-butyl-1,3,5-dithiazinane **21c** and 5-*tert*-butyl-1,3,5-dioxazinane **30** with 2 mol of 1,3,5-triazinane **29** leads to disproportionation, i.e., 5-methyl-1,3,5-dithiazinane **9** is formed from *tert*-butyldithiazinane with a yield of up to 90%, whereas *tert*-butyldioxazinane **30** is converted into a mixture of alkyl-substituted oxazinones. 5-*tert*-Butyl-1,3-dimethyl-1,3,5-triazinane **31** is formed preferentially under these conditions.



21c **29** **9** 90%



The treatment of isopropyl- and *tert*-butyl-1,3,5-oxazinanes with 2 mol of methylamine in the PhH/H_2O two-phase system gave 5-isopropyl(*tert*-butyl)-1,3-dimethyl-1,3,5-triazinanes **31** and **33** with yields of 87 and 70% respectively.

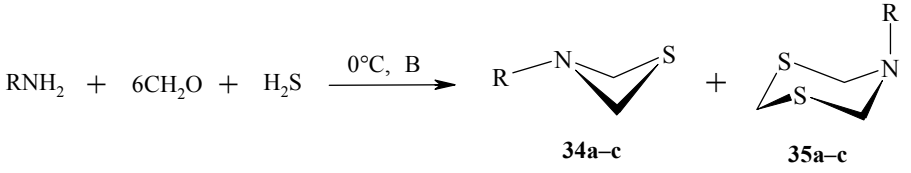


30, **31** R = *t*-Bu; **32**, **33** R = *i*-Pr; **31** 87%, **33** 70%

Analysis of the obtained results indicates that 1,3-thiazetidines **1** are formed preferentially during the cyclothiomethylation of aliphatic amines with formaldehyde and H_2S (NaHS) at 0°C with the initial reagents in ratios of 1:2:1 (methods A and B) and 1,5-dithia-3,7-diazacyclooctanes **4** are formed preferentially with the initial reagents in ratios of 1:(6-8):2; at temperatures between 20 and 80°C with ratios of 1:3:2 1,3,5-dithiazinanes are formed. The synthesis of 1,3,5-thiadiazinanes **3** can be realized during the cyclothiomethylation of lower amines ($MeNH_2$, $EtNH_2$, *i*-$PrNH_2$, and *t*-$BuNH_2$) at 0°C in an aqueous medium.

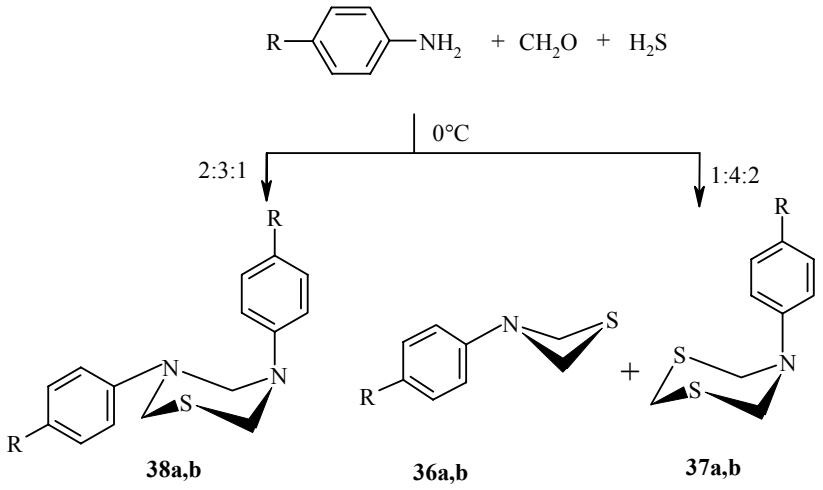
1.2. Reaction of Aromatic Amines with CH_2O and H_2S

According to [42-46] aromatic primary amines like aliphatic amines also enter readily into reaction with CH_2O and H_2S, giving the corresponding four-, six-, and eight-membered N,S-containing heterocycles with various structures. Thus, thiazetidines and dithiazinanes were obtained from benzyl-, *p*-anisyl-, and 2,4,6-trimethylphenylamines with formaldehyde and H_2S (1:6:2) by method B at 0°C [45].



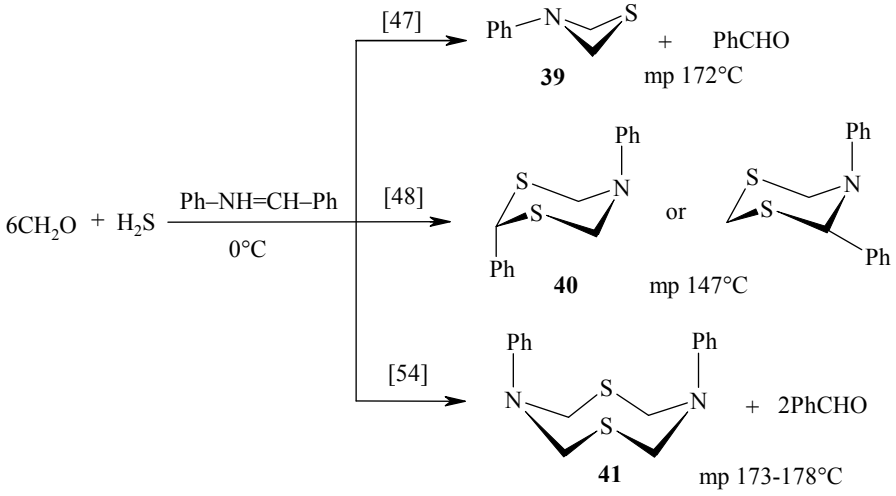
34, 35a R = $PhCH_2$, **b** R = 4-$MeOC_6H_4$, **c** R = 2,4,6-$Me_3C_6H_2$

In a continuation of these investigations based on *p*-phenetidine or *p*-chlorobenzylamine by method A a mixture of aromatic 1,3-thiazetidines **36a,b** and 1,3,5-dithiazines **37a**,**b** with various structures was obtained in the reaction with formaldehyde and H_2S (1:4:2) in ethanol solution at 0°C. The heterocycles **36a**,**b** and **37a**,**b** were isolated by fractional crystallization from ethanol. The 1,3,5-thiadiazinanes **38a**,**b** were obtained by a similar procedure with the initial reagents amine, CH_2O, and H_2S in ratios of 2:3:1. The synthesized N,S-containing heterocycles were patented as antimicrobial and fungicidal preparations [14].



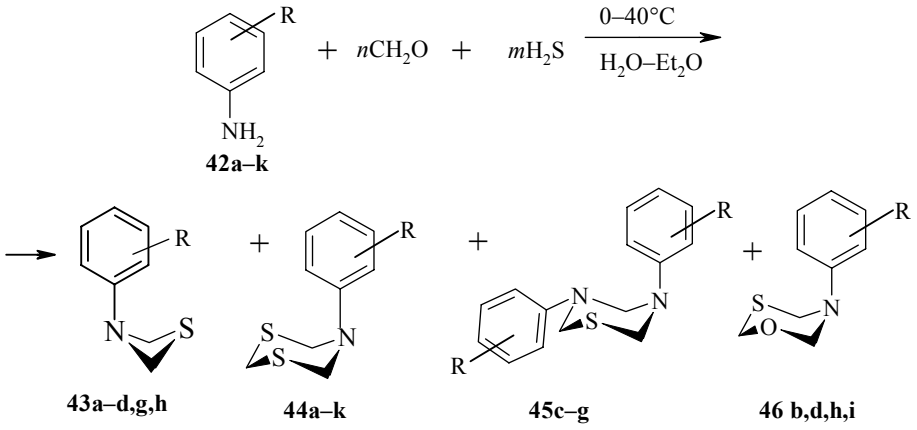
a R = Et, **b** R = Cl

Unfortunately, the published papers [46, 48, 49] give different results for the same aliphatic and aromatic amines in reaction with H_2S and CH_2O and also different structures for the obtained N,S-heterocycles. This makes it difficult to analyze and interpret the results obtained by these authors objectively. Thus, the production of 3-phenyl-1,3-thiazetidine **39** (mp 172°C) from benzylidenebenzylamine with CH_2O and H_2S was described in [47]. In [48] examples are given of the use of Schiff bases, including benzylidenebenzylamine, in condensation with H_2S and CH_2O with the production of 2(or 4),5-diphenyl-substituted 1,3,5-dithiazinanes **40**. Some time later [54] the symmetrical 3,7-diphenyl-1,5-diazacyclooctane **41** with the empirical formula $C_{16}H_{18}N_2S_2$ (mp 173-178°C, M_{ebull} = 308) and the same elemental composition as **39** was obtained under the same conditions.



In view of the discrepancy in the results of these works the authors of [55] attempted to study in detail the cyclothiomethylation of various aromatic amines with H_2S and CH_2O. The liquid-phase cyclothiomethylation of primary aromatic amines by the action of formaldehyde and H_2S was conducted in the water–diethyl ether two-phase system, which ensures the solubility of the formaldehyde and H_2S in the water

and the aromatic amines in the diethyl ether. The subjects of the investigation were aniline **42a**, *o*-, *m*-, and *p*-toluidines **42b**,**c**,**d**, *o*-, *m*-, and *p*-anisidines **42e-g**, *o*-phenetidine **42h**, *p*-xylidine **42i**, *p*-bromoaniline **42j**, *o*-iodoaniline **42k**, and α-naphthylamine **42l** [55]. It was established that the formation of compounds **43-46** is observed when hydrogen sulfide is bubbled through a solution of formaldehyde (in a molar ratio of 2:3) with the subsequent addition of a solution of the amine in diethyl ether to the reaction mixture according to method A at 0-40°C. The reaction takes with 90% conversion of the initial amines. The exceptions are α-naphthylamine **42l** and the *ortho*-substituted amines; thus, for example, the conversion amounts to 15% for α-naphthylamine, 40% for *o*-toluidine **42b**, 20% for *o*-anisidine **42e**, and 50% for *o*-phenetidine **42h**. As seen, the structure of the initial amines has a strong effect on the direction of heterocyclization, and this is probably due to the solubility and stereochemical structure of the aromatic bases. In the case of the *ortho*-substituted amines **42e**,**h** the decrease in activity may result from the formation of a hydrogen bond (the *ortho* effect).



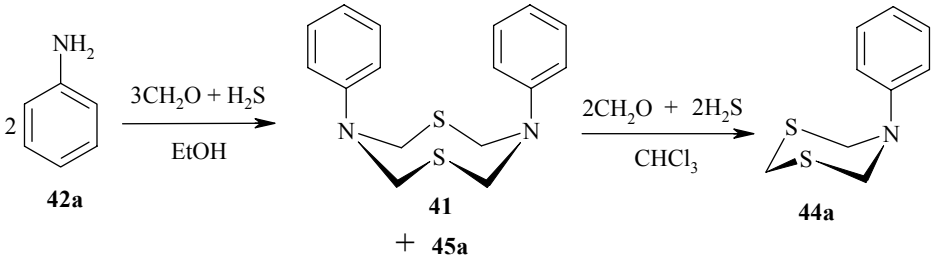
a R = H; **b** R = *o*-Me; **c** R = *m*-Me; **d** R = *p*-Me; **e** R = *o*-OMe; **f** R = *m*-OMe; **g** R = *p*-OMe; **h** R = *o*-OEt; **i** R = 2,5-Me_2; **j** R = *p*-Br; **k** R = *o*-I; *n* = 2, 6, *m* = 1, 2

In the case of the aniline **42a** at 20 and 40°C the dithiazinane **44a** is formed with a yield 40%, and in the case of the substituted anilines *m*-**42c**,**f** and *p*-**42d**,**g** a mixture of compounds **43**-**45** with a preference for **43c**,**g** and **44d**,**f** is obtained. As mentioned by the authors, the composition of the obtained heterocycles **43**-**45** depends on the structure of the initial amines, the ratio of the reagents, and the reaction temperature. For example, at 20-40°C with ratios 1:3:2 the dithiazinane **44b** and a minor amount of **43b** are mainly formed from *o*-toluidine **42b** while *m*-toluidine gives mainly the thiazetidines **43c**. The dithiazines **44** were obtained for all the above-mentioned anilines, while the thiadiazinanes **45** were obtained from *p*-toluidine **42d**. These results can probably be explained by the different mobility of the hydrogen atoms in the initial anilines. Thus, for example, the less basic *m*-toluidine **42c** forms the thiazetidine **43c** while the more basic *p*-toluidine **42d** forms the thiadiazinane **45d**. This agrees with known published data [56], according to which the rate of reaction of the toluidines with formaldehyde decreases in the order: *m*-toluidine > *o*-toluidine > *p*-toluidine. The heterocycle **46** was only obtained in the experiments on the cyclothiomethylation of *o*-toluidine **42b**, *p*-toluidine **42d**, *p*-xylidine **42i**, and *o*-phenetidine **42h**, and its yield was not greater than ~6%.

On the basis of the experimental data the authors established that the cyclothiomethylation of aromatic amines takes place more effectively than that of aliphatic amines as a result of their weaker basicity arising from the conjugation between the free pair of electrons at the nitrogen atom and the π-electrons of the aromatic ring (*p*, π-conjugation). As a result a mixture of thiazetidines, dithiazinanes, and thiadiazinanes is formed. The formation of 1,3,5-dithiazinanes is characteristic of all the anilines described above.

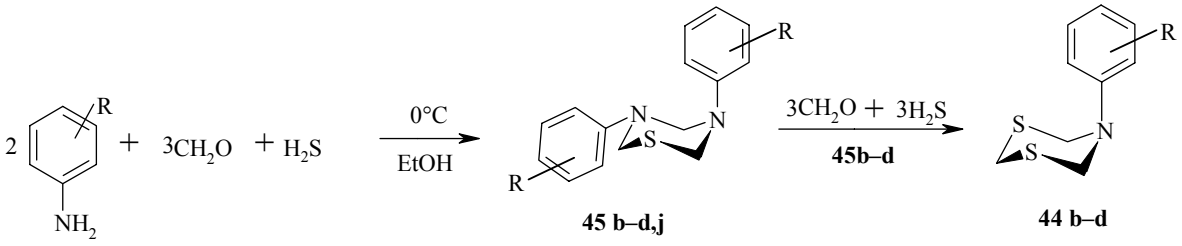
It is known that N-alkyl-substituted thiadiazinanes are unstable compounds and readily disproportionate with the formation of dithiazinanes [45, 57, 58], whereas aryl-substituted thiadiazinanes are stable products [55].

It can be supposed that a regioselective synthesis of N-aryl-1,3,5-thiadiazinanes is possible on the basis of aromatic amines. During study of the effect of the nature of the solvent on the direction of cyclothiomethylation of aromatic amines at 0°C it was established that aniline with formaldehyde and H_2S (2:3:1) in EtOH–H_2O at 0°C forms 1,5-dithia-3,7-diazacyclooctane **41** and a smaller amount of the thiazinane **45a** with yields of ~80 and 10%, whereas *o*-, *m*-, and *p*-toluidines and *p*-bromoaniline tend to form mostly 1,3,5-thiadizaninanes **45b-d**,**j** under these conditions. The authors of this review found that the obtained heterocycles **41** and **45b-d** disproportionate under the influence of formaldehyde and H_2S in $CHCl_3$ solution after 6-12 h into the corresponding N-aryl-substituted 1,3,5-dithiazinanes with yields of ~60-70%. At the same time the synthesis of the latter by method A (amine–CH_2O–H_2S, 1:3:2, 20-30°C) is accompanied by the formation of heterocyclic side products – thiazetidines **43a-d**,**g**,**h** and thiadiazinanes **45a-g** depending on the structure of the employed aniline. It should be noted that the formation of the molecules of the dithiazinanes **44b-d** from the thiadiazinanes **45b-d** under the conditions of cyclothiomethylation requires more time since the latter are more stable compounds than 1,5-dithia-3,7-diazacyclooctane **41**.



42a **41** + **45a** **44a**

The obtained results indicate that for the majority of dithiazinanes synthesized by the cyclothiomethylation of aromatic amines with formaldehyde and H_2S in an aqueous medium this reaction takes place nonselectively and a mixture of thiazetidines, thiadiazinanes, and oxathiazinanes is formed, whereas increased regioselectivity is observed in the EtOH–H_2O medium. Thus, *o*- and *p*-nitroanilines react with CH_2O and H_2S in ratios of 1:3:2 (20°C) by method A with the formation of only 1,3,5-dithiazinanes, while *m*-nitroaniline reacts with the formation of a mixture of 1,3,5-dithiazinane and 3,7-di-1,5-dithiacyclooctane (5:1). Consequently, the structural features of the initial aromatic amines also affect the reaction.



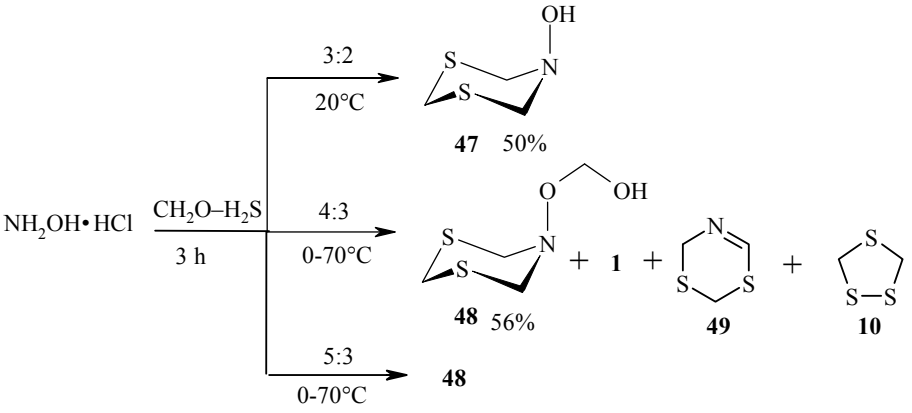
42 b–d,j **45 b–d,j** **44 b–d**

It is perfectly clear that for further development of the chemistry and technology of aryl-substituted nitrogen- and sulfur-containing heterocycles, which are of interest as photochromic and photosensitive materials, it is extremely important to look for regioselective methods for construction of the heterocycles on the basis of the cyclothiomethylation of aromatic amines with formaldehyde and H_2S.

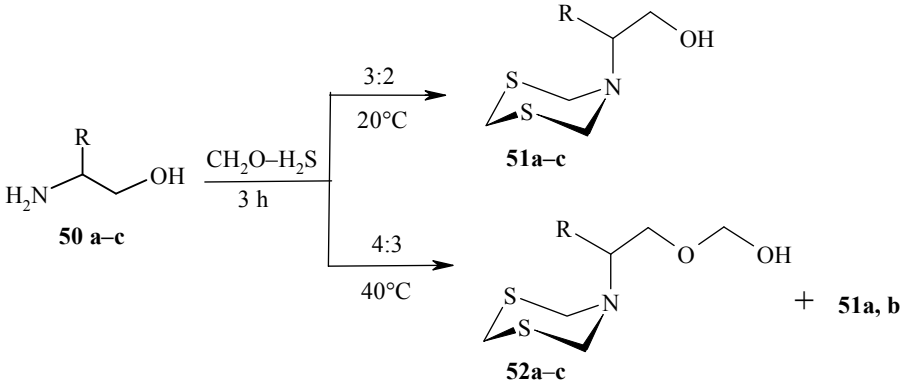
2.1. Aliphatic Amino Alcohols in Cyclothiomethylation with H_2S and CH_2O

The authors of [59] suggested that the introduction of hydroxyl groups into the molecules of the primary amines would promote increase in the mobility of the hydrogen atoms of the NH_2 groups, which could lead to an increase of the activity of the latter in cyclothiomethylation.

Thus, for example, hydroxylamine reacts with formaldehyde giving 1,3,5-trihydroxy-1,3 5-triazinane exclusively [60]. In the reaction of hydroxylamine with CH_2O and H_2S in ratios of 1:2:1 at 20°C 5-hydroxy-1,3,5-dithiazinane (**47**) is formed with a ~31% yield. Under conditions with the stoichiometric ratio of the reaction components NH_2OH–CH_2O–H_2S, 1:3:2, at temperatures between 20 and 70 °C the yield of the dithiazinane **47** amounts to ~50%. If the concentration of the thiomethylating mixture NH_2OH–CH_2O–H_2S in the reaction is increased, 1:4:3, (1,3,5-dithiazinan-5-yloxy)methanol (**48**) is formed preferentially with a yield of ~56%. It must be assumed that the compounds **48** are formed under the selected conditions by successive oxy- and thiomethylation of hydroxylamine initially at the amino group and then at the hydroxyl group. In these experiments 4H-1,3,5-dithiazinane (**49**) (~3%) and 1,2,4-trithiolane **10** (~2%) were detected as side products. Further increase in the concentration of the thiomethylating mixture (CH_2O–H_2S, 5:3) leads to the predominant formation of compound **48**.

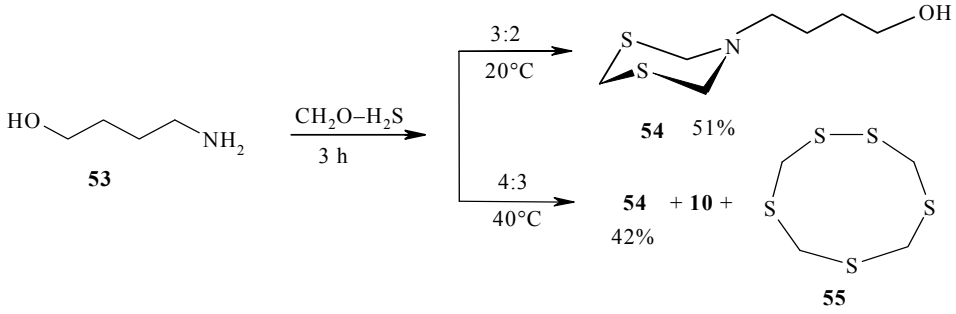


During the cyclothiomethylation of monoethanolamine **50a**, R-(−)-2-aminobutanol **50b**, and 2-amino-3-hydroxypropionic acid with CH_2O and H_2S in a ratio of 3:2 in relation to the initial amino alcohol the corresponding dithiazinanes **51a-c** are formed with yields of 56-73%. If the concentration of CH_2O and H_2S is increased (amine–CH_2O–H_2S, 1:4:3), as in the experiments with hydroxylamine, oxymethylation of the 2-amino alcohols at the hydroxyl group is observed, leading to [2-(1,3,5-dithiazinan-5-yl)ethoxy]methanol (**52a**) (18%) and **51a**, (*R*)-[2-(1,3,5-dithiazinan-5-yl)butoxy]methanol (**52b**) (52%) and **51b**, and 2-(1,3,5-dithiazinan-5-yl)-3-(hydroxymethoxy)propionic acid **52c** (64%).



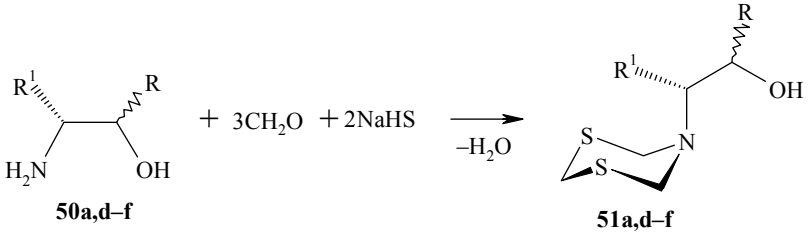
a R = H, **b** R = Et, **c** R = COOH

The cyclothiomethylation of 4-aminobutanol **53** with formaldehyde and hydrogen sulfide (1:4:3) gives 4-(1,3,5-dithiazinan-5-yl)-1-butanol (**54**) with a yield of ~42% and small amounts of the products from the condensation of CH_2O and H_2S–1,2,4-trithiolane **10** and 1,2,4,6,8-pentathiononane (**55**) – the contents of which in the reaction mixture amount to 5 and 3% respectively.

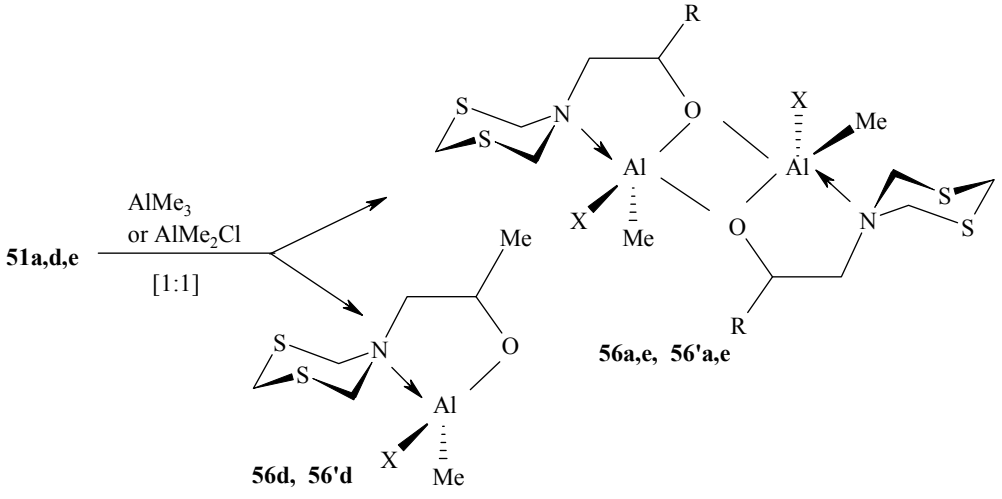


It should be noted that in all the experiments the authors did not observe the formation of products from intramolecular cyclization during cyclothiomethylation, although there are examples in the literature [61-64] of the condensation of 2-amino alcohols with CH_2O to 1,3-oxazolidines. This is apparently due to the fact that the amino group in the amino alcohols is more nucleophilic than the hydroxyl group and the reaction with CH_2O and H_2S takes place in stages, i.e., initially at the NH_2 group with the formation of the dithiazines **51a-c**, and subsequent oxymethylation of the obtained N-hydroxyalkyldithiazines by an excess of CH_2O leads to the corresponding 1,3,5-dithiazinan-5-ylalkoxymethanols **52a-c**.

A report on the possibility of cyclothiomethylation of ethanolamine with CH_2O and H_2S to dithiazinane first appeared in 1964 [12]. As mentioned by the authors, the obtained heterocycles are of interest as sorbents for gold and silver. The method was used for the production of dithiazinanes **51a**,**d-f** [65, 66], which gave stable complexes **56a**,**d**,**e**) with Lewis acids.

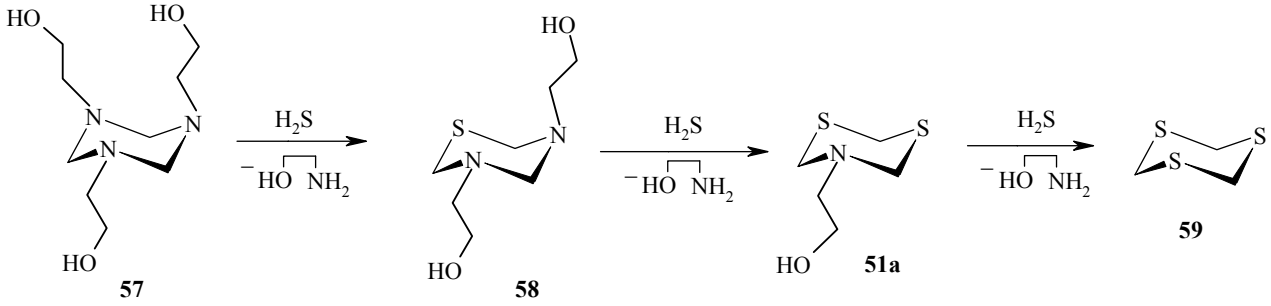


50, 51a R = H, R^1 = H, **d** R = Me, R^1 = H, **e** R = Ph, R^1 = H, **f** R = Ph, R^1 = Me



56a R = H, **e** R = Ph, **a,d,e** X = Me; **56'a** R = H, **e** R = Ph, **a,d,e** X = Cl

The reaction of 1,3,5-*tris*-(2-hydroxyethyl)-*s*-triazinane **57**, synthesized from ethanolamine and formaldehyde, with H_2S (method B) gave 1,3,5-thiadiazinane **58** and 1,3,5-dithiazinane **51a**, which were converted into trithiane **59** in reaction with an excess of H_2S [67].



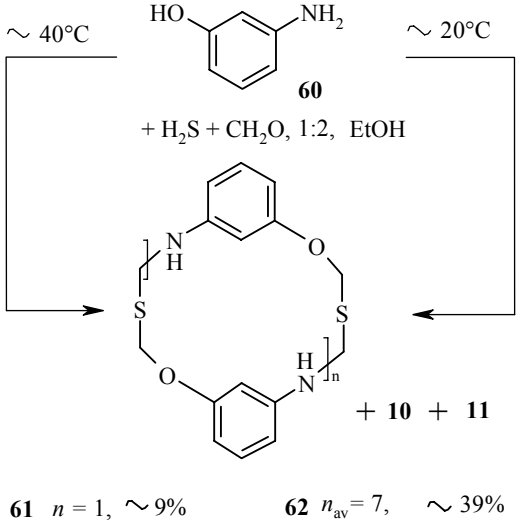
2-Hydroxy-1-(dithiazinan-5-yl)ethane (**51a**) was patented [68] as an effective agent for the suppression of the growth of sulfate-reducing bacteria in various industrial media used in the petroleum industry.

Thus, the use of the cyclothiomethylation of various amino alcohols with H_2S and CH_2O both by method A and by method B opens up a promising and effective path to the synthesis of previously difficult-to-obtain hydroxy-containing 1,3,5-dithiazinanes.

2.2. Aminophenols in Cyclothiomethylation

According to published data [69] the aminomethylation of the simplest phenols takes place in the aromatic ring with the formation of aminomethyl derivatives. In [70] it was noticed that in contrast to aromatic amines and phenols the direction of thiomethylation of aminophenols is determined by the structure of the latter.

Thus, for example, reaction of *m*-aminophenol **60** with H_2S and CH_2O in ratios of 1:2:2 (95% ethanol, 3 h, ~40°C) leads to the formation of a mixture of cyclic sulfides consisting of 1,2,4-trithiolane **10**, 1,2,4,6-tetrathiepane **11**, and the sulfur-containing macrocyclic heterocycle **61** with an overall yield of ~40% [70].



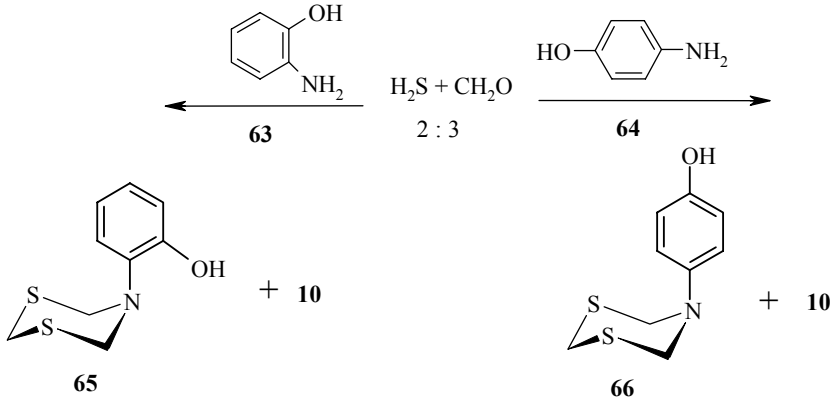
61 n = 1, ~9% **62** n_{av} = 7, ~39%

The structure of 2,12-dioxa-4,14-dithia-6,16-diazatricyclo[15.3.1.1^{7,11}]docosa-1(20),7(22),8,10,17(21),18-hexaene was presented for compound **61** on the basis of data from the ^{1}H and ^{13}C NMR spectra.

It was found that the overall yield of **61** increases with increase in the concentration of the initial reagents, i.e., *m*-aminophenol, CH_2O, and H_2S (1:2:2), in solution in 95% ethanol; in these experiments, however, a mixture of the macrocyclic heteroatomic compounds **62**, which contain two or more aminophenol residues (M_{cr}^{12} = 1333 ± 10, numerical mean of the degree of cyclooligocondensation ~8) is formed together with compound **61**. Here the solubility of the obtained macroheterocycles in the organic solvents is greatly reduced, and this complicates the purification and isolation of these compounds of unique structure.

During the condensation of **60** with CH_2O and H_2S in ratios of 1:3:2 the formation of poorly soluble oligomers extremely difficult to identify is observed.

Unlike *m*-aminophenol the *o*- and *p*-isomers enter into multicomponent condensation with CH_2O and H_2S giving the corresponding dithiazinanes – 2-[1,3,5-dithiazinan-5-yl]phenol (**65**) and 4-[1,3,5-dithiazinan-5-yl]phenol (**66**) – with yields of 86 and 71% respectively.

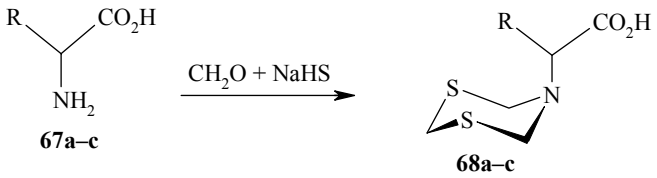


It should be noted that the synthesis of *p*-dithiazinylphenol **66** by the cyclothiomethylation of *p*-aminophenol **64** with CH_2O and NaHS has been described in the literature [12], but the authors did not give the physicochemical characteristics of the compound.

Thus, the direction of the cyclocondensation of the isomeric aminophenols with formaldehyde and H_2S depends on the positions of the functional groups in the aromatic ring and on their mutual influence. As found, of the three aminophenols only the *m* isomer , which has the NH_2 group with the lowest basicity and the OH group with the highest acidity, undergoes condensation at both functional groups simultaneously giving the macroheterocycles, and this opens up a simple and original path to the construction of new classes of nitrogen- and sulfur-containing macroheterocycles with various structures [71].

3.1. Cyclothiomethylation of Aliphatic Amino Acids

The cyclothiomethylation of the simplest aliphatic amino acids with NaHS and CH_2O was first realized with satisfactory yields in [12] with the formation of the corresponding 1,3,5-dithiazinanylcarboxylic acids **68**.



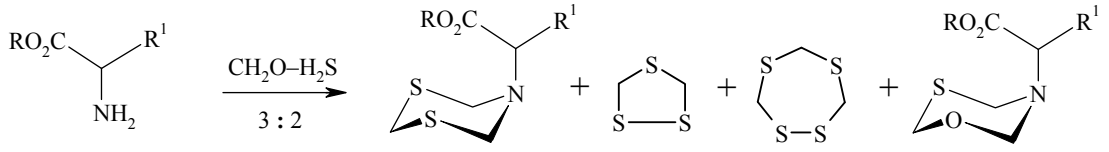
a R = H, **b** R = Me, **c** R = CH_2OH

Almost 40 years later during the development of investigations into the cyclothiomethylation of compounds of various types containing active primary amino groups the authors of [72] attempted to extend the multicomponent condensation of amines with CH_2O and H_2S to amino acids and their derivatives with the aim of developing effective preparative methods for the synthesis of dithiazinanecarboxylic acids with high yields.

To develop optimum conditions for the production of 1,3,5-dithiazinecarboxylic acids with high yields on the basis of the CH_2O–H_2S reagent, excluding the formation of acyclic thioesters, the model reaction of glycine with CH_2O and H_2S was studied [73]. Here the effect of the concentration of the initial reagents, the order of mixing, and the reaction temperature on the overall yield and composition of the products was investigated.

It was established that the largest yield of (1,3,5-dithiazinan-5-yl)acetic acid **68a** was obtained with the addition of glycine **67a** to an aqueous solution of formaldehyde that had been previously saturated with H_2S with the amino acid, formaldehyde, and H_2S in ratios of 1:3:2 (method A). In addition to the desired heterocycle **68a** (58%) 1,2,4-trithiolane **10** and 1,2,4,6-tetrathiepane **11** were formed with yields of 4 and 11% respectively.

Derivatives of glycine–the potassium salt **69** and the methyl ester **70** – were also brought into heterocyclization with a mixture of formaldehyde and H_2S under the developed conditions [73].



67a–h, 69, 70 **71a–h, 72** **10** **11** **73b–d**

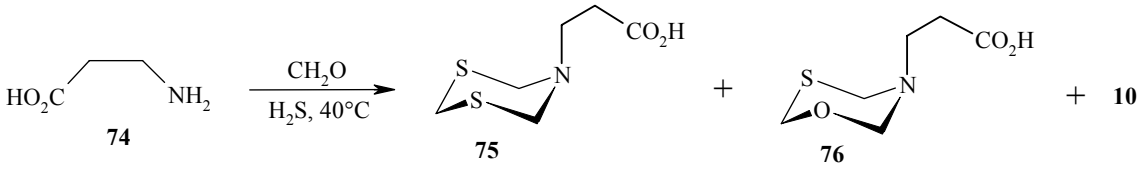
67, **71**, **73** R = H; **69**, **71** R = K; **70**, **72** R = Me; **67**, **71a** R^1 = H; **67, 71, 73b** R^1 = Et, **c** R^1 = *i*-Pr;
d R = CH_2OH; **67**, **71** **e** R = CH_2COOH, **f** R = CH_2CH_2COOH, **g** R = CH_2Ph, **h** R = CH_2SH

During the cyclothiomethylation of potassium glycinate **69**, methyl glycinate **70**, and its hydrochloride only the dithiazinane-substituted glycinates **71a** and **72** were formed but with lower yields (~23%). The free amino acid **67a**, which exists in the form of an intramolecular salt in aqueous solutions, probably dissolves better in water than its derivatives **69** and **70**, securing its more complete involvement in the reaction and, consequently, a higher yield of the heterocyclization product **71a**.

The cyclothiomethylation of substituted amino acids **67b-h** under the developed conditions leads to the formation of oxathiazinanes **73b-d** in addition to the dithiazinanes **71b-h**. The exceptions are α-aminosuccinic **67e** and α-aminoglutaric **67f** acids, for which the formation of only dithiazinanes **71e**,**f** with yields of 89 and 52% respectively is observed.

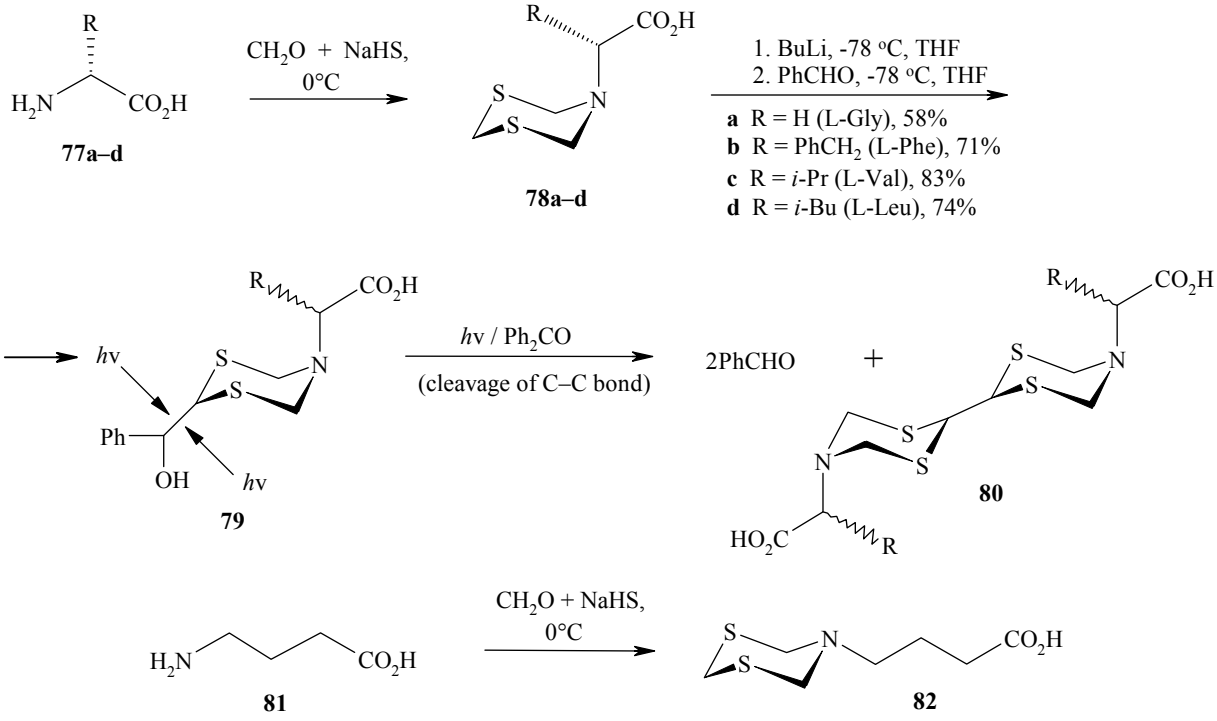
Cysteine **67h** and β-aminopropionic acid **74** entered into cyclothiomethylation with low degrees of conversion, and the yields of the dithiazinanes **71h** and **75** amounted to 11 and 13% respectively. In the case of β-aminopropionic acid **74** increase in the cyclothiomethylation temperature to 40°C leads to the formation of the oxathiazinane **76** (12%) in addition to the dithiazinane **75** (41%). The reactivity of the initial amino acids is affected substantially by the mobility of the hydrogen atoms of the amino group in the initial amino acids. The higher mobility of the hydrogen atoms attached to the nitrogen atoms in the initial amino acids compared with aliphatic primary amines is probably due to steric factors – a feature of the molecular configuration of the amino acids in which the nitrogen atom projects from the plane of the remainder of the molecule (by 0.26 Å for glycine **67a**) and there is an increase in the interatomic C–N distance compared with the generally accepted standards for the lengths of the corresponding covalent bonds [74]. In addition the carboxyl group and the aromatic ring reduce the basicity of the α-amino group, leading to an increase in the mobility of the hydrogen atoms. The most active in cyclothiomethylation are the aminodicarboxylic acids **67e**,**f**, phenylalanine **67g**, and

glycine **67a**. The decrease of the mobility of the hydrogen atoms in β-aminopropionic acid **74** can be explained by the smaller effect of the more distant carboxyl group on the basicity of the nitrogen atom. Concerning the low reactivity of the cysteine **67h** it can be supposed that the initial amino acid is transformed under the reaction conditions into cysteine [75], in which there is a decrease in the length of the C–N bond leading to change in the mobility of the hydrogen atoms in the amino group.



As known, nitrogen- and sulfur-containing heterocycles are widely used for the extraction and purification of precious metals such as silver and gold. The recovery of small concentrations of silver from the waste products of photo and cine materials is problematic since the silver-containing colloidal solutions in the form of a multicomponent mixture form difficultly extracted complexes of silver. For the realization of the most effective reagents in industry 1,3,5-dithiazinan-5-ylacetic acid (**71a**), the capacity of which amounts to 0.9g/g, was used as sorbent for the recovery of silver from the waste products of the photo and cine industry [73]. It was also established [76] that N-substituted dithiazine **71a** are promising as biocides – special reagents for suppressing the activity of sulfate-reducing bacteria in various industrial materials. The starting material **71a** is nontoxic, inhibits corrosion, and has low solubility in petroleum, surpassing in many respects the well known reagent "Don" widely used in oil production [77].

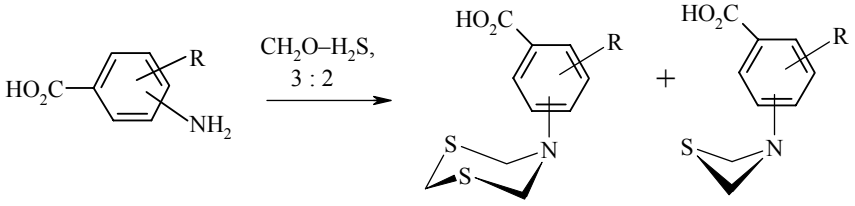
The synthesis of 2-substituted 1,3,5-dithiazinan-5-ylcarboxylic acids **78a-d** and **82** by the reaction of NaHS with formaldehyde and amino acids **77a-d** and **81** at 0°C was described in [76]. By successive treatment of the obtained acids **77a-d** and **81** with *n*-BuLi and benzaldehyde in THF at -78°C it is possible to insert a (hydroxy)benzyl group into the dithiazinane molecule. These compounds are of interest as biological photosensitive "locks" that link various molecular blocks and release them during photoirradiation.



3.2. Aromatic Amino Acids and Their Derivatives in Cyclothiomethylation

According to data from the authors of [72, 73, 78], aromatic acids and their esters have been used in cyclothiomethylation in addition to aliphatic amino acids. In particular, *o*- and *p*-aminobenzoic acids (**83a** and **83b**), 4- and 5-aminosalicylic acids (**83c** and **83d**), and ethyl (**86e**) and β-diethylaminoethyl (**86f**) *p*-aminobenzoates were chosen as subjects for investigation [78]. In the case of *o*- and *p*-aminobenzoic acids (**83a** and **83b**) and 4- and 5-aminosalicylic acids (**83c** and **83d**) the effect of the position of the COOH group in the aromatic ring on the activity of the NH_2 and OH groups in cyclothiomethylation was studied.

Thus, the condensation of *o*-aminobenzoic acid **83a** with CH_2O and H_2S in ratios of 1:3:2 leads exclusively to *o*-(1,3,5-dithiazinan-5-yl)benzoic acid **84a** with a yield of 61%, while *p*-aminobenzoic acid **83b** under these conditions forms a mixture of *p*-(1,3,5-dithiazinan-5-yl)- and *p*-(1,3-thiazetidin-3-yl)benzoic acids **84b** and **85b** with yields of 51 and 34% respectively. At 60°C the dithiazinanes **84** is formed selectively with a yield of ~95%.



83a–d **84a–d** **85b,d**

a,**b** R = H; **c**,**d** R = 2-OH; position of NH_2: **a** R = 2-NH_2, **b**,**c** R = 4-NH_2, **d** R = 5-NH_2

Like the amino acid **83a**, 4-aminosalicylic acid **83c** reacts with CH_2O and H_2S with the exclusive formation of 4-(1,3,5-dithiazinan-5-yl)-2-hydroxybenzoic acid (**84c**) with a yield of ~89%, while 5-amino-salicyclic acid gives a mixture of 5-(1,3,5-dithiazinan-5-yl)-2-hydroxybenzoic and 5-(1,3-thiazetidin-3-yl)-2-hydroxybenzoic acids **84d** and **85d** with yields of 32 and 22% respectively.

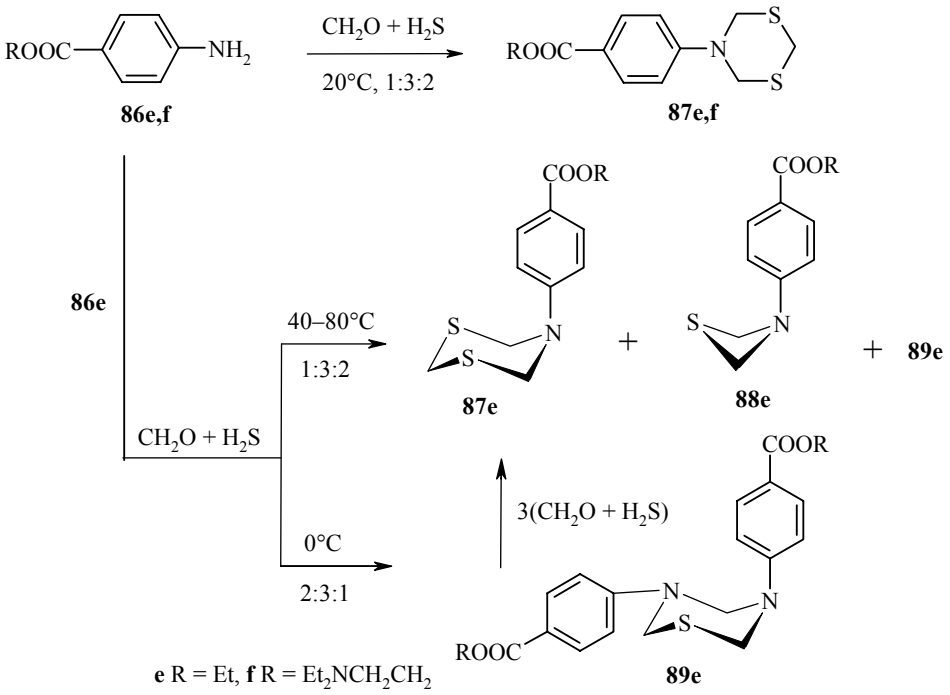
As seen, as for the aminophenols the direction of cyclothiomethylation of the isomeric aromatic amino acids with CH_2O and H_2S depends on the positions of the functional groups (OH, COOH) in the aromatic ring and on their mutual effects.

The heterocycle **84a** was obtained earlier [12] with an 81% yield by the cyclocondensation of **83a** with NaHS and CH_2O, for which there are no physicochemical data.

The reaction of ethyl (**86e**) or β-diethylaminoethyl (**86f**) *p*-aminobenzoate with CH_2O and H_2S in ratios of 1:3:2 at 20°C gave the dithiazinanes **87e**,**f**. During the cyclothiomethylation of the amino ester **86e** at 40-80°C ethyl 4-(1,3-thiazetidin-3-yl)benzoate (**88e**) and 3,5-di(4-ethoxycarbonylphenyl)-1,3,5-thia-diazinane **89e** were obtained together with ethyl 4-(1,3,5-dithiazinan-5-yl)benzoate (**87a**) with yields of 18, 15, and 56% respectively; the compounds were separated by column chromatography and were identified by spectroscopic methods.

In the course of investigation of the cyclothiomethylation of aromatic amino acids and their derivatives the authors of [78] found that by changing the ratio of the initial reagents it is possible to direct the reaction toward intermolecular condensation, i.e., two molecules of the initial amino acid with CH_2O and H_2S.

Thus, in the reaction of the esters of *p*-aminobenzoic acids with the thiomethylating mixture CH_2O–H_2S in amine–CH_2O–H_2S ratios of 2:3:1 the main reaction product is **89e** (93%), which is converted completely into the corresponding dithiazine **87e** by the action of a three-mole excess of the CH_2O–H_2S thiomethylating mixture at room temperature; this opens up a promising path to the synthesis of N-substituted bifunctional monomers for the production of new polymeric materials, sorbents, extractants, and water-soluble biologically active compounds.



Thus, aromatic amino acids and their derivatives react with CH_2O and H_2S at the NH_2 group. Substituents at the *p*-position (COOH and COOR) lead to an increase in the activity of the amino groups, and this leads to an increase in the yield of the 1,3,5-dithiazinanes.

Analysis of the published data shows that the cyclothiomethylation of acyclic and cyclic aliphatic, aromatic, and heteroatom-containing primary amines with CH_2O and H_2S is one of the most promising and preparatively convenient methods for the synthesis of tetra-, hexa-, and macrocyclic N,S-containing heterocycles – thiazetidines, dithiazinanes, and thiadiazinanes and their derivatives.

The availability of the initial compounds and the possibility of a one-pot synthesis of these types of organic compounds in an aqueous or aqueous-organic medium make the method extremely effective for the creation of contemporary ecologically balanced technologies for the production of a wide range of useful substances and materials.

These investigations are at an early stage of development, and further new and unexpected results can be expected.

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