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SYNTHESIS OF THIAMONO- AND THIABICYCLANES FROM SODIUM SULFIDE AND METHANETHIOLATE

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1-[5-Acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone was obtained by the interaction of sodium sulfide and sodium methanethiolate with formaldehyde and acetone. The intramolecular crotonate condensation of the product leads to 4-methyl-1-methylthiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one. The participation of 3-methylthiomethyl-3-buten-2-one in the formation of a thiamonocyclane is clarified. A probable scheme for the conversions is proposed.

Keywords: 1-[5-acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone, 4-methyl-1-methylthiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one, sodium methanethiolate, sodium sulfide, condensation.

In recent years methods have been developed for obtaining aliphatic and alicyclic γ-keto, γ,γ'-diketo, bissulfides, thiamono-, and thiabicyclanes [1-3] by the alkylthiomethylation of ketones using sodium sulfide and/or thiolate of alkaline sulfide solutions (ASS) from gas or oil refining operations as sulfur-containing reagents.

In the present work the four-component condensation of acetone with formaldehyde and sodium sulfide and methanethiolate present in ASS has been studied. The effect of reaction conditions on the composition and yield of the products obtained has been investigated.

The condensation of sodium sulfide and methanethiolate of ASS with a twofold excess of formaldehyde and acetone at 20°C leads after 10 min to 1-[5-acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone (**1**) in 78% yield (on sodium sulfide). The yield of thiamonocyclane **1** grows on increasing the consumption of formaldehyde (Table 1, expt. Nos.1-4) and the content of sodium sulfide in ASS (expt. Nos. 3, 5, 6). An increase in the duration of the reaction aids a reduction in the content of thiamonocyclane **1** due to its conversion into 4-methyl-1-methyl-thiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one (**2**), described by us previously in [4], the amount of which in the reaction mixture was 32% after 1 h. Complete conversion of compound **1** into **2** was reached after 13 h at 50-60°C.

The alkylthiomethylation of acetone by formaldehyde and sodium methanethiolate, leading to 5-thiahexan-2-one **3** and 1,1-bis(methylthiomethyl)propan-2-one **4** occurs in addition to the formation of thiamono- and thiabicyclanes **1** and **2**. Depending on the concentration of sodium methanethiolate in ASS the yield of γ-keto sulfides **3** and **4** was 3-6 and 32-52% (10 min, 20°C) respectively. 3-Methylthiomethyl-3-buten-2-one (**5**) was detected in the reaction mixture with the aid of IR spectroscopy and GLC.

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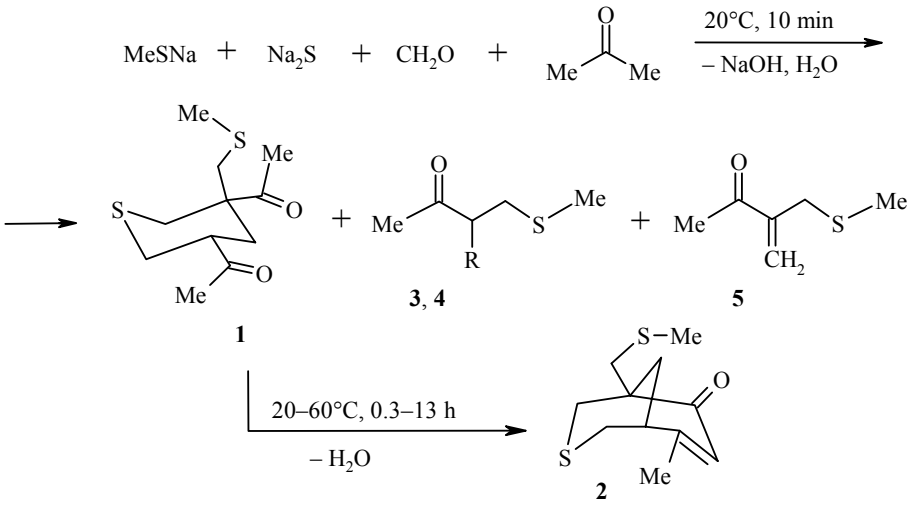


3 R = H, **4** R = CH_2SMe

According to GLC data, after 3 min reaction 32% compound **5**, 36% compound **1**, and 26% compound **4** are formed (Fig.1). After 10 min the content of sulfide **5** is reduced due to conversion into compounds **1** and **4**, the amounts of which grew to 53 and 36% respectively. After 20 min a fall in thiamonocyclane **1** content (to 45%) was observed as well as the appearance of compound **2** (13%).

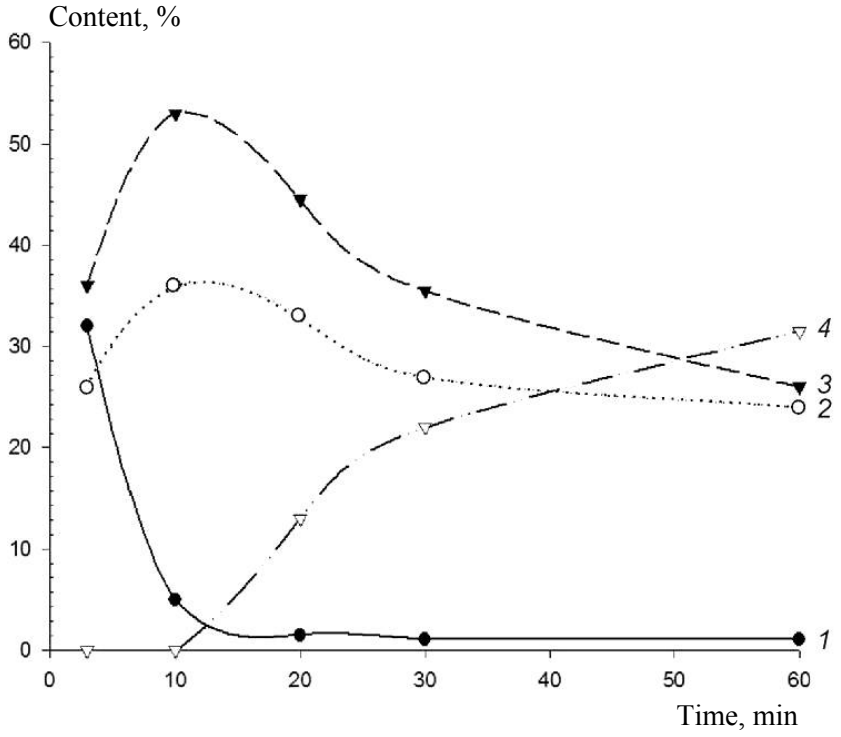
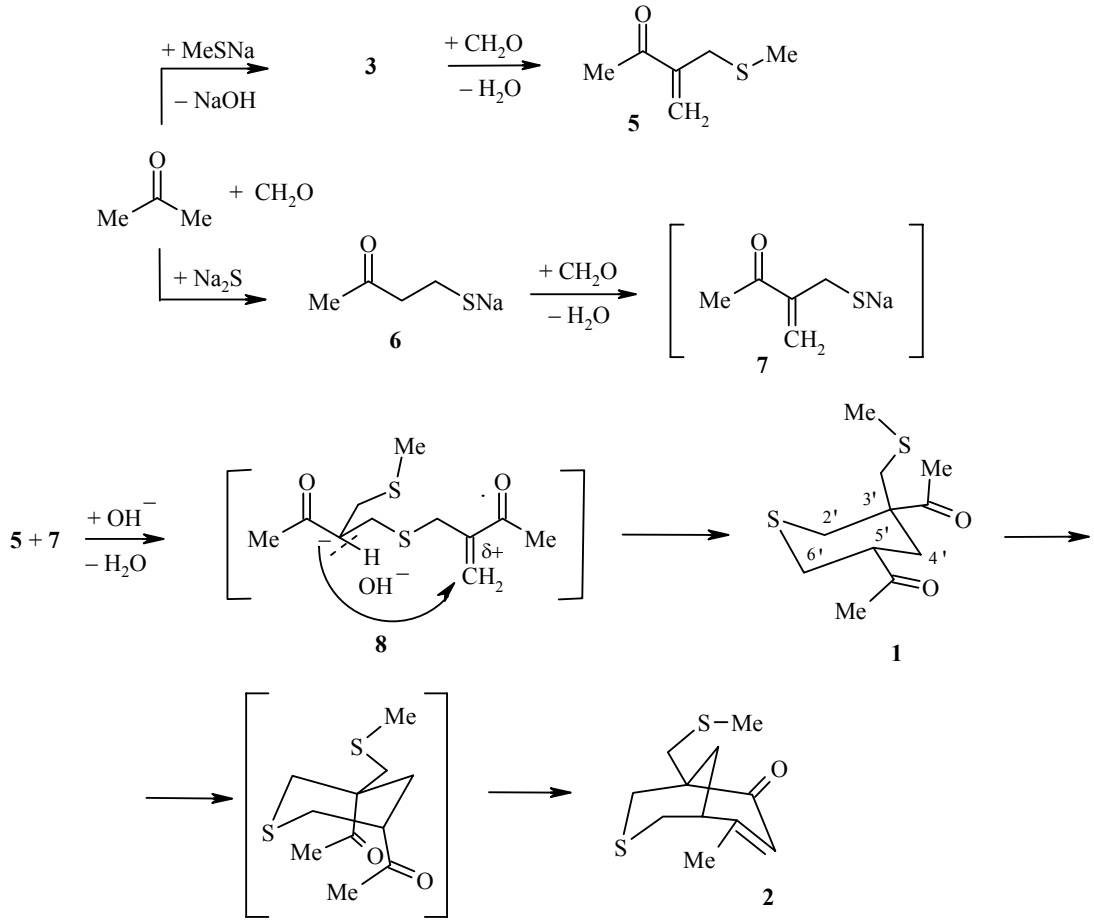


Fig. 1. Dependence of reaction product content on time for the interaction of sodium sulfide and methanethiolate with formaldehyde and acetone (conditions of expt. 3, see Table 1); 1 – 3-methylthiomethyl-3-buten-2-one (**5**); *2* – 1,1-bis(methylthiomethyl)propan-2-one (**4**), *3* – 1-[5-acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone (**1**); *4* – 4-methyl-1-methylthiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one (**2**).

The obtained data permit the following scheme to be proposed for the formation of thiamono- and thiabicyclanes **1** and **2**. Initially alkylthiomethylation of acetone by formaldehyde, sodium methanethiolate, and sulfide occurs with the formation of 5-thiahexan-2-one (**3**) and sodium 3-oxo-butanethiolate (**6**), the subsequent condensation of which with formaldehyde leads to 3-methylthiomethyl-3-buten-2-one (**5**) and sodium 2-acetyl-2-propene-1-thiolate (**7**), respectively. The thiolate anion **7** is then added to the multiple bond of ketoallylsulfide **5** with the formation of 3-(2-methylthiomethyl-3-oxobutylthiomethyl)-3-buten-2-one (**8**), which is cyclized intramolecularly according to Michael into compound **1**. In the subsequent stage an intramolecular crotonate condensation of thiamonocyclane **1** occurs leading to thiabicyclane **2**.



The formation of sodium butanethiolate **6**, the intermediate product of the alkylthiomethylation of acetone with formaldehyde and sodium sulfide was confirmed by the appearance of a potential discontinuity, characteristic for thiols [6], of -400 to +100 mV in the potentiometric argentometric titration curve of the reaction mixture.

The composition and structure of compounds **1-5** were confirmed by elemental analysis and data of spectral investigations. The physicochemical constants and spectral characteristics of compounds **2-4** and **5** correspond with those published in [4] and [5]. In the ^{1}H NMR spectrum of thiamonocyclane **1,** together with signals for the protons of methine and methylene groups of the ring, singlet signals were observed for protons of thiomethyl (2.11 ppm) and two acetyl (2.21 and 2.31 ppm) groups, the carbonyl carbons of which correspond to signals at 209.17 and 209.61 ppm in the ^{13}C NMR spectra. In the ^{1}H NMR spectrum a doublet of doublets and a

TABLE 1. Condensation of Sodium Sulfide and Methanethiolate in ASS with Formaldehyde and Acetone (20°C, 10 min)

Experiment	Sulfur content of SAS, wt. %		Molar ratio CH_2O:ketone per mol sulfur	Extent of sulfur conversion, %		Compound **1** content in mixture, %	Yield on sodium sulfide, %
	Sulfide	Thiolate		Sulfide	Thiolate		
1	1.90	5.27	1.3:1.3	70	84	42	43
2	1.90	5.27	1.5:1.3	89	84	51	56
3	1.90	5.27	2:2	99	95	58	78
4	1.90	5.27	2.2:2	100	96	68	89
5	2.17	4.14	2:2	99	97	64	85
6	2.61	2.69	2:2	99	94	73	91

triplet of triplets at 1.19 and 2.85 ppm belong to the H-4' and H-6' protons respectively. Values of the coupling constants correspond to an axial-axial interaction between H-4',5' ($J_{4'a,5'a}$ = 12.5) and H-6',5' ($J_{6'a,5'a}$ = 12.0 Hz) and indicate that for thiamonocyclane **1** a chair conformation with an equatorial disposition of the acetyl substituents is the most probable. An equatorial orientation of the bulky substituents enables unfavorable steric interactions to be avoided in the molecule, however it does not enable its cyclization due to the separation of the acetyl groups. The formation of thiabicyclane **2** evidently proceeds on inversion of the thiopyran ring into a conformation with spatially adjacent axially-disposed acetyl substituents.

The investigation carried out therefore enables clarification of the dependence of the composition of the obtained products on the duration of the condensation of acetone with formaldehyde, sodium sulfide, and methanethiolate of ASS and the development of a one-stage method for the synthesis of thiamonocyclane **1**. Subsequently it is cyclized into thiabicyclane **2**, which is promising for subsequent purpose-directed preparation of biologically active substances [1].

EXPERIMENTAL

The IR spectra were recorded on a Specord M 80 (in nujol), the ^{13}C and ^{1}H NMR spectra, and the experiment on two-dimensional ^{1}H NMR COSY spectroscopy, were carried out on a Bruker AM 300 (75 and 300 MHz respectively) spectrometer in $CDCl_3$, internal standard was TMS. The GLC analysis was carried out on a Chrom-5 chromatograph, column 2.4 m x 3 mm, stationary phase SE 30 (5%) on chromaton N-AW-DMCS (0.16-0.20 mm), operating temperature 50-300°C, flame ionization detector, carrier gas helium. The internal standard method (hexadecane) was used to determine the content of compounds **1, 2, 4**, and **5**. The content of sulfide and mercaptide sulfur was determined by potentiometric titration with potassium iodate and ammoniacal silver nitrate respectively [6].

For the synthesis of thiamono- and thiabicyclanes ASS was used from Orenburg gas processing plant, containing 1.90 (2.17; 2.61) wt. % sulfide and 5.27 (4.14; 2.69) wt. % mercaptide sulfur, predominantly sodium methanethiolate (95%).

Synthesis of 1-[5-Acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone (1) and 4-Methyl-1-methylthiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one (2). A 30% formaldehyde solution (41 ml, 0.45 mol) and acetone (33 ml, 0.45 mol) were added sequentally with stirring to ASS (100 g), containing sulfide (1.90 g, 0.059 mol) and mercaptide sulfur (5.27 g, 0.165 mol). When obtaining thiamonocyclane **1** the mixture was stirred for 10 min at 20°C and for thiabicyclane **2** 13 h at 60°C. The organic layer was separated and the aqueous phase extracted with chloroform (3×50 ml). The extract, combined with the previously separated organic layer, was washed with 10% HCl, with water (1:1 by vol.), and dried over $MgSO_4$. Chloroform was distilled off and mixtures of substances **1, 3-5** and **2-5** (19.54 and 19.04 g respectively) were obtained, which were redistilled in vacuum and processed as described below.

1-[5-Acetyl-3-(methylthiomethyl)tetrahydro-3-thiopyranyl]-1-ethanone (1) was obtained from the fraction with bp 187-197°C (5 mm Hg) (2 g) by chromatography on a column of silica gel (eluent ethyl acetate–hexane, 1:4). Yield of compound **1** was 1.16 g (78%); mp 46-47°C (ethyl acetate–hexane, 1:4). IR spectrum, ν, cm^{-1}: 1710, 1695 (C=O), 1369, 1350 (CH_3-C=O). ^{1}H NMR spectrum, δ, ppm (*J,* Hz): 1.19 (1H, dd, J_{gem} = 13.5, $J_{4'a,5'a}$ = 12.5, H-4'a); 2.11 (3H, s, SCH_3); 2.21 (3H, s, 2"-CH_3); 2.31 (3H, s, 2-CH_3); 2.57 (1H, d, J_{gem} = 12.0, H-6'e); 2.60-2.65 (4H, m, H-5',4'e, CH_2S); 2.72 (1H, d, J_{gem} = 14.1, H-2'e); 2.85 (1H, tt, J_{gem} = $J_{6'a,5'a}$ = 12.0, $J_{6'a,4'e}$ = $J_{6'a,2'a}$ = 3.3, H-6'a); 2.96 (1H, dd, J_{gem} = 14.1, $J_{2'a,4'e}$ = 2.0, $J_{2'a,6'a}$ = 3.3, H-2'a). ^{13}C NMR spectrum, δ, ppm: 18.07 (CH_3S); 26.31 ($\underline{C}H_3C$=O); 28.33 [$\underline{C}H_3C$(1")=O]; 29.08 (C-6'); 34.40 (C-4'); 34.45 (C-2'); 45.17 (CH_2S); 48.32 (C-5'); 53.20 (C-3'); 209.17 (C-1'=O); 209.61 (C=O). Found, %: C 53.70; H 7.11; S 26.09. $C_{11}H_{18}O_2S_2$. Calculated, %: C 53.62; H 7.36; S 26.03.

4-Methyl-1-methylthiomethyl-7-thiabicyclo[3.3.1]non-3-en-2-one (2). Crystals of compound **2** separated from the fraction with bp >108°C (1 mm Hg) and were filtered off and recrystallized from EtOH. Yield was 9.7 g (72%); mp 74-75°C (ethanol), which agrees with the data of [4].

REFERENCES

1. A. D. Ulendeeva, T. S. Nikitina, L. A. Baeva, L. V. Spirikhin, L. T. Karachurina, R. Yu. Khisamutdinova, N. S. Makara, F. S. Zarudii, and N. K. Lyapina, *Khim.-farm. Zh.*, **38**, No. 12, 15 (2004).
2. A. D. Ulendeeva, L. A. Baeva, O. R. Valiullin, T. S. Nikitina, D. D. Arslanova, L. V. Spirikhin, and N. K. Lyapina, *Neftekhim.*, **46**, 139 (2006).
3. L. A. Baeva, A. D. Ulendeeva, A. R. Gaisina, O. V. Shitikova, E. G. Galkin, and N. K. Lyapina, *Neftekhim.*, **47**, 134 (2007).
4. A. D. Ulendeeva, L. A. Baeva, E. G. Galkin, E. V. Vasil'eva, and N. K. Lyapina, *Neftekhim.*, **38**, 214 (1998).
5. L. A. Baeva, A. D. Ulendeeva, A. R. Gaisina, O. V. Shitikova, E. G. Galkin, and N. K. Lyapina, *Neftekhim.*, **47**, 412 (2007).
6. I. A. Rubinshtein, Z. A. Kleimenova, and E. P. Sobolev, in: *Methods of Analysis of Organic Petroleum Compounds, Mixtures, and Derivatives* [in Russian], Moscow (1960), p. 74.