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SYNTHESIS AND STRUCTURE OF 7-ALKOXYALKYL-3-THIA-7-AZABICYCLO[3.3.1]NONAN-9-ONES AND SEVERAL OF THEIR DERIVATIVES

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New 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones were synthesized by the double Mannich cyclization of tetrahydrothiopyran-4-one with suitable alkoxyalkylamines and paraformaldehyde in acetous methanol. Wolff–Kishner decarbonylation of these bicyclic ketones gave 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonanes. The reduction of 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones by alkali metal hydride complexes leads to a mixture of two stereoisomeric secondary alcohols, which are epimers at $C_{(9)}$. Active analgesic, antiarrhythmic, and antibacterial compounds were found among these products.

Keywords: 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one and its derivatives, synthesis, ^{13}C NMR spectra, structure, pharmacological properties.

The present communication presents the continuation of work carried out at the pharmacological chemistry laboratory at the A. B. Bekturov Institute of Chemical Sciences of the Ministry of Science and Education of the Republic of Kazakhstan. In previous work [1, 2], we showed that 3,7-diazabicyclo[3.3.1]nonanes with various alkoxyalkyl groups at the nitrogen atom show different pharmacological activity. Hence, we undertook a study to determine the changes resulting from the substitution of one alkoxyalkylamino group by a sulfur atom in 3,7-dialkoxyalkyl-3,7-diazabicyclo[3.3.1]nonane systems and study the chemical behavior, stereochemical aspects, and pharmacological properties of these compounds. In the present communication, we describe the synthesis and some properties of 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones and several of their derivatives obtained by reported procedures [3-5].

The reaction of tetrahydrothiopyran-4-one (**1**) with paraformaldehyde and different primary amines (2-methoxyethyl-, 2-ethoxyethyl-, 3-ethoxypropyl-, 3-butoxypropyl-, and 3-isopropoxypropyl-) in mixtures of acetic acid and methanol gave 7-[(2-methoxyethyl)- (**2**), (2-ethoxyethyl)- (**3**), (3-ethoxypropyl)- (**4**), (3-butoxypropyl)- (**5**), and (3-isopropoxypropyl]-3-thia-7-azabicyclo[3.3.1]nonan-9-ones (**6**) in yield from 33 to 86%.

The IR spectra of 3-thia-7-azabicyclo[3.3.1]nonan-9-ones **2-6** show strong carbonyl bands at 1724-1728 cm^{-1} and strong ether bands at 1112-1128 cm^{-1} (Table 1).

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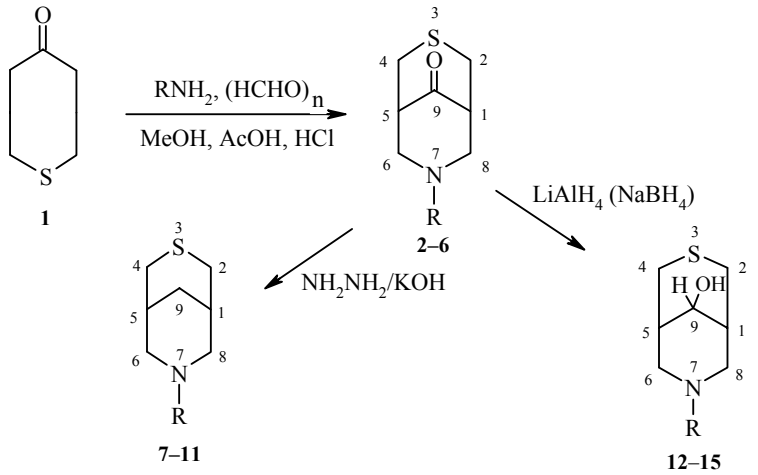

1 **2–6** **7–11** **12–15**

2, 7 R = $CH_2CH_2OCH_3$, **3, 8, 12** R = $CH_2CH_2OCH_2CH_3$, **4, 9, 13** R = $CH_2CH_2CH_2OCH_2CH_3$,

5, 10, 14 R = $CH_2CH_2CH_2OCH_2CH_2CH_2CH_3$, **6, 11, 15** R = $CH_2CH_2CH_2OCH(CH_3)_2$

The ^{13}C NMR spectral data for 3-thia-7-azabicyclo[3.3.1]nonan-9-ones **2-6** [6-8] fully support the proposed structure. The assignment of the carbon atoms was made using the shape of the multiplets in the ^{13}C NMR monoresonance spectra. A carbon atom singlet characteristic for the carbonyl group is seen at 213.1-213.4 ppm. The bicyclic structure is indicated by the doublets for $C_{(1)}$ and $C_{(5)}$ with intensity for two carbon atoms at 46.7-47.1 ppm and also the triplets for $C_{(2)}$ and $C_{(4)}$ at 34.3-34.8 ppm and for $C_{(6)}$ and $C_{(8)}$ at 58.2-58.7 ppm also with intensity for two carbon atoms. The finding of signals for the carbon atoms of the alkoxyalkyl groups at the piperidine nitrogen atom are also in accord with a bicyclic structure.

The reaction of 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones **2-6** with hydrazine hydrate in the presence of KOH in triethyleneglycol gave the corresponding 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonanes **7-11** in 72-91% yield. The IR spectra of these compounds lack carbonyl group bands (Table 1).

The ^{13}C NMR monoresonance spectra with complete proton decoupling (Table 2) do not show signals for a ketonic carbon atom. A triplet for the methylene group carbon at $C_{(9)}$ is seen in the upfield region of the monoresonance spectrum (28.9-29.3 ppm). Furthermore, an upfield shift is observed for the signals of $C_{(1)}$ and $C_{(5)}$ (26.6-26.9 ppm) and of $C_{(2)}$ and $C_{(4)}$ (31.3-31.7 ppm).

In a continuation of attempts to synthesize new pharmacological agents and study the dependence of their properties on the composition and structure, we prepared 7-(2-ethoxyethyl)-, 7-(3-ethoxypropyl)-, 7-(3-butoxypropyl)-, and 7-(3-isopropoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ols **12-15**, respectively, by reduction of the corresponding 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones **3-6** with $LiAlH_4$ in absolute ether or $NaBH_4$ in 2-propanol (Table 3).

Thin-layer chromatography showed that a mixture of two isomeric secondary alcohols forms in each case. The separation of these alcohols was carried out by column chromatography on alumina using 15:1 benzene–ethanol as the eluent. This permitted the isolation of pure stereoisomers of alcohols **12** and **13** in small amounts. The yields of alcohols **12** and **13** relative to the total amount of the product mixture were, respectively, 36 and 39% (for isomer *A*) and 20 and 32% (for isomer *B*). Alcohols **14** and **15** could not be separated into isomers by column chromatography due to their instability during the separation procedure and these compounds were characterized as mixtures of two isomers.

The IR spectra of products **12-15** lack a carbonyl group band but show a broad hydroxyl group band at 3400-3448 cm^{-1}.

TABLE 1. Physicochemical Characteristics of Compounds **2-11**

Compound	R	Empirical formula	R_f*	Found, % / Calculated, %				IR spectrum, ν, cm^{-1}		Yield, %
				C	H	N	S	C=O	C–O	
2	C_2H_4OMe	$C_{10}H_{17}NO_2S$	0.83	55.56 / 55.78	7.85 / 7.95	6.70 / 6.50	14.77 / 14.86	1724	1116	33
3	C_2H_4OEt	$C_{11}H_{19}NO_2S$	0.20	57.69 / 57.60	8.35 / 8.35	6.34 / 6.10	13.98 / 13.98	1728	1112	61
4	C_3H_6OEt	$C_{12}H_{21}NO_2S$	0.22	59.26 / 59.22	8.65 / 8.68	6.02 / 5.76	13.13 / 13.13	1728	1128	86
5	C_3H_6OBu	$C_{14}H_{25}NO_2S$	0.42	61.95 / 61.95	9.33 / 9.28	5.49 / 5.16	11.79 / 11.81	1728	1112	78
6	C_3H_6O–Pr-*i*	$C_{13}H_{23}NO_2S$	0.31	61.05 / 60.83	9.26 / 9.01	5.41 / 5.44	12.52 / 12.46	1728	1128	81
7	C_2H_4OMe	$C_{10}H_{19}NOS$	0.18	59.00 / 59.65	9.18 / 9.50	6.70 / 6.95	15.60 / 15.92	—	1114	73
8	C_2H_4OEt	$C_{11}H_{21}NOS$	0.13	61.42 / 61.35	9.86 / 9.83	6.44 / 6.50	15.07 / 14.98	—	1112	83
9	C_3H_6OEt	$C_{12}H_{23}NOS$	0.14	62.75 / 62.75	9.96 / 10.11	6.05 / 6.11	13.86 / 13.98	—	1112	91
10	C_3H_6OBu	$C_{14}H_{27}NOS$	0.16	65.39 / 65.34	10.62 / 10.57	5.49 / 5.44	12.69 / 12.45	—	1120	87
11	C_3H_6O–Pr-*i*	$C_{13}H_{25}NOS$	0.12	64.23 / 64.15	9.36 / 9.35	5.79 / 5.75	13.20 / 13.17	—	1112	72

* 20:1 benzene–ethanol used as solvent system for thin-layer and column chromatography of these products.

TABLE 2. ^{13}C NMR Spectra of **2-11** and 7-Alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ols **12-15***

Compound	Chemical shifts, δ, ppm										
	$C_{(1)}, C_{(5)}$	$C_{(2)}, C_{(4)}$	$C_{(6)}, C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$	$C_{(12)}$	$C_{(13)}$	$C_{(14)}$	$C_{(15)}$	$C_{(16)}$
2	47.1	34.8	58.7	213.5	56.05	70.85	58.7				
3	46.8	34.3	58.5	213.1	55.7	65.9	68.3	14.9			
4	46.7	34.4	58.2	213.1	53.3	27.2	65.8	68.1	14.8		
5	46.7	34.4	58.2	213.1	53.3	27.2	68.3	70.4	31.4	19.0	13.6
6	46.7	34.3	58.2	213.1	53.2	27.5	65.5	71.1	21.8		
7	26.9	31.7	58.8	29.2	58.1	70.7	58.7				
8	26.6	31.3	58.6	28.9	57.8	65.9	68.2	14.9			
9	26.7	31.3	58.4	29.3	55.1	26.8	65.7	68.6	14.9		
10	26.7	31.3	58.4	29.3	55.1	26.7	68.7	70.3	31.5	19.0	13.6
11	26.7	31.3	58.2	29.3	55.1	27.0	65.9	70.9	21.8		
***A*-12**	34.0	33.9	55.9	72.0	52.2	66.0	67.7	14.8			
***B*-12**	33.0	26.5	58.6	70.6	56.7	65.9	68.3	14.9			
***A*-13**	34.2	26.8	54.0	72.3	52.3	26.8	66.2	68.7	15.1		
***B*-13**	34.0	34.2	58.3	71.4	54.1	27.1	65.9	68.4	14.9		
14	33.0; 33.9	26.5; 33.9	58.2; 53.7	72.0; 68.2	52.0; 54.2	31.4; 33.9	68.5; 68.2	70.4; 70.4	26.9; 26.5	19.0; 19.0	13.6; 13.6
15	33.0; 33.9	26.5; 33.9	58.2; 54.1	71.0; 72.0	52.0; 54.1	27.3; 26.5	65.8; 65.8	70.8; 71.1	21.8; 21.8		

* Alcohols **14** and **15** obtained as mixtures of isomers *A* and *B*.

TABLE 3. Physicochemical Characteristics of 7-Alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ols **12-15***

Compound	R	Empirical formula	Found, % / Calculated, %				IR spectrum, ν, cm^{-1}		Yield, %	
			C	H	N	S	OH	C–O	isomer mixture	isomer
A-**12**	C_2H_4OEt	$C_{11}H_{21}NO_2S$	57.02 / 57.11	9.20 / 9.15	5.98 / 6.05	13.40 / 13.85	3424	1116	56	36
B-**12**										20
A-**13**	C_3H_6OEt	$C_{12}H_{23}NO_2S$	58.53 / 58.74	9.35 / 9.45	5.74 / 5.70	12.96 / 13.06	3448	1112	71	39
B-**13**										32
14	C_3H_6OBu	$C_{14}H_{27}NO_2S$	61.21 / 61.49	9.64 / 9.95	5.04 / 5.12	11.68 / 11.72	3424	1112	79	—
15	C_3H_6O-Pr-*i*	$C_{13}H_{25}NO_2S$	60.20 / 60.19	9.65 / 9.71	5.43 / 5.39	12.25 / 12.36	3400	1112	93	—

* Alcohols **12-15** obtained as oils.

The ^{13}C NMR spectra of the pure isomers given in Table 2 lack a singlet for the carbonyl carbon atom but show a doublet for $C_{(9)}$ at 68.2-72.3 ppm. The ^{13}C NMR spectra of **14** and **15**, which are unresolved isomer mixtures, show doubling of the carbon atom signals for the ring and substituent. In particular, two signals are seen for $C_{(9)}$, indicating two isomers *A* and *B*. The major reason for the difference in the chemical shifts is the presence of the OH group axial to the piperidine ring and, thus, equatorial to the other ring. The ^{13}C NMR data indicated that alcohols **12-15** are 2:1 mixtures of stereoisomeric alcohols.

The ^{1}H NMR spectra hold information useful for establishing the precise three-dimensional structure of **12-15**. The results of this analysis will be given in a subsequent communication.

A pharmacological investigation showed that 3-thia-7-azabicyclo[3.3.1]nonanes have low toxicity [9-11]. In a study of the properties of these compounds as local anesthetics, we found that 7-(3-butoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonane hydrochloride (**10**) [11] is superior to the lidocaine standard in duration of anesthesia. As expected [12, 13], the 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonane products have antiarrhythmic activity. Of all the compounds compared, the most active compound preventing calcium chloride-induced cardiac arrhythmia and on a model of fatty occlusion of the coronary artery is 7-(2-ethoxyethyl)-3-thia-7-azabicyclo[3.3.1]nonane (**8**) [9]. The ethoxyethyl (**8**) and ethoxypropyl derivatives (**9**) produce general analgesia in experiments on rats, exceeding the duration of such analgesia for Tramal [9, 10]. We should note that 7-(3-butoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonane (**10**) [11] significantly suppresses the growth of intestinal bacilli and staphylococci in beef peptone bullion, while ethoxypropyl analog **9** displays some activity against staphylococci.

EXPERIMENTAL

The reaction course and purity of the products were checked by thin-layer chromatography on grade II activity alumina with iodine detection of the spots. The IR spectra were taken on a Specord-80 spectrometer for KBr pellets. The ^{13}C NMR spectra were taken on a Varian Mercury-300 spectrometer at 300 MHz for solutions in $CDCl_3$ with HMDS as the internal standard.

7-Alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones 2-6 (Table 1). A stream of nitrogen was bubbled through a stirred reaction mixture consisting of absolute methanol (40 ml), paraformaldehyde (6.19 g, 0.206 mol), concentrated hydrochloric acid (1.08 ml, 1.26 g, 0.013 mol), glacial acetic acid (2.22 ml, 2.32 g, 0.038 mol), and the corresponding alkoxyalkylamine (0.026 mol) for 2 h and then a solution of tetrahydrothiopyran-4-one (**1**) (3.0 g, 0.026 mol) in methanol (10 ml) was added in a single batch. The reaction mixture was heated at reflux for 8 h with stirring in a nitrogen stream. The methanol was completely distilled off and the resultant oil was dissolved in water (80 ml) and brought to pH 1-2 by adding hydrochloric acid. The mixture was extracted with ether (3 × 40 ml) and the ethereal extracts were discarded. The acidic aqueous solution was brought to pH 10 by adding NaOH and extracted with ether (4× 40 ml). The combined extracts were dried over $MgSO_4$. The solvent was evaporated to yield an oil. Hexane (150 ml) was added to the thick oil and heated at reflux for 30 min on a water bath. The suspension obtained was decanted and the solvent was distilled off to yield nonanones **2-6** as thick oils.

7-Alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonanes 7-11 (Table 1). A sample of 95% hydrazine hydrate (0.83 ml, 0.85 g, 0.026 mol) was added to a solution of **2-6** (0.0046 mol) in triethyleneglycol (15 ml). The reaction mixture was heated to 60°C and 85% KOH (1.45 g, 0.026 mol) was added. After dissolution of the KOH, the temperature was raised to 160-170°C on a Wood's bath and heated at reflux for 4 h. Then, the reflux condenser was replaced with a distillation condenser and the unreacted hydrazine hydrate and water were distilled off, bringing the temperature to 200°C to achieve complete decomposition of the hydrazone formed. After cooling to room temperature, water (30 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined ethereal extracts were washed with 10% aq. NaOH (2 × 25 ml) and dried over

$MgSO_4$. The solvent was distilled off to give 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonanes **7-11** as light-yellow oils.

7-(2-Ethoxyethyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (12) (Table 3). A mixture of $NaBH_4$ (1.01 g, 0.027 mol) and 7-(2-ethoxyethyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**3**) (1.0 g, 0.0044 mol) in 2-propanol (10 ml) was stirred for 20 h at room temperature. The solvent was distilled off and water (10 ml) was added to the residue. The mixture was made acidic by adding 10% hydrochloric acid and extracted with ether (3 × 20 ml). The aqueous layer was cooled on ice, made basic by adding 10% aq. NaOH, and extracted with chloroform. The combined extracts were dried over Na_2SO_4 and the solvent was removed to give 0.81 g (89%) 7-(2-ethoxyethyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (**12**) as a light-yellow oil containing two isomers. The mixture was separated on an alumina column using benzene, 10:1 benzene–ethanol, and 15:1 benzene–ethanol as the eluent to give 0.29 g isomer *A* (R_f 0.73, 36% of the total mixture) and 0.16 g isomer *B* (R_f 0.47, 20% of the total mixture) as light-yellow oils.

7-(3-Ethoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (13) (Table 3). A solution of 7-(3-ethoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**4**) (1 g, 0.0041 mol) in benzene (20 ml) and ether (60 ml) was added dropwise to a suspension of $LiAlH_4$ (0.156 g, 0.0041 mol) in absolute ether. The mixture was stirred for 4 h and then decomposed with water (5 ml). The $Al(OH)_3$ formed was filtered off and the reaction mixture was evaporated to give 1.0 g (99%) **13** as a light-yellow oil containing two isomers, which was separated on an alumina column using benzene, and 10:1 benzene–ethanol, 15:1 benzene–ethanol as the eluent. This procedure gave 0.39 g isomer *A* (R_f 0.69, 39% of total isomer mixture) and 0.32 g isomer *B* (R_f 0.50, 32% of total isomer mixture) as light-yellow oils (Table 3).

(7-(3-Butoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (14) (Table 3). A solution of 7-(3-butoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**5**) (1 g, 0.0037 mol) in ether (20 ml) was added dropwise to a suspension of $LiAlH_4$ (0.139 g, 0.0037 mol) in absolute ether. The reaction mixture was stirred for 4 h and then decomposed with water (5 ml). The $Al(OH)_3$ formed was filtered off and the reaction mixture was evaporated to give 0.80 g (79%) **14** as a light-yellow oil containing two isomers with R_f 0.76 and 0.54 (15:1 benzene–ethanol as eluent).

7-(3-Isopropoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (15) (Table 3). A solution of 7-(3-isopropoxypropyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**6**) (1 g, 0.0039 mol) in a mixture of ether (5 ml) and benzene (2 ml) was added dropwise to a suspension of $LiAlH_4$ (0.147 g, 0.0039 mol) in absolute ether. The reaction mixture was stirred for 4 h and then heated for 30 min at 40°C. After cooling to room temperature, the mixture was decomposed with 5 ml water. The $Al(OH)_3$ formed was filtered off and the reaction mixture was evaporated to give 0.94 g (93%) **15** as a light-yellow oil, which is a mixture of stereoisomers with R_f 0.80 and 0.66 (15:1 benzene–ethanol as eluent).

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