A STUDY OF THE CONDITIONS OF THE FORMATION OF THE cis AND trans ISOMERS OF N-SUBSTITUTED 4-AMINOTHIOLAN-3-OL 1,1-DIOXIDES

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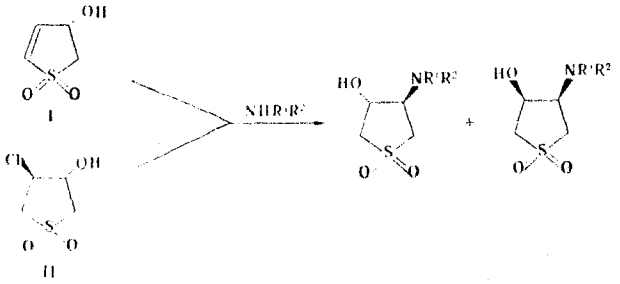
UDC 547.733.07:541.634

A mixture of cis- and trans-4-alkyl(heteryl, aryl)aminothiolan-3-ol 1,1-dioxides and (3-hydroxy-1,1-dioxothiolan-4-ylamino)acetic acids have been obtained by the reaction of 2,3-dihydrothiophene-3-ol 1,1-dioxide with aliphatic, heterocyclic, and aromatic amines and aminoacetic acid. The structures of the compounds isolated has been shown by chemical and spectral methods.

It has been reported [1] that 3,4-epoxythiolane 1,1-dioxide reacts with aliphatic amines at room temperature to form N-substituted 4-aminothiolan-3-ol 1,1-dioxides, the stereochemistry of which has not been established. It has been shown [2] that this reaction takes place through a stage of the isomerization of a 3,4-epoxythiolane 1,1-dioxide into a 2,3-dihydrothiophene-3-ol 1,1-dioxide, which adds the amine to the double bond.

We have investigated the addition of aliphatic, heterocyclic, and aromatic amines to 2,3-dihydrothiophene-3-ol 1,1-dioxide (I) and have established that a mixture of cis and trans isomers is formed which it has been possible to separate by fractional crystallization (Table 1). We have obtained the same substances with similar yields by the reaction of amines with 4-chlorothiolan-3-ol 1,1-dioxide (II):



In a detailed study of the products of the reaction of 3,4-epoxythiolane 1,1-dioxide (III) with amines, we have established that mixtures of isomeric compounds are also formed with aliphatic and heterocyclic amines, while with arylamines the reaction takes place stereospecifically with the formation of the cis isomer alone. In the latter case, in contrast to the reaction with compounds (I) and (II), the yield of reaction products depends little on the nature of a substituent in the aromatic ring and amounts to 90-95%. If the reaction of the epoxide (III) with arylamines is performed in the presence of their hydrochlorides, a mixture of cis- and trans-4-arylaminothiolan-3-ol 1,1-dioxides is formed, the yield of which depends on the nature of a substituent in the aromatic nucleus (it rises on the introduction of an electron-donating substitute into the ring and falls for an electron-accepting substituent).

A mixture of isomeric compounds is formed by the reaction of compounds (I)-(II) with potassium (sodium) aminoacetates.

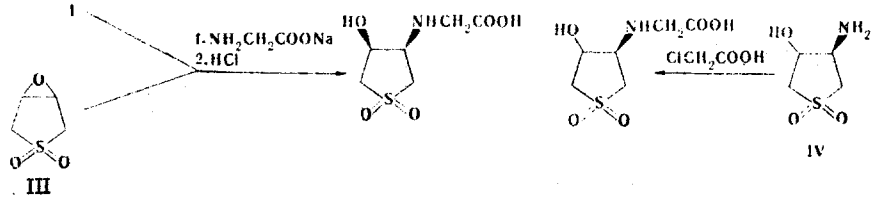
Petrochemistry Sector, Institute of Physical Organic Chemistry. Coal Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiya Geterotskiklicheskikh Soedinenii, No. 4, pp. 475-478, April, 1980. Original article submitted January 5, 1979; after revision September 5, 1979.

0009-3122/80/1604-0359$07.50

TABLE 1. N-substituted 4-Aminothiolan-3-ol 1,1-dioxides

№	R_1	R_2	Isomer	mp[a], °C	Found, % N	Found, % S	Empirical formula	Calculated, % N	Calculated, % S	Yield, % in the reaction[b] with I	II	III
1	C_6H_5	H	trans	129—130	6,0	14,4	$C_{10}H_{13}NO_3S$	6,1	14,1	48	45	85
2			cis	100—101	6,1	13,9				14	15	—
3	p-$CH_3C_6H_4$	H	trans	178—180	6,0	13,5	$C_{11}H_{15}NO_3S$	5,8	13,3	54	39	94
4			cis	121—122	5,7	13,0				37	40	—
5	p-$CH_3OC_6H_4$	H	trans	165—166	5,6	12,3	$C_{11}H_{15}NO_4S$	5,4	12,5	53	40	93
6			cis	145—146	5,5	12,5				30	40	—
7	p-ClC_6H_4	H	trans	172—173	5,2	12,6	$C_{10}H_{12}ClNO_3S$	5,3	12,3	33	30	88
8			cis	118—119	5,2	12,2				23	20	—
9	m-$CH_3C_6H_4$	H	cis	102—103	5,6	13,3	$C_{11}H_{15}NO_3S$	5,8	13,3	—	—	95
10	o-$CH_3C_6H_4$	H	cis	104—105	5,7	13,3	$C_{11}H_{15}NO_3S$	5,8	13,3	—	—	93
11	m-$CH_3OC_6H_4$	H	cis	88—90	5,3	12,4	$C_{11}H_{15}NO_4S$	5,4	12,5	—	—	95
12	o-ClC_6H_4	H	cis	123—124	5,3	12,5	$C_{10}H_{12}ClNO_3S$	5,3	12,5	—	—	86
13	m-BrC_6H_4	H	cis	118—119	4,5	10,7	$C_{10}H_{12}BrNO_3S$	4,8	10,5	—	—	90
14	C_4H_9	H	trans	116—117	7,0	15,7	$C_8H_{17}NO_3S$	6,7	15,5	43	—	—
15			cis	106—110[c]	6,9	15,6				40	—	—
16	$(CH_2)_5$		trans	171—172	6,3	14,7	$C_9H_{17}NO_3S$	6,3	14,6	43	42	—
17	$(CH_2)_5$		cis	102—103[d]	6,4	14,5		6,3	14,6	41	41	—
18	$(CH_2)_4O$		trans	210—211	6,8	14,6	$C_8H_{15}NO_4S$	6,4	14,5	42	—	—
19	$(CH_2)_4O$		cis	154—155[d]	6,6	14,7	$C_8H_{15}NO_4S$			40	—	—
20	CH_2COOH	H	trans	270—271[e]	6,4	15,2	$C_6H_{11}NO_5S$	6,7	15,3	52	—	50
21			cis	254—256	7,1	15,4				36	—	35

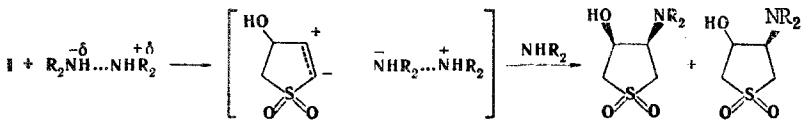
[a]Recrystallization from methanol containing 10% of water for the trans isomer and 30% of water for the cis isomer. [b]Without HCl. [c]From ether—isopropanol (5:1). [d]From butanol. [e]From water.



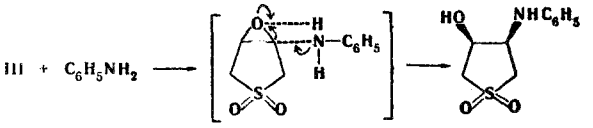
We obtained the same results in the reaction of compound (I) and (III) with aminoacetic acid in the presence of bases.

The compounds were separated in the form of the acids by fractional crystallization. The trans isomer was identified by means of a sample synthesized from trans-4-aminothiolan-3-ol 1,1-dioxide (IV) and monochloroacetic acid.

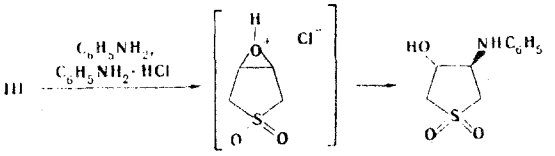
To identify the 4-aminothiolan-3-ol 1,1-dioxides their PMR spectra were compared with the spectra of cis- and trans-(3-hydroxy-1,1-dioxothiolan-4-ylamino)acetic acids. For comparison we selected the signal of the proton attached to the ring carbon atom with the hydroxy group (multiplet in the 390-410 Hz region). The chemical shift of this proton is diminished under the influence of the electronegative oxygen atom, because of which the signal was clearly separated from the signals of the other protons of the molecule. For the cis isomer, the signals of these protons (sextets with a distance between the extreme lines of d ~15 Hz) lie in a weaker field than the signals of the trans compounds (broadened quartet with d ~8 Hz) and are analogous in shape, respectively, to the signals of the cis and trans isomeric amino acids. The value of d in the multiplets is the algebraic sum of the vicinal spin—spin constants of the coupling of the 3-H proton with the 2-H (2H) and 4-H protons. The close values of these constants in the spectra of the compounds compared indicates an analogy of their structures. The spatial orientation of the substituents was definitely confirmed by the results of x-ray structural analysis of the isomeric 4-anilinothiolan-3-ol 1,1-dioxides [3]. The mechanism of the addition of the amines and amino acids to the sulfones (I) has not been investigated. By analogy with the work of Shvets et al. [4], we explain the formation of isomers by the fact that in the reaction with arylamines the ion pair $Ar\overset{+}{N}H_3\overset{-}{X}$, and in the reaction with aliphatic and heterocyclic amines the associate $R_2\overset{-\delta}{N}—H\ldots\overset{+\delta}{N}HR_2$ activates the double bond of 2,3-dihydrothiophene-3-ol 1,1-dioxide in the transition complex by stabilizing the carbocation on the carbon atom in position 3 of the ring:



A subsequent attack of the carbocation by a free amine molecule leads to the formation of the reaction products. The reaction of amines and amino acid salts with the sulfone (II) probably takes place through a stage of the formation of compound (I) through the elimination of HCl under the action of the amine. In favor of this hypothesis is the formation of the sulfone (I) on the reaction of compound (II) with aniline at 100°C, while when the same reagents are heated to 180°C the isomeric 4-anilinothiolan-3-ol 1,1-dioxides are formed. We explain the stereospecificity of the reaction of the sulfone (III) with arylamines in the absence of catalysts, taking literature information into account [5], by a nucleophilic attack by the amine on the carbon atom of the epoxide ring and the formation of an intermediate complex in which the amine is a proton donor and the oxygen atom of the oxide an acceptor.



In the presence of HCl, the reaction probably takes place by the above-described scheme and through an oxonium ion, which undergoes attack by a molecule of the amine from the side opposite to that of the oxygen bridge, with the formation of the trans isomer



EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-487 instrument with a working frequency of 80 MHz at 10°C using HMDS as internal standard in $CDCl_3$ for the 4-aminothiolan-3-ol 1,1-dioxides and in D_2O for the (3-hydroxy-1,1-dioxothiolan-4-ylamino)acetic salts.

cis- and trans-4-p-Toluidinothiolan-3-ol 1,1-dioxides (Compounds 3 and 4 in Table 1). A. A mixture of 1.3 g (0.01 mole) of 2,3-dihydrothiophene-3-ol 1,1-dioxide, 1.1 g (0.01 mole) of p-toluidine, and 1.4 g (0.01 mole) of p-toluidine hydrochloride was heated at 170°C for 4 h, and it was then cooled and washed with water to eliminate p-toluidine hydrochloride. The residue was crystallized from a mixture of methanol and 10% of water. This yielded the trans isomer. The filtrate was evaporated and the residue was crystallized from a mixture of methanol and 30% of water, which gave cis-4-p-toluidinothiolan-3-ol 1,1-dioxide.

B. Under the conditions described above, 1.7 g (0.01 mole) of trans-4-chlorothiolan-3-ol 1,1-dioxide and 1.2 g (0.02 mole) of p-toluidine gave cis- and trans-4-p-toluidinothiolan-3-ol 1,1-dioxides.

C. Under the same conditions, 3.1 g (0.01 mole) of 4-tosyloxythiolan-3-ol 1,1-dioxide and 2.1 g (0.01 mole) of p-toluidine gave 32% of cis- and 40% of trans-4-p-toluidinothiolan-3-ol 1,1-dioxides.

D. Similarly, when 1.3 g (0.01 mole) of 3,4-epoxythiolan 1,1-dioxide, 1.1 g (0.01 mole) of p-toluidine, and 1.4 g (0.01 mole) of its hydrochloride were heated, cis- and trans-4-p-toluidinothiolan-3-ol 1,1-dioxides were obtained.

Compounds 1, 2, and 5-8 (Table 1) were obtained by methods A and B.

cis- and trans-4-Piperidinothiolan-3-ol 1,1-dioxides (Compounds 16 and 17 in Table 1). A. A solution of 1.3 g (0.01 mole) of 2,3-dihydrothiophene-3-ol 1,1-dioxide and 5.1 g (0.06 mole) of piperidine in 40 ml of methanol was heated at 60°C for 6 h. The methanol and the excess of amine were distilled off. The residue was washed with 10 ml of cold water and was

crystallized from a mixture of methanol and 30% of water. This gave trans-4-piperidinothiolan-3-ol 1,1-dioxide. The filtrate was evaporated, and the cis isomer was isolated from the residue by crystallization from butanol.

B. Under similar conditions, trans- and cis-4-piperidinothiolan-3-ol 1,1-dioxides were obtained from 1.7 g (0.01 mole) of trans-4-chlorothiolan-3-ol 1,1-dioxide and 5.1 g (0.06 mole) of piperidine.

Substances 14 and 15, and 18 and 19 (Table 1) were synthesized under the same conditions.

cis-4-o-Chloroanilinothiolan-3-ol 1,1-dioxide (Compound 12 in Table 1). A mixture of 1.36 g (0.01 mole) of 3,4-epoxythiolan 1,1-dioxide and 2.3 g (0.01 mole) of o-chloroaniline was heated at 175° for 5 h, cooled, and crystallized from a mixture of methanol with 30% of water. This gave cis-4-(o-chloroanilino)thiolan-3-ol 1,1-dioxide.

Compounds 9-13 (Table 1) were obtained similarly.

cis- and trans-(3-Hydroxy-1,1-dioxothiolan-4-ylamino)acetic Acids. (Compounds 20 and 21 in Table 1). A. A mixture of 3 g (0.04 mole) of glycine, 5.36 g (0.04 mole) of 2,3-dihydrothiophene-3-ol 1,1-dioxide, and 2.46 g (0.044 mole) of KOH in 30 ml of water was stirred at room temperature for 6 h. The solution was filtered from the suspension of polysulfone, and the filtrate was acidified with hydrochloric acid. The residue was separated by crystallization from water into trans and cis isomers.

B. Under similar conditions, 3 g (0.04 mole) of glycine, 2.24 g (0.04 mole) of caustic potash, and 5.36 g (0.04 mole) of 3,4-epoxythiolane 1,1-dioxide yielded the trans and cis amino acids (compounds 20 and 21, Table 1).

trans-(3-Hydroxy-1,1-dioxothiolan-4-ylamino)acetic Acid. A mixture of 3.02 g (0.02 mole) of trans-4-aminothiolan-3-ol 1,1-dioxide, 1.89 g (0.02 mole) of chloroacetic acid, 2.1 g (0.02 mole) of sodium acetate, in 20 ml of water was stirred at 20°C for 1 h. The water was distilled off and the residue was treated with methanol. The methanolic extract was diluted with 10 ml of water and acidified with hydrochloric acid. The precipitate was separated off and recrystallized from water.

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