MASS-SPECTROMETRIC STUDY OF THE FRAGMENTATION OF STEREOISOMERIC FORMS OF 2-(4'-ALKOXYCARBONYLBUTYL)-3-HYDROXY-4-UREIDOTETRAHYDROTHIOPHENE UNDER ELECTRON IMPACT

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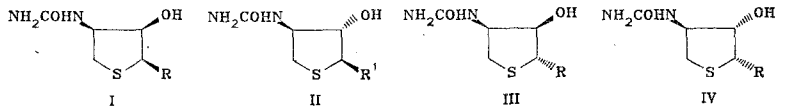
The dependence of the characteristic fragmentation under electron impact on the spatial orientation of the substituents of cis and trans isomers of 2-(4'-alkoxycarbonylbutyl)-3-hydroxy-4-ureidotetrahydrothiophenes was studied. The possibility of the identification of these isomers on the basis of the intensity ratios of the peaks of the ions formed via two competitive fragmentation pathways with splitting out of the substituents from the $C_{(3)}$ and $C_{(4)}$ positions was demonstrated.

The present paper is a continuation of a mass-spectrometric study of the fragmentation of stereoisomers of di- and trisubstituted tetrahydrothiophenes [1, 2] under electron impact. In the case of the cis and trans derivatives of 4-benzamido-3-hydroxytetrahydrothiophene it was established that the introduction of a third substituent in the 2 position of the tetrahydrothiophene ring leads to a substantial dependence of the fragmentation on the stereochemistry of substituted tetrahydrothiophenes [2].

It seemed of interest to examine the fragmentation of the analogous cis- and trans-trisubstituted hydroxyaminotetrahydrothiophene with a carbamido grouping in the 4 position. We investigated the cis and trans isomers of 2-(4'-alkoxycarbonylbutyl)-3-hydroxy-4-ureidotetrahydrothiophenes (I-IV).



I, III, IV $R=(CH_2)_4COOCH_3$; II $R^1=(CH_2)_4COOC_2H_5$

The fragmentation of I and IV is presented in the general scheme. The same fragmentation scheme is also identical for II and III.

The principal processes in the fragmentation of I, II, and IV were confirmed by metastable ions (by the defocusing method). The relative intensities of the peaks of ions a-e and i in the mass spectra of tetrahydrothiophenes I-IV obtained at ionizing-electron energies of 75 and 15 eV and expressed in percent relative to the total ion current are presented in Table 1. The complete mass spectra of the investigated tetrahydrothiophenes at 75 eV are given in Table 2. The compositions of ions a-e and i were determined from the high-resolution mass spectra.

Two principal pathways of fragmentation of the compounds with the elimination of the substituents attached to the $C_{(3)}$ or $C_{(4)}$ atom in the form of neutral molecules and with the retention of the tetrahydrothiophene ring are observed in the fragmentation of 4-ureidotetrahydrothiophenes I-IV; a third principal pathway involves direct fragmentation of the tetrahydrothiophene ring.

The first fragmentation pathway ($M^+ \rightarrow a \rightarrow c \rightarrow e$) consists in initial dehydration with the elimination of the substituent attached to the $C_{(3)}$ atom and the formation of ion *a*, subsequent detachment of H_2NCONH_2 to give ion c, and splitting out of alcohol from the aliphatic chain to give ion e.

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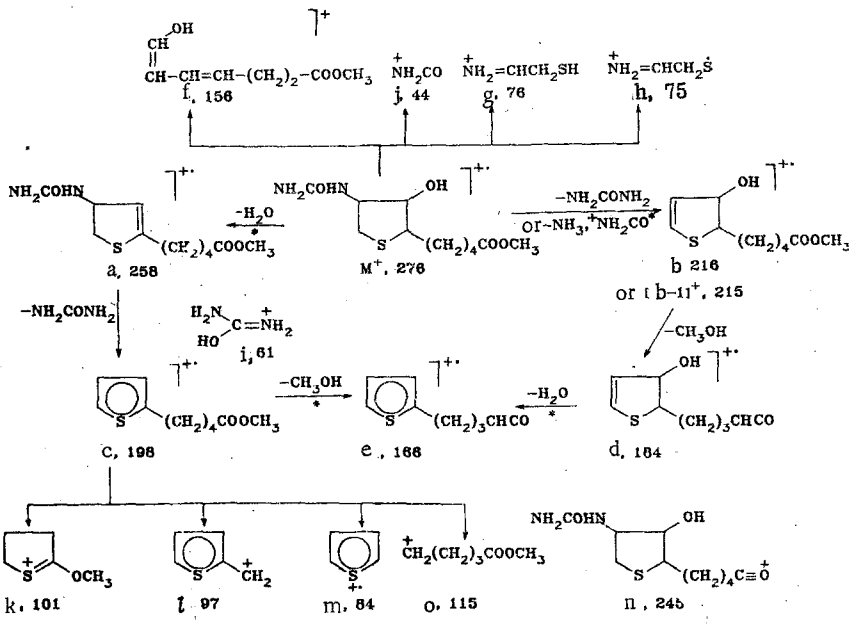
TABLE 1. Intensities of the Peaks of the M^+ and a-j Ions in the Mass Spectra of Tetrahydrothiophenes I-IV (relative intensities of the ion peaks in percent of the total ion current)

Compound		I		II		III		IV	
ions	*m/z*	75 eV	15 eV	75 eV	15 eV	75 eV	15 eV	75 eV	15 eV
M+	276*	0,1	1,3	—	0,5	—	—	0,1	—
a	258*	—	—	0,4	2,5	0,7	2,2	0,5	2,2
b	216*	7,5	43,9	0,4	2,1	0,3	2,1	0,2	1,0
c	198*	3,2	12,1	5,1	23,5	9,0	23,1	8,6	24,4
d	184	9,8	11,4	4,8	7,3	3,2	3,6	1,5	2,9
e	166	8,0	5,0	8,7	13,0	8,5	8,6	10,8	12,1
f	156	2,5	—	—	—	1,3	—	0,8	—
g	76	4,8	—	8,5	→	7,4	—	7,2	—
h	75	7,1	—	15,7	—	13,6	—	14,3	—
i	61	6,7	3,6	5,1	4,7	4,9	4,7	7,3	8,2
j	44	6,5	—	4,3	—	4,0	—	4,2	—

*For II (m/z): M^+ 290, *a* 272, b 230, and c 212.



*The observed metastable transitions are designated by asterisks.

The fragmentation of II-IV for which cis and trans configurations of the substituents are characteristic, proceeds via the first pathway and, to a lesser extent, via the second pathway (see below). The elements of water are ejected in the form of a neutral particle from molecular ion M^+, and ion *a* (m/z 258 for III and IV and 272 for II) is formed; at 15 eV the intensity of ion *a* amounts to only 2.2-2.5% (II-IV), whereas at 75 eV the intensity becomes extremely low (0.4-0.7%). Ion *a* is evidently readily formed and then rapidly gives stable ion c (m/z 198) with high intensities 23.1-24.4% (15 eV) → 5.1-9.0% (75 eV); the substituent is ejected from the 4 position in the form of neutral H_2NCONH_2, and the tetrahydrothiophene ring is dehydrogenated completely to give a thiophene ring. The formation of ion c is not very stereospecific, and its intensity becomes maximal at 15 eV for all isomers II-IV.

The detachment of a molecule of alcohol from the aliphatic chain of ion c leads to the formation of ion e with m/z 166, which is common to both the first and second fragmentation pathways; it is difficult to form a judgment regarding the competitive effect of one or another pathway on the fragmentation process from this overall ion. The intensities of ion e are as follows (for 15 eV → 75 eV): 13.0 → 8.7% (for II), 8.6 → 8.5% (III), and 12.1 → 10.8% (IV).

TABLE 2. Mass Spectra of Tetrahydrothiophenes I-IV at 75 eV*

Compound	m/z values (relative intensities of the ion peaks in percent of the maximum peak)
I	276 (1,0), 245 (7,4), 228 (8,4), 216 (76,7), 198 (32,2), 184 (100,0), 166 (81,1), 156 (26,0), 151 (9,8), 139 (31,1), 138 (18,4), 115 (13,3), 111 (11,2), 110 (17,5), 101 (18,8), 100 (9,6), 97 (40,1), 95 (9,2), 87 (57,3), 81 (15,5), 76 (49,0), 75 (72,4), 61 (68,4), 59 (24,5), 55 (35,4), 45 (27,9), 44 (66,5), 43 (91,4)
II	272 (2,9), 245 (11,8), 230 (2,8), 229 (2,9), 228 (2,4), 219 (1,6), 214 (2,5), 213 (4,5), 212 (32,3), 196 (3,9), 186 (3,1), 185 (8,4), 184 (30,9), 173 (1,3), 172 (1,7), 168 (6,0), 167 (22,6), 166 (55,5), 139 (15,8), 138 (9,5), 101 (11,9), 100 (10,4), 99 (6,7), 97 (16,1), 87 (21,8), 86 (10,2), 85 (9,4), 84 (3,7), 81 (8,6), 77 (6,9), 76 (54,2), 75 (100,0), 67 (9,1), 62 (1,0), 61 (32,5), 57 (8,4), 55 (13,2), 45 (6,5), 44 (27,5), 43 (44,3), 41 (11,3)
III	258 (5,5), 245 (10,4), 216 (2,3), 215 (5,1), 199 (11,2), 198 (66,4), 185 (5,7), 184 (23,4), 168 (5,9), 167 (22,7), 166 (63,2), 156 (9,8), 151 (6,0), 144 (5,9), 139 (12,6), 138 (12,3), 116 (3,3), 115 (10,2), 111 (8,9), 110 (11,3), 102 (11,9), 101 (19,8), 100 (7,0), 97 (25,8), 95 (5,2), 91 (4,7), 87 (20,6), 86 (9,0), 85 (10,3), 84 (5,4), 81 (9,7), 76 (54,7), 75 (100,0), 61 (36,0), 59 (12,1), 57 (12,0), 55 (17,0), 44 (29,7), 43 (45,7)
IV	277 (1,0), 258 (3,8), 245 (8,2), 216 (1,2), 215 (3,1), 212 (1,2), 199 (7,9), 198 (59,8), 184 (10,2), 167 (24,8), 166 (75,2), 156 (5,6), 151 (4,5), 139 (10,5), 138 (13,7), 111 (9,9), 110 (13,7), 101 (10,4), 100 (13,7), 97 (33,3), 87 (22,1), 86 (10,3), 84 (8,1), 81 (9,3), 76 (50,5), 75 (100,0), 61 (50,8), 60 (8,5), 59 (12,2), 55 (18,9), 45 (10,6), 44 (29,4), 43 (55,7)

*The intensities of the ion peaks > 1% are presented.

Ion c undergoes even more profound fragmentation with almost complete splitting out of the side aliphatic chain, which undergoes ring closing to give a partially hydrogenated substituted furan [ion k (m/z 101)] and a substituted thiophene [ion l (m/z 97)], or undergoes fragmentation to a cyclic product [thiophene ion radical m (m/z 84)] and to a complete aliphatic chain [ion o (m/z 115)].

The second fragmentation pathway ($M^+ \rightarrow b \rightarrow d \rightarrow e$) consists in the detachment of H_2NCONH_2 and the formation of ion b with subsequent splitting out of CH_3OH (I, III, IV) or C_2H_5OH (II), which leads to the production of ion d, with subsequent dehydration with the detachment of the elements of water with the formation of aromatized ion e. The principal fragmentation process via both pathways ultimately leads to the production of ion e.

The stereochemistry of the molecule has a particularly pronounced effect on the formation of ion b (pathway $M^+ \rightarrow b$). Thus the fragmentation of absolute cis-2-(4'-methoxycarbonylbutyl)-3-hydroxy-4-ureidotetrahydrothiophene (I) proceeds primarily via the second pathway and differs markedly from the pathways of fragmentation of cis and trans II-IV. For I the intensity of the b ion peak (m/z 216) is 43.9% (15 eV) → 7.5% (75 eV), and ion d [11.4% (15 eV) → 9.8% (75 eV)] is obtained as a result of further fragmentation of ion b with splitting out of a molecule of alcohol from the side chain. Labile ion *a* was not detected in the fragmentation of I under electron impact. However, ion c with peak intensity 12.1 → 3.2% (at 15 and 75 eV) was detected; this provides a basis for the assumption that a relatively small amount of I also undergoes fragmentation via the first pathway, since we were unable to detect the formation of ion c as a fragment from the fragmentation of ion b by a thorough examination of the metastable transitions.

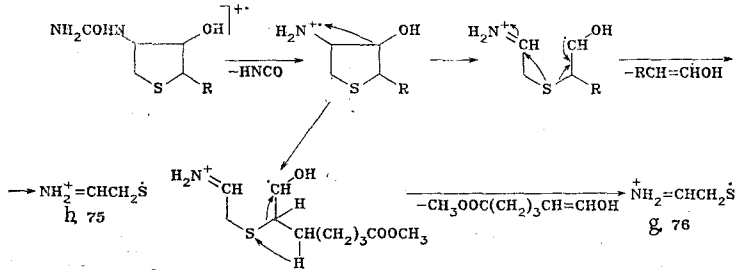
The partial fragmentation if II-IV via the second pathway leads to the formation of ion b with intensities 1.0-2.1% (15 eV) → 0.2-0.4% (75 eV) and then to ion d with the following intensities: 3.6-2.9% (15 eV) → 3.2-1.5% (75 eV) for III and IV and 7.3 → 4.8% (at 15 and 75 eV) for II.

Another variant of the fragmentation of tetrahydrothiophenes II-IV is the elimination of 61 amu from M^+, which leads to the formation of $[b - 1]^+$ ions with m/z 215 (for III and IV) and 229 (for II). The intensities of the peaks of these ions are even higher than for ion b. The formation of $[b - 1]^+$ ions can evidently be explained in accordance with [3] by the elimination of the substituent at $C_{(4)}$—NH_3 with the subsequent ejection of $[H_2NCO]^+$ and a rearrangement process, which leads to the formation of a $[b - 1]^+$ ion rather than ion radical b.

The third fragmentation pathway ($M^+ \rightarrow f + j + g + h$) leads to complete fragmentation of the tetrahydrothiophene ring at the $C_{(3)}$—$C_{(4)}$ bond (β cleavage with respect to the nitro-

gen atom), at the S—$C_{(2)}$ bond, and at the —CO—NH— bond. In addition to ions f (m/z 156) and j (m/z 44), this process leads to the formation of ion g (m/z 76) and ion radical h (m/z 75) with very high intensities in the mass spectra of all I-IV. At an ionizing-electron energy of 75 eV the intensities of the h ion peak amount to 13.6-15.7% (for II-IV) and 7.1% (I) and are maximal for II-IV and ∿75% for I, whereas the intensities of the g ion peak amount to 7.2-8.5% (II-IV) and 4.8% (I), i.e., ∿50-70% of the intensity of the h ion peak.

According to the high-resolution mass spectra, the composition of ion h corresponds to the formula $H_2N^+{=}CHCH_2S$. The pathway via which this is formed is evidently as follows:



It indicates the rearrangement character of the formation of this ion.

High intensity of the peak of ion radical h (up to 65 rel. %) was observed among the disubstituted derivatives only for 4-ureido-3-hydroxytetrahydrothiophenes [2]. Since the formation of ion radical h and ion g with cleavage of the $C_{(3)}$—$C_{(4)}$ bond proceeds with a high probability, the stereospecificity of the fragmentation of I-IV is leveled out somewhat.

It is interesting to note that the intensity of the g ion peak increases to a great extent with respect to the intensity of the peak of ion radical h under milder ionization conditions (15 eV) (in the case of I the intensity of the g ion peak becomes even somewhat higher than that of ion h). This can be explained by the same mechanism of the formation of ion radical h, except that at an ionizing-electron energy of 15 eV the last step in its formation proceeds somewhat differently.

The third pathway in the fragmentation of I-IV is similar to that observed for aliphatic and cyclic amines [4, 5]. It should be noted that when there is an amido group in the 4 position of the tetrahydrothiophene ring, the fragmentation proceeds via the scheme that is characteristic for amides [2, 5].

The stereochemically independent formation of acyl ion n (m/z 245) occurs for all of the investigated stereoisomers I-IV in the fragmentation of M^+ at the ester grouping of the substituting aliphatic acid.

One of the peculiarities of the fragmentation of I-IV is the less pronounced regularity in the formation of ions a-d on passing from I to IV as compared with the tetrahydrothiophenes examined in [2]. Using the criterion that characterizes the stereospecificity of the fragmentation of the molecules of the isomers of substituted tetrahydrothiophenes in the form of ratios of the overall intensities of the peaks of ion formed via one or another competitive fragmentation pathway $(I_a + I_b)/(I_c + I_d)$ (where I is the relative intensity of the peak of the corresponding fragment at 15 eV), one can establish ratios of 0.22, 2.77, 4.44, and 6.82 for the cis- and trans-ureido derivatives of tetrahydrothiophene of the I-IV series. These ratios were 0.17, 0.8, 2.1, and 7.0 for the corresponding cis- and trans-benzamido derivatives of tetrahydrothiophene [2].

Thus mass spectroscopy can be used to establish the stereochemical structures of cis- and trans-2,3,4-trisubstituted tetrahydrothiophenes.

EXPERIMENTAL

Trisubstituted tetrahydrothiophenes I-IV were synthesized and their configurations were established by PMR spectroscopy by the methods in [6].

The mass spectra and the spectra of the metastable ions obtained by the defocusing method were measured with a Jeol JMS-01-SG-2 high-resolution mass spectrometer with direct introduction of the samples into the ion source at 140-160°C; the ionization-chamber tem-

perature was 130°C, the ionizing voltages were 75 and 15 eV, and the emission current was 250 μA.

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RESEARCH IN THE CHEMISTRY OF HETEROCYCLIC QUINONEIMINES.

5.* EFFECT OF BENZANNELATION OF PHENOTHIAZIN-3-ONE ON ITS REACTION WITH O- AND S-NUCLEOPHILES

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Benzo[a]phenothiazin-5-one reacts with alkoxides, thiols, or thiolates to give 6-alkoxy- and 6-alkyl(aryl)thiobenzo[a]phenothiazin-5-ones, respectively. Benzannelation of phenothiazin-3-one in the quinoneimine fragment markedly hinders reactions with O- and S-nucleophiles with retention of the reaction center in the quinoneimine fragment of the molecule.

The areas of application found for a number of benzo[a]phenothiazin-5-one derivatives (laser technology [2], color photography [3], and pharmacological activity [4]) have stimulated the search for methods for the synthesis of compounds of this series [3, 5, 6]. A number of new studies [6, 7] have been devoted to the direct introduction of substituents into benzo[a]phenothiazin-5-one by its reaction with radical agents under conditions of chemical and photochemical generation. It seemed of promise to study the direct nucleophilic substitution of hydrogen in benzo[s]phenothiazin-5-one, since the latter is easy to prepare, and reactions of this sort have been unknown for it up until now.

Benzannelation in the quinoneimine fragment in the case of phenoxazin-3-one markedly decreases its reactivity with respect to nucleophiles; however, under conditions of activation of the substrate with mineral acid p-thiocresol reacts with benzo[a]phenoxazin-5-one to give a product of substitution in the aryl fragment of the molecule [8].

In contrast to phenothiazin-3-one [1, 9], the reactions of benzo[a]phenothiazin-5-one with both thiols and thiolates and alkoxides are also markedly hindered as a result of blocking of the most electrophilic centers of the molecule by benzannelation. The most essential condition for the reactions with all of the three examined series of nucleophiles is the polarity of the solvent. The reactions do not occur in benzene and tetrahydrofuran (THF); good results are obtained when the reactions are carried out in dimethylformamide (DMF) at ∿100°C.

*See [1] for Communication 4.

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