RING-CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES.

13.* MERCAPTOALKYLATION OF HYDRAZONES

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The reaction of thiiranes with hydrozones leads primarily to 2-mercaptoalkylhydrazones that are capable of undergoing reversible isomerization to the corresponding perhydro-1,3,4-thiadiazines or (in the case of unsubstituted aldohydrazones) to 3-aminothiazolidines. The reaction mixtures, which contain products of side and secondary reactions, were analyzed by chromatographic mass spectrometry. It is shown that the principal products of mercaptoethylation and mercaptopropylation of acetone hydrazone exists in the form of tautomeric mixtures of chain and ring forms and that the introduction of a methyl substituent in the 6 position of the ring leads to a shift of the equilibrium to favor the perhydro-1,3,4-thiadiazine.

The nucleophilic opening of the thiirane ring by alkylhydrazines has been used for the preparation of vicinal N-alkylhydrazinothiols [3, 4]. However, we were unable to use this method for the synthesis of hydrazino thiols that contain only a mercaptoalkyl group as a substituent attached to the nitrogen atom, which are of interest, in particular, in connection with the study of the ring-chain tautomerism of their alkylidene derivatives. Attempts to subject hydrazine hydrate or anhydrous hydrazine to reaction with lower thiiranes with the use of a large number of solvents led to the formation of only products of polymerization of the thiiranes. We therefore investigated the reaction of thiiranes with hydrazones in order to obtain alkylidene derivatives directly. The possibility of the preparation of hydroxyalkyl derivatives from hydrazones and oxiranes has been demonstrated [5].

The reaction of thiiranes Ia-c with hydrazones IIa-d was carried out by heating a mixture of the components in benzene (at 100°C, with a I:II molar ratio of 1:4). The reaction products were analyzed by means of chromatographic mass spectrometry (Table 1), and the principal component of the reaction mixture was isolated preparatively in most cases. The structures of the compounds obtained were confirmed by data not only from mass spectrometry but also from IR and PMR spectroscopy (Tables 2 and 3).

The reaction of thiiranes with hydrazones of ketones leads primarily to 2-mercaptoalkylhydrazones III, which usually undergo reversible isomerization to perhydro-1,3,4-thiadiazines IV (see below). Let us note here that, regardless of the form (chain or ring) that predominates in the tautomeric mixture at room temperature, the molecular ion that is formed upon electron impact evidently has a chain structure for all of the tautomeric or potentially tautomeric compounds. The fragmentation of mercaptoalkylation products of this type is subject to virtually the same principles as in the case of the fragmentation of monoalkylhydrazones [6]: Thus β cleavage with respect to the sp^3-hybridized nitrogen atom is one of the principal pathways of fragmentation of the molecular ion in all cases.

The formation of monomercaptoalkylation products III (IV) is complicated by side and secondary processes, the degree of occurrence of which depends on the reactivities of the starting reagents. Thus, according to the PMR spectroscopic data, the principal product of the reaction of thiirane with acetone hydrazone (IIIa $\rightleftarrows$ IVa) contained an impurity that we were unable to separate by distillation or gas–liquid chromatography (GLC). A singlet at 1.50 ppm (in CCl_4; its intensity was 8% of the overall intensity of the signals of all of

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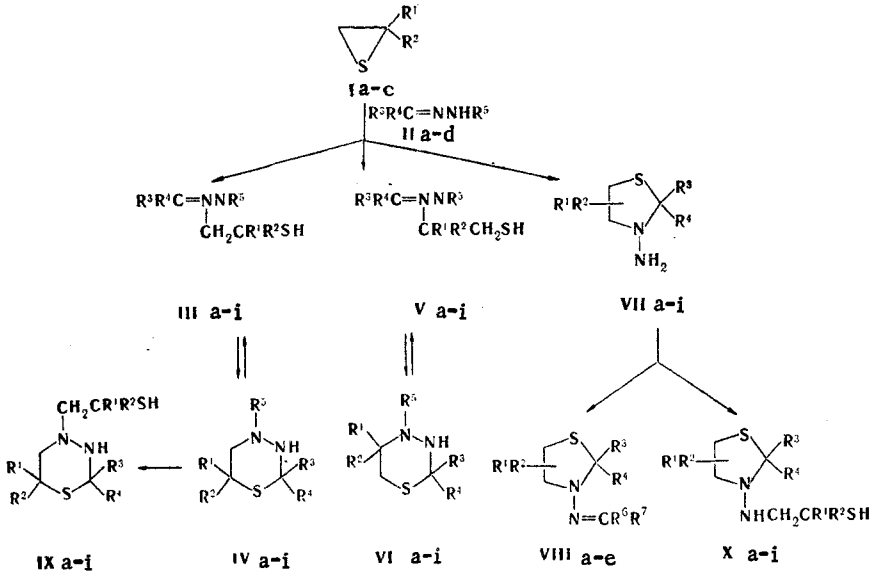
the methyl groups of the two tautomeric forms) which remained unchanged when the temperature of the sample was lowered −50°C (in deuterochloroform), and vanished when the substance was treated with acetone, corresponded to this impurity in the PMR spectrum. The assumption that the impurity is aminothiazolidine VIIa, which was made on this basis, is confirmed



I a*, b R^1=Me; c R^1=R^2=Me; II a R^3=R^4=Me; b R^3=Me, R^4=*t*-Bu; c R^3=*i*-Pr; d R^3=Me, R^5=*i*-Pr; III—VII, IX, X a R^3=R^4=Me; b R^3=Me, R^4=*t*-Bu; c R^1=R^3=R^4=Me; d R^1=R^3=Me, R^4=*t*-Bu; e R^1=R^2=R^3=R^4=Me; f R^3=*i*-Pr; g R^1=Me, R^3=*i*-Pr; h R^1=R^2=Me, R^3=*i*-Pr; i R^3=Me, R^5=*i*-Pr; VIII a R^3=R^4=R^6=R^7=Me; b R^3=R^6=*i*-Pr; c R^1=Me, R^3=R^6=*i*-Pr; d R^1=R^2=Me, R^3=R^6=*i*-Pr; e R^3=*i*-Pr, R^6=R^7=Me

*Here and subsequently, the fact that R = H is not indicated.

by the formation of isopropylidene derivative VIIIa on treatment with acetone. The structure of VIIIa, which, because of the small amount present, was not isolated in pure form, is in agreement with the data from PMR spectroscopy and chromatographic mass spectrometry. Its mass spectrum, which is similar to the spectra of other alkylideneaminothiazolidines (see below), contains, in addition to an intense molecular-ion peak, peaks of $(M - CH_3)^+$, $[M - N{=}C(CH_3)_2]^+$, $M - C_2H_4S)^{+\cdot}$ and $(M - C_2H_4S - CH_3)^+$ fragment ions (the formation of all of these ions is confirmed by the presence of the corrsponding metastable ions).

An adduct of two molecules of the thiirane and one molecule of the hydrazone, which, in conformity with the PMR spectrum, has structure IXa, was isolated from the same reaction mixture (Ia + IIa). Whereas splitting out of a CH_2SH group (m/e 85) with subsequent ejection of a molecule of formaldimine (m/e 56) is characteristic for hydrazone IIIa upon electron impact, successive splitting out of a CH_2SH group (m/e 145), a molecule of thiirane (m/e 85), and a molecule of formaldimine (m/e 56) is observed for perhydrothiadiazine IXa (all of these fragmentation processes are confirmed by the corresponding metastable ions); the same ion peak with m/e 85 has the maximum intensity in both cases.

In addition to these two mercaptoalkylation products we also obtained the previously unknown simplest vicinal hydrazinothiol, viz., 2-hydrazinoethanethiol, which undergoes sublimation during removal of hydrazone IIIa by distillation. The possibility of its presence in the reaction mixture remains undecided, since this extremely labile compound decomposes under the chromatographic conditions. The formation of the hydrazinothiol is apparently a consequence of an exchange reaction between mercaptoalkylation product IIIa and starting hydrazone IIa (although one also cannot completely exclude the possibility of mercaptoalkylation of the hydrazine that is formed as a result of disproportionation of hydrazone IIa under the reaction conditions).

The reaction of the thiirane with the much less reactive pinacolone hydrazone (IIb) leads exclusively to mercaptoalkylation product IIIb; however, the reaction proceeds very slowly, and mercaptoethylhydrazone IIIb was isolated in low yield. In addition, the latter

TABLE 1. Data from a Chromatographic Mass-Spectrometric Analysis of the Reaction Mixtures

Starting reagents	Components of the mixtures[a]	m/e (relative intensity, %)[b]
1	2	3
Ia + IIa	IIIa ⇄ IVa	132 (M^+, 19), 86 (5), 85 (100), 72 (6), 61 (4), 57 (6), 56 (76), 42 (9), 41 (6) [m^* 54,7; 36,9]
	IXa (3,9 : 1)	192 (M^+, 25), 147 (4), 146 (6), 145 (66), 132 (5), 105 (3), 101 (4), 88 (19), 86 (6), 85 (100), 74 (4), 61 (30), 60 (8), 59 (12), 58 (22), 57 (5), 56 (29), 47 (4), 45 (9), 44 (5), 43 (4), 42 (17), 41 (8) [m^* 109,5; 53,4; 49,8; 36,9]
Ia+IIb	IIIb	174 (M^+, 17), 128 (8), 127 (87), 117 (20), 114 (5), 99 (4), 87 (3), 84 (4), 76 (5), 72 (5), 69 (5), 61 (7), 59 (6), 58 (9), 57 (100), 56 (4), 55 (6), 47 (5), 45 (4), 43 (8), 42 (40), 41 (28) [m^* 92,7; 78,7; 37,1; 29,4; 25,6]
Ib+IIa	IIIc⇄IVc, Vc⇄VIc	146 (M^+, 17), 99 (28), 86 (6), 85 (100), 72 (7), 58 (8), 57 (7), 56 (86), 47 (4), 44 (3), 42 (9), 41 (13) [m^* 67,1; 49,5; 36,9; 31,7]
	IXc (6,2 : 1)	220 (M^+, 13), 160 (4), 159 (41), 157 (8), 146 (4), 102 (12), 99 (4), 86 (6), 85 (100), 75 (19), 74 (6), 73 (5), 61 (4), 59 (8), 58 (15), 57 (38), 56 (22), 47 (8), 45 (6), 44 (4), 43 (5), 42 (16), 41 (25) [m^* 114,9; 45,4; 36,9]
Ib+IIb	IIId, Vd	188 (M^+, 10), 155 (4), 141 (8), 131 (9), 128 (7), 127 (76), 114 (4), 69 (5), 61 (3), 58 (7), 57 (100), 56 (5), 55 (4), 47 (3), 43 (4), 42 (25), 41 (27) [m^* 91,3; 85,8; 37,1; 29,5; 25,6]
Ic + IIa	IIIe, Ve	162 (5), 161 (8), 160 (M^+, 84), 147 (4), 146 (7), 145 (79), 127 (16), 113 (9), 96 (5), 89 (5), 88 (8), 87 (11), 86 (27), 85 (100), 77 (5), 76 (13), 75 (17), 74 (12), 73 (40), 72 (34), 71 (58), 70 (6), 61 (4), 60 (5), 59 (30), 58 (24), 57 (54), 56 (43), 55 (51), 54 (10), 53 (5), 47 (8), 46 (4), 45 (63), 44 (12), 43 (20), 42 (22), 41 (47) [m^* 131,4; 37,1]
Ia+IIc	VIIf	146 (M^+, 7), 105 (5), 104 (5), 103 (100), 99 (17), 75 (4), 71 (4), 61 (5), 59 (5), 57 (4), 56 (4), 55 (5), 45 (5), 44 (4), 43 (19), 42 (4), 41 (7) [m^* 72,7; 56,4]
	VIIIb	200 (M^+, 3), 159 (5), 158 (9), 157 (100), 97 (3), 88 (22), 84 (3), 61 (7), 60 (5), 59 (4), 56 (3), 55 (6), 45 (3), 44 (4), 43 (19), 42 (4), 41 (10) [m^* 123,2; 49,3; 42,3; 37,1]
	Xf (4,3 : 1 : 1)	208 (4), 207 (5), 206 (M^+, 43), 204 (3), 163 (25), 161 (4), 160 (7), 159 (74), 157 (5), 115 (4), 103 (38), 100 (7), 99 (100), 90 (3), 89 (4), 88 (19), 72 (10), 71 (4), 70 (11), 62 (3), 61 (46), 60 (11), 59 (10), 58 (4), 57 (6), 56 (9), 55 (12), 54 (4), 47 (6), 46 (3), 45 (11), 44 (7), 43 (27), 42 (15), 41 (12) [m^* 129,0; 122,7; 65,1; 61,6; 49,6]
Ib+IIc	VIIg	160 (M^+, 6), 119 (5), 118 (6), 117 (100), 99 (3), 85 (3), 75 (4), 73 (4), 71 (4), 60 (3), 57 (3), 56 (4), 55 (5), 45 (5), 43 (14), 42 (4), 41 (12) [m^* 85,6; 48,3; 45,7; 37,1]
	IIIg⇄IVg Vg⇄VIg	160 (M^+, 11), 117 (34), 113 (22), 100 (7), 99 (100), 75 (4), 72 (3), 71 (5), 70 (6), 61 (4), 59 (3), 58 (5), 57 (4), 56 (8), 55 (6), 47 (5), 45 (4), 44 (15), 43 (55), 42 (8), 41 (26) [m^* 85,6; 49,7; 37,1]
	VIIIc	214 (M^+, 2), 173 (6), 172 (11), 171 (100), 102 (18), 99 (3), 97 (4), 84 (5), 75 (5), 74 (4), 59 (3), 58 (7), 56 (5), 55 (8), 45 (4), 43 (23), 42 (6), 41 (23) [m^* 136,6; 60,8; 37,1; 33,1]

TABLE 1. (cont.)

1	2	3
	Xg (14 : 1 : 2,8 : 1,3)	235 (4), 234 (M^+, 25), 232 (3), 191 (11), 185 (40), 174 (4), 173 (39), 171 (16), 118 (4), 117 (29), 102 (18), 100 (7), 99 (100), 85 (6), 83 (3), 75 (3), 74 (8), 73 (10), 72 (10), 71 (5), 70 (11), 69 (4), 61 (8), 60 (5), 59 (8), 58 (8), 57 (8), 56 (9), 55 (10), 47 (12), 45 (12), 44 (6), 43 (26), 42 (18), 41 (41) [m^* 127,9; 56,7; 49,6; 37,1]
Ic+IIc	VIIh	174 (M^+, 8), 133 (5), 132 (8), 131 (100), 99 (4), 98 (4), 87 (5), 85 (4), 82 (3), 74 (3), 72 (4), 71 (9), 70 (6), 59 (4), 58 (6), 57 (4), 56 (6), 55 (19), 53 (3), 45 (7), 44 (5), 43 (27), 42 (6), 41 (16) [m^* 98,6; 73,3; 37,1]
	IIIh⇄IVh	174 (M^+, 8), 141 (4), 131 (17), 100 (7), 99 (100), 87 (3), 75 (5), 74 (3), 72 (4), 70 (8), 69 (3), 59 (4), 57 (4), 56 (6), 55 (12), 45 (5), 44 (3), 43 (39), 42 (5), 41 (19) [m^* 49,6; 37,1]
	VIIId (5,0 : 1,2 : 1)	228 (M^+, 2), 187 (5), 186 (12), 185 (100), 116 (8), 115 (3), 89 (5), 87 (3), 84 (5), 82 (4), 72 (6), 70 (4), 56 (5), 55 (20), 45 (3), 43 (16), 42 (4), 41 (16) [m^* 150,1; 72,7; 68,3; 37,1]
Ia+IId	IVi	162 (3), 161 (6), 160 (M^+, 60), 145 (6), 117 (4), 114 (7), 113 (87), 87 (7), 85 (32), 74 (3), 73 (8), 72 (9), 71 (100), 70 (10), 61 (18), 60 (9), 59 (7), 58 (7), 57 (6), 56 (15), 45 (9), 44 (24), 43 (43), 42 (16), 41 (14) [m^* 79,8; 49,8; 44,6]

[a]The components of the reaction mixtures are presented in the order of their emergence from the chromatographic column, and their ratios are indicated in parentheses.
[b]Fragment ions with m/e values less than 41 and relative intensities less than 3% are not presented.

TABLE 2. Spectral Characteristics of 2-Mercaptoalkylhydrazones III and Perhydro-1,3,4-thiadiazines IV and IX

Compound	δ, ppm (J, Hz)					ν, cm^{-1} ($CHCl_3$)		
	R^1	R^2	CH_2—N	R^3	R^4	C=N	S—H	N—H
IIIa ↓↑ IVa	2,63 t (6,0)		3,19 t (6,0)	1,70 s	1,85 s	1640 m	2550 w	3200—3400 m
	2,50—3,40 m			1,46 s				
IIIb	2,60 t (6,5)		3,20 t (6,5)	1,64 s	1,04 s	1625 m	2570 w	3200—3300 w
IIIc ↓↑ IVc	1,28 d (6,5)	2,53—3,36 m		1,68 s	1,83 s	1635 m	2550 w	3200 m
	1,03 d (6,5)	2,53—3,36 m 2,19 dd ($5\text{-}H_a$; 10,5, 12,5)		1,30 s	1,57 s			
IIIe	1,31 s		3,18 d (5,5)	1,67 s	1,81 s	1600 m	2580 w	3210 w
IVi[a]	2,29 ($5\text{-}H_a$), 2,82 ($5\text{-}H_e$), 2,60 ($6\text{-}H_e$), 3,16 ($6\text{-}H_a$), (5a5e −11,5, 5a6a 11,4, 5a6e 2,5, 5e6a 3,0, 5e6e 2,5, 6a6e −12,5)			1,27 d (6,7)	4,31 m (CHCH 7,0, CHNH 11,0)	—	—	3160
IXa	2,46—3,12 m[b]			1,47 s		—	2580 w	3160 w

[a]Signals of substituent R^5: δ 0.96 d and 1.01 d (J = 6.5 Hz; diastereotopic methyl groups) and 2.80 m (CH). [b]The methylene protons of the exocyclic mercaptoethyl group resonate in the same region.

is difficult to isolate by distillation in connection with the formation of the high-boiling pinacolone azine under the reaction conditions. In addition to a peak corresponding to splitting out of a CH_2SH particle (m/e 127), the peak of an ion that arises as a result of α cleavage relative to the azomethine bond $(M - C_4H_9)^+$ is observed in the mass spectrum of IIIb, and the most intense peak is that of the tert-butyl ion, which is formed from the ion with m/e 127 (all of these fragmentation pathways are confirmed by metastable ions).

The nucleophilic opening of unsymmetrically substituted thiiranes may proceed via two pathways [7]. Although according to the data from analysis by GLC, acetone and pinacolone hydrazones form individual monomercaptoalkylation products with methylthiirane, the mass spectra of these hydrazones indicate the presence of two isomers of the III and IV type with considerable predominance of the product of "normal" opening of the thiirane ring. Ion peaks corresponding to splitting out of both CH_2CHSH (for IIIc, m/e 85 and m* 49.5; for IIId, m/e 127 and m* 85.8) and CH_2SH (for IIIc, m/e 99 and m* 67.1; for IIId, m/e 141) groups are observed in the mass spectra of the mercaptolakylhydrazones, and the intensity of the $(M - 61)^+$ ion is several times higher than that of the $(M - 47)^+$ ion. The distilled IIIc $\rightleftarrows$ IVc hydrozone contains 11% of the product of alternative opening of the thiirane ring (Vc $\rightleftarrows$ VIc) according to the PMR data. Pinacolone hydrazone reacts with methylthiirane even more sluggishly than with unsubstituted thiirane such that the yield of the sole mercaptoalkylation product does not exceed 10% even after prolonged (6 h) heating of the reagents. We were unable to isolate hydrazone IIId in the individual state (the distilled preparation contained a considerable amount of pinacolone azine). Its formation is confirmed by both the PMR spectrum [singlets at 1.05 and 1.65, doublet at 1.30 (J = 6.5 Hz), and multiplet at 2.5-3.4 ppm; the intensity ratio is 3:1:1:1] and by the mass spectrum, a peculiarity of which is the appearance of a low-intensity $(M - SH)^+$ ion, which is characteristic for secondary and tertiary thiols [8].

Fragmentation of the "thiol" type is even more appreciable for the product of mercaptoalkylation of acetone hydrazone with 2,2-dimethylthiirane (IIIe), which, according to the GLC data, is the only reaction product and contains a tertiary mercapto group. However, in this case ion peaks that correspond to splitting out of both a $C(CH_3)_2SH$ group and a CH_2SH group and constitute evidence for opening of the thiirane ring in two directions are observed in the mass spectrum. Judging from the intensities of the signals that can be assigned to hydrazone Ve, the distilled preparation contains $\sim$ 5% of the latter.

In conformity with the known decrease in the reactivities on passing from thiirane to substituted thiiranes [7], the yields of the products of mercaptoalkylation of the ketone hydrazones generally decrease in this order. In all cases the conversion of the thiiranes was not complete; however, an increase in the reaction time is usually accompanied by the formation of undesired impurities.

When unsubstituted aldohydrazones are subjected to reaction with thiiranes, addition of the thiirane to the azomethine bond, which leads to 3-aminothiazolidines VII and their derivatives VIII and X, becomes the principal process. This pathway is also realized as a side process in the reaction of acetone hydrazone with unsubstituted thiirane. The fact that the relative reactivity of the second nucleophilic center (the sp^2-hybridized nitrogen atom) increases in the case of aldohydrazones is in all likelihood due to deactivation of the amine fragment as a result of more intensive p, π conjugation in the aldohydrazones as compared with the hydrazones of ketones [9].

The reaction of thiirane (Ia) with isobutyraldehyde hydrazone (IIc) gives mainly aminothiazolidine VIIf, the structure of which is proved by, in addition to spectral data (Tables 1 and 3), conversion to isopropylidene derivative VIIIe. Isobutylideneamino derivative VIIIb, the formation of which can be imagined to be the result of an exchange reaction of aminothiazolidine VIIf with the starting hydrazone or addition of thiirane to isobutyraldehyde azine — the product of disproportionation of hydrazone IIc — was also isolated from the reaction mixture Ia + IIc. The third component of the reaction mixture is bis(mercaptoalkylation) product Xf. It structure is confirmed in particular by the fact that it is formed (as proved by chromatography) by treatment of aminothiazolidine VIIf with insufficient thiirane. The ion peak corresponding to detachment of an isopropyl group is the most intense peak in the mass spectrum of aminothiazolidine VIIf; in addition, only the peaks of the ion with m/e 99 and the isopropyl cation have appreciable intensities. In the mass spectrum of VIIIe the intensities of the latter two peaks decrease, but an intense ion with m/e 56 (cleavage at the nitrogen—nitrogen bond) appears; in the spectrum of VIIIb the ion

with m/e 99 disappears completely, but an ion with m/e 88, which corresponds to ejection of a molecule of isobutyronitrile by the $(M - \text{iso-Pr})^+$ ion (m/e 157, m* 49.3), is observed. The $(M - \text{iso-Pr})^+$ and $(M - CH_2SH)^+$ ions, which subsequently split out a molecule of thiirane, are characteristic for mercaptoalkyl derivative Xf (all of these fragmentation pathways are confirmed by metastable ions).

In the case of methylthiirane the principal product of the reaction with hydrazone IIc is also a 3-aminothiazolidine (VIIg). However, the presence in the PMR spectrum of two equally intense sets of signals of 2-H and methyl protons indicates the formation of a pair of isomers. The same thing also occurs in the case of alkylidene derivative VIIIc. Taking into account the fact that the mass spectra of aminothiazolidines VIIg, VIIIc, and Xg are completely analogous to the mass spectra of the derivatives obtained from hydrazone IIc and unsubstituted thiirane, with the characteristic peculiarity that a C_2H_5S grouping is split out during fragmentation here and elsewhere instead of a group with the composition CH_3S, it may be assumed that the reaction with participation of the azomethine bond proceeds regiospecifically to give a mixture of stereoisomers. The data available to us do not make it possible to determine the precise position of the methyl group in the ring, but its presence in the 5 position seems more probable. In contrast to thiirane, methylthiirane reacts with hydrazone IIc to give a very small amount of a product of mercaptoalkylation at the amine nitrogen atom, viz., a mixture of mercaptoalkylhydrazones IIIg and Vg, which undergo reversible isomerization to the corresponding perhydrothiadiazines. This impurity is not separated completely from aminothiazolidine VIIg by distillation: The low-intensity doublet signals at δ 4.00 (J = 5.5 Hz; the signal becomes broader at 35°C, but this broadening vanishes at 90°C) and 6.91 ppm (J = 5.0 Hz) in the PMR spectrum correspond to it.

Chromatographic mass-spectrometric analysis of the reaction mixture obtained from 2,2-dimethylthiirane and hydrazone IIc provides evidence for the formation of three compounds, viz., the product of addition of the thiirane to the azomethine bond of VIIh, its isobutylidene derivative VIIId, and the product of mercaptoalkylation of the sp^3-hybridized nitrogen atom — hydrazone IIIh. Judging from the mass spectrometric data, both nucleophilic centers of the hydrazone open up the thiirane ring regiospecifically. We were unable to separate the three-component mixture by distillation: The isolated sample was also a mixture of all three compounds. Doublet signals of the 2-H protons of aminothiazolidine VIIh [3.96 ppm (J = 6.7 Hz)], of the 2-H and CH=N protons of a mixture of tautomers IIIh and IVh [4.08 (J = 6.0 Hz) and 6.85 ppm (J = 6.0 Hz)], and of 2-H and CH=N protons of alkylideneaminethiazolidine VIIId [4.56 (J = 6.2 Hz) and 6.91 ppm (J = 6.0 Hz)] are observed in the PMR spectra. This assignment was made in conformity with the data from quantitative chromatographic analysis; the strong-field region of the spectrum is too complex for interpretation.

The formation of aminothiazolidines is probably the first example of the addition of thiiranes to the azomethine bond, although a similar reaction with nitriles, which leads to thiazolines, is known [10]. The latter reaction is catalyzed by acids. It is possible that under catalytic conditions the reaction of thiiranes with compounds that contain a C=N bond may serve as a convenient method for the synthesis of thiazolidines, and we have begun studies in this direction. In the absence of a catalyst the observed reaction is characteristic only for unsubstituted aldohydrazones: The attachment of an alkyl group to the "amine" nitrogen atom of the aldohydrazone increases the nucleophilicity of this reaction center and thus slows down addition to the azomethine bond. Thus, only a mercaptoalkylation product that exists entirely in cyclic tautomeric form IVi is formed from acetaldehyde isopropylhydrazone (IId) and thiirane. The structure of this compound was confirmed by alternative synthesis from 2-(1-isopropylhydrazino)ethanethiol and acetaldehyde.

Although all of the 2-mercaptoalkylhydrazones (III) obtained are potentially tautomeric systems, reversible conversion to ring isomer IV was found to be characteristic only for IIIa and IIIc. Both the reversible temperature dependence of the change in the relative intensities of the signals of the methyl groups in the PMR spectra and the change in the refractive indexes of both freshly distilled preparations up to the equilibrium values indicate the tautomeric character of these systems. We determined the thermodynamic parameters of the tautomeric conversion from the temperature dependence of the tautomeric equilibrium constants $K_T = [III]/[IV]$ (Table 4). It is apparent from these data that the introduction of a methyl substituent in the mercaptoethyl group of the hydrazone leads to an increase in the enthalpy of the acyclic form as compared with the ring form probably as a consequence

TABLE 3. Spectral Characteristics of 3-Amino- and 3-Alkylideneaminothiazolidines

Compound	δ, ppm(J, Hz)						$\nu_{C=N}$, cm^{-1}	ν_{N-H}, cm^{-1}	δ_{NH_2}, cm^{-1}
	R^1	CH_2CH	R^3	R^4	R^6	R^7			
VII f	2,54—3,40 m		0,96 d 1,04 d (6,7)[a], 1,75 m[b]	3,96 d (10,0)				3210 w 3350 m	1590 s
VII g	1,31 d (6,0), 1,33 d (6,5)	2,0—3,9 m	1,02d (6,7), 1,5—2,0 m	3,89 d (9,5), 4,23 d (9,5)				3220 w 3355 m	1595 s
VIII b	2,75—3,81 m		0,96 d 1,06d (6,5)[a], 1,82 m[b]	4,25 d (8,0)	1,06 d (6,5), 2,41 m	7,03 d (5,4)	1640 m		
VIII e	2,64—3,56 m		0,94 d 0,98 d (6,5)[a], 1,71 m[b]	4,05 d (8,5)	1,89 s	2,01 s	1640 m		

[a]Diastereotopic methyl groups of the isopropyl grouping. [b]Methylidyne proton of the isopropyl grouping.

TABLE 4. Thermodynamic Parameters of the III ⇄ IV Tautomeric Equilibrium

Hydrazone	K_T					ΔH^0, kJ·mole^{-1}	ΔS^0, J·mole^{-1}·deg^{-1}	ΔG^0_{25}, kJ·mole^{-1}
	30°	35°	52°	72°	92°			
III a	7,00	—	9,09	12,8	17,1	13,4±1,0	60±3	−4,5±0,1
III c	1,81	1,98	3,41	4,31	5,05	15,8±2,1	57±7	−1,3±0,3

TABLE 5. Products of Mercaptoalkylation of the Hydrazones

Compound	bp, °C (mm)	n_D^{20}	d_4^{20}	MR_D		Found, %			Empirical formula	Calculated, %			Yield, %
				Found, %	Calc., %	C	H	S		C	H	S	
IIIa⇄IVa	89—90 (14)	1,5194[a]	1,0299[a]	38,99[a]	39,14/38,22[b]	45,1	9,1	24,2	$C_5H_{12}N_2S$	45,4	9,1	24,2	47
IIIb	90—95 (8)	1,5010	0,9665	53,13	53,08	55,7	10,5	19,1	$C_8H_{18}N_2S$	55,1	10,4	18,4	8
IIIc⇄IVc	82—83 (11)	1,5084[a]	1,0031[a]	42,50[a]	43,79/42,90[b]	48,6	9,9	21,8	$C_6H_{14}N_2S$	49,3	9,6	21,9	45
IIIe	82—86 (10)	1,4954	0,9608	48,69	48,30	52,2	9,8	20,3	$C_7H_{16}N_2S$	52,4	10,1	20,0	29
IVi[c]	76—78 (11)	1,4922	0,9701	47,95	47,98	52,3	10,3	19,8	$C_7H_{16}N_2S$	52,4	10,1	20,0	20
VIIf	87—88 (8)	1,5177	1,0518	42,12	43,13	49,4	9,8	22,0	$C_6H_{14}N_2S$	49,3	9,6	21,9	27
VIIg	88—90 (8)	1,5035	1,0157	46,69	47,78			19,8	$C_7H_{16}N_2S$			20,0	17
VIIIb	70—71 (2)	1,5037	0,9731	60,93	60,67			16,1	$C_{10}H_{20}N_2S$			16,0	14
VIIIe	98—99 (7)	1,5081	0,9852	56,38	56,02	58,0	9,8	17,1	$C_9H_{18}N_2S$	58,0	9,7	17,2	48
IXa	124—127 (11)	1,5440	1,1096	54,72	54,42	42,6	8,8	35,4	$C_7H_{16}N_2S_2$	43,7	8,4	33,3	9

[a]For equilibrium mixtures. [b]Chain/ring. [c]The hydrochloride had mp 118-119°C.

of the increase in the number of skew interactions, which are absent in the ring form (see [11]). However, the appearance of a second methyl group in the same position leads to a complete shift of the equilibrium to favor the acyclic tautomer (IIIe). A sterically demanding substituent attached to the azomethine carbon atom has a similar effect, and a ring form also cannot be detected in the case of pinacolone derivatives IIIb, d. On the other hand, the appearance of a substituent attached to the nitrogen atom shifts the equilibrium markedly to favor the perhydrothiadiazine, and IVi and IXa do not contain any appreciable amounts of the acyclic tautomer. Similar effects of substituents have been noted in a number of N-alkyl-N-(2-hydroxyalkyl)hydrazones; however, data on the tautomeric equilibrium constants are not available for the oxygen analogs of the 2-mercaptoalkylhydrazones investigated in the present research that do not have a second substituent attached to the nitrogen atom, since cyclic tautomers have not been detected at all for such analogs [12]. A considerably greater tendency for cyclization of the mercapto derivatives as compared with the hydroxy derivatives of hydrazones is clearly apparent in this case. One of the possible reasons for such a substantial difference is in all likelihood the pronounced weakening of the intramolecular hydrogen bonds that stabilize the open tautomeric form in the sulfur compounds as compared with the oxygen compounds. It is known that SH...N and NH...S hydrogen bonds are much weaker than OH···N and NH···O hydrogen bonds [13]. The weakening of the steric strain in the ring form of the sulfur derivatives due to the greater length of the C—S bond (1.82 Å) as compared with the C—O bond (1.43 Å) is also noteworthy. The shift of the equilibrium to favor the ring form in such tautomeric systems is sometimes [14] linked with an increase in the nucleophilicity of the sulfur atom as compared with the oxygen atom, i.e., with the higher rate of addition of the SH group, as compared with the OH group, to the azomethine bond. This sort of kinetic approach is not sufficiently rigorous, since it does not take into account the ratio of the reverse reaction, viz., ring opening, in both types of tautomeric systems.

An analysis of the PMR spectra of perhydro-1,3,4-thiadiazines makes it possible to draw several conclusions regarding the three-dimensional structures of these compounds. Thus, the ratio of the constants of spin-spin coupling of the methylene protons of perhydrothiadiazine IVi makes it possible to determine the R factor [15] that corresponds to the N—C—C—S torsion angle (60°), i.e., a chairlike conformation of the ring. The high value of the vicinal J_{23} constant (11.0 Hz) indicates that, as in the case of perhydrooxadiazines [12], the proton of the N—H group in the molecule of this compound is primarily axially oriented. The signals of both methyl groups in the spectra of 2,2-dimethylperhydrothiadiazines IVa and IXa at the usual working temperature are observed in the form of one singlet as a consequence of the rapid (on the PMR time scale) interconversions of the two equivalent conformations of the ring. However, this singlet is split into two signals corresponding to axially and equatorially oriented methyl groups even in the case of a relatively small decrease in the temperature. The difference in the chemical shifts of this pair of signals is 31 Hz (for IVa) and 26 Hz (for IXa). An estimate of the barrier to conversion of the ring at the coalescence temperature gives 51.0 kJ/mole for IVa (at 253°K) and 52.7 kJ/mole for IXa (at 259°K; in calculations by means of the Eyring equation the transmission coefficient was assumed to be 0.5; the error in the determination of the size of the barrier was ± 1.5 kJ/mole). These barrier values are also in agreement with a chairlike conformation of the ring and are close to the barrier found for 3,4-dimethylperhydro-1,3,4-thiadiazine [16].

EXPERIMENTAL

Gas chromatographic analysis of the reaction mixtures was carried out immediately after their preparation with a Tsvet-101 chromatograph with a flame-ionization detector and a 1.8 m by 2 mm glass silanized column filled with 5% SE-30 on Inerton AW (0.125-0.16 mm); the column temperature was 150°C, and the carrier gas was nitrogen or argon. The following conditions were used for recording the mass spectra (with an LKV-2091 spectrometer): The ionizing-electron energy was 70 eV, the ionization current was 25 μA, the accelerating voltage was 3.5 kV, the separator temperature was 180°C, and the ion-source temperature was 200°C. The mass spectra were recorded at the maxima of the chromatographic peaks, and the scanning time was 2-4 sec. The PMR spectra of 20% solutions or (at low temperatures) 1 M solutions of the compounds in deuterochloroform were obtained with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane as the internal standard. The temperature dependence of the tautomeric equilibrium constants was determined from the PMR spectra of 1 M solutions

in tetrachloroethylene with hexamethyldisiloxane as the external standard; the results were processed by the method of least squares. The IR spectra of thin layers or 5% solutions of the compounds in chloroform were recorded with a UR-20 spectrometer.

Mercaptoethylation of Acetone Hydrazone. An 11.3-g (0.19 mole) sample of thiirane was added with stirring to a solution of 54.5 g (0.76 mole) of freshly distilled acetone hydrazone in an equal volume of benzene, and the mixture was placed in a steel autoclave and heated at 100°C for 3 h. A 1-ml sample of the mixture was removed for chromatographic mass-spectrometric analysis, the benzene and acetone hydrazone were removed by distillation, and the residue was subjected to distillation with a column to give 11.9 g of hydrazone IIIa (Tables 2 and 5) containing ∿8% aminothiazolidine VIIa. Treatment of the substance with an equimolar amount of acetone led to the formation of isopropylideneaminothiazolidine VIIIa, which was distilled to give a product containing hydrazone IIIa. Singlets at 1.42 (ring 2-CH_3) and 1.90 and 1.97 ppm (CH_3 groups attached to the azomethine carbon atom) are observed in the PMR spectrum of the VIIIa-enriched fraction. Mass spectrum of VIIIa (which has a longer retention time than hydrazone IIIa), m/e (relative intensity, %): 174 (3), 173 (7), 172 (M^+, 59), 158 (4), 157 (40), 139 (5), 125 (20), 116 (37), 115 (4), 113 (4), 112 (33), 102 (5), 98 (5), 97 (55), 88 (16) 85 (37), 84 (6), 83 (5), 82 (4), 74 (8), 73 (4), 72 (4), 71 (6), 70 (42), 69 (5), 68 (4), 61 (6), 60 (20), 59 (30), 58 (11), 57 (8), 56 (100), 55 (12), 54 (7), 46 (4), 45 (15), 43 (4), 42 (28), (m* 143.3; 84.0; 72.9; 78.2; 66.8; 37.1). The mass spectrum of hydrazone IIIa after treatment with acetone (i.e., the peaks of the fragment ions of admixed VIIa are absent) is presented in Table 1. Crystalline 2-hydrazinoethanethiol sublimed during the distillation of hydrazone IIIa. After washing with pentane and drying in vacuo, we obtained 1.4 g of the hydrazinothiol in the form of colorless hygroscopic crystals that are readily oxidized in air (the yields in different experiments varied but did not exceed 8%). The product had mp 64-65°C. PMR spectrum (CD_3OD): 2.68 and 2.95 ppm (triplets, J = 6.5 Hz, CH_2CH_2). IR spectrum: 1610 (δ_{NH_2}), 2580 (ν_{SH}), and 3360 cm^{-1} (ν_{NH}). Found: C 26.2; H 8.6; S 34.8%. $C_2H_8N_2S$. Calculated: C 26.1; H 8.7; S 34.8%. The PMR spectrum of the product of the reaction of the hydrazinothiol with an equimolar amount of acetone coincided with the spectrum of hydrazone IIIa. Subsequent distillation of the reaction mixture gave 1.6 g of 4-(2-mercaptoethyl)-2,2-dimethylperhydro-1,3,4-thiadiazine (IXa) (Tables 2 and 5).

The other mercaptoalkylation reactions were carried out similarly. In order to increase the yield, after selection of a sample for analysis, reaction mixture Ib + IIb was heated under the same conditions for another 3 h, while mixture Ic + IIc was heated for 6 h. The physicochemical and analytical characteristics of the isolated reaction products are presented in Table 5.

2-Methyl-4-isopropylperhydro-1,3,4-thiadiazine (IVi). A) The reaction of isopropylhydrazine with thiirane in benzene solution [3] gave 2-(1-isopropylhydrazino)ethanethiol, with bp 80-81°C (11 mm), d_4^{20} 0.9696, and n_D^{20} 1.4899, in 61% yield. PMR spectrum (CCl_4): δ 1.00 (d, J =6.0 Hz, CH_3), 2.35 (broad s, NH_2, SH), 2.62 (m, CH_2), and 2.79 ppm (sp, J = 6.0 Hz, CH). IR spectrum: 1590 (δ_{NH_2}), 2570 (ν_{SH}), and 3230 and 3370 cm^{-1} (ν_{NH}). Found: C 44.6, H 10.8%; MR_D 40.02. $C_5H_{14}N_2S$. Calculated: C 44.7; H 10.5%; MR_D 40.38. A 3.8-g (0.086 mole) sample of freshly distilled acetaldehyde was added dropwise with cooling (with flowing water) and stirring to a solution of 11 g (0.082 mole) of 2-(1-isopropylhydrazino)ethanethiol in 50 ml of benzene, and the mixture was maintained at room temperature for 1 h. It was then refluxed for 1 h, after which the aqueous layer was separated, and the benzene solution was dried with sodium sulfate and vacuum distilled to give 8.7 g (66%) of perhydrothiadiazine IVi.

B) The reaction of acetaldehyde isopropylhydrazone with thiirane was carried out as described above, and perhydrothiadiazine IVi was obtained in 20% yield. The physicochemical properties (Table 5) and spectral characteristics (Tables 1 and 2) of the preparations obtained by the two methods were in complete agreement.

2-Isopropyl-3-isopropylideneaminothiazolidine (VIIIe). A 0.90-g (0.016 mole) sample of acetone was added to 2.28 g (0.016 mole) of 2-isopropyl-3-aminothiazolidine (VIIf), and the mixture was maintained at room temperature for 1 h. It was then heated on a boiling-water bath for 2 h, after which 10 ml of benzene was added, and the organic layer was separated, dried with potassium carbonate, and distilled to give 1.4 g of VIIIe (Tables 3 and 5). Mass spectrum, m/e (relative intensity, %): 186 (M^+, 12), 145 (5), 144 (9), 143 (100), 88 (5), 84 (3), 83 (4), 60 (5), 59 (4), 58 (4), 57 (4), 56 (49), 55 (6), 45 (4), 43 (4), 42 (9), 41 (9) (m* 109.9).

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REACTIVITIES OF 5-ALKYL-2-THIOXOPYRROLIDINES

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The chemical transformations of 5-alkyl-2-thioxopyrrolidines with nucleophilic and electrophilic reagents were studied and compared with the reactivities of their oxygen analogs. On the basis of the experimental data obtained from alkylation, hydroxyethylation, and condensation reactions it was established that, depending on the conditions and the character of the reagent, 5-alkyl-2-thioxopyrrolidines undergo the indicated reactions in the thiolactam or thiolactin form.

The reactivities of 5-alkyl-2-thioxopyrrolidines have not been adequately studied. It is known that unsubstituted 2-thioxopyrrolidines react with alkyl halides and mercuric chloride to give salts [1] and undergo condensation with α-halo ketones [2].

Considering the promising character of 5-alkylthioxopyrrolidines for the preparation of biologically active substances, we studied their reactions with nucleophilic and electrophilic reagents and compared them with the reactivities of their oxygen analogs.

It was established on the basis of alkylation, hydroxyethylation, and condensation reactions that, depending on the conditions and the character of the reagent, 5-alkyl-2-thioxopyrrolidines (Ia-c) undergo reaction at the S or N atom.

5-Alkyl-2-thioxopyrrolidines react with alkyl halides in the presence of sodium methoxide to give S-substituted derivatives (IIa-f).

The direction of alkylation was confirmed by the difference in the physical constants

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