REACTION OF THIIRANES WITH AZOMETHINE COMPOUNDS

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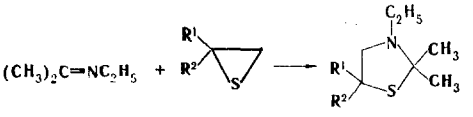
Thiiranes add to imines and oximes to give thiazolidines. The addition of asymmetrical thiiranes is regioselective. The reaction of derivatives of asymmetrical carbonyl compounds with methylthiirane leads to mixtures of cis and trans stereoisomers of thiazolidines. In the N-arylideneethylamine series the reaction is accelerated by donor substituents and is retarded by acceptor substituents.

We have already reported [1] that thiiranes react with azomethines to give thiazolidines. This process can be classified with the well-known [2] additive reactions with the participation of three-membered heterocycles and polar multiple bonds. However, the addition of thiiranes to the azomethine bond has thus far been observed only in individual cases [3, 4]. The aim of the present research was therefore primarily to establish the boundaries of applicability of the reaction and its regio- and stereoselectivity and to obtain data on the mechanism of the formation of thiazolidines. Despite the fact that thiazolidines are widely known, the addition of thiiranes to azomethines opens up a new route to the synthesis of some representatives of this class of compounds that are difficult to obtain by other methods and is of definite synthetic interest.

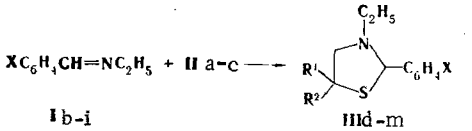
In the case of N-isopropylideneethylamine (Ia) we found that aliphatic azomethines react with thiiranes II under the conditions that are used for opening of the episulfide ring by more reactive amines (by heating the reagents in benzene [5, p. 213]) to give alkyl-substituted thiazolidines IIIa-c in 30-50% yields. The yields of thiazolidines can be increased substantially by carrying out the reaction in a mixture of alcohol with benzene.



Ia IIa-c IIIa-c

II-III* b $R^2=CH_3$; c $R^1=R^2=CH_3$

Less reactive arylideneamines do not react at all with thiiranes in benzene. The reaction is best carried out in a mixture of benzene with alcohol (as in the reaction of aniline with thiiranes [5, p. 213]). The yields of 2-arylthiazolidines in this case amount to 30-50%. Products of oligomerization of the thiiranes are formed as side products, and the unchanged imine can be regenerated from the reaction mixture:



Ib-i IIId-m

I b X=H; c X=3-Cl; d X=4-Cl; e X=3-CH_3O; f X=4-CH_3O; g X=4-Br; h X=4-F; i X=4-CN; III d X=H; e X=3-Cl; f X=4-Cl; g X=3-CH_3O; h X=4-CH_3O; i X=4-Br; j X=4-F; k X=H, $R^2=CH_3$; *l* X=4-CH_3O, $R^2=CH_3$; m X=H, $R^1=R^2=CH_3$

In order to study the effect of the polar factor on the reactivities of aromatic imines we used the method of competitive reactions to obtain data on the relative rates of addition of thiirane (IIa) to N-arylideneethylamines (Ib-i) in alcohol–benzene (1:1) at 75°C. We

*Here and subsequently, the compounds with R = H are not presented.

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TABLE 1. Relative Rate Constants for the Addition of Thiirane to N-Arylideneethylamines ($XC_6H_4CH{=}NC_2H_5$)

X	k_X/k_H
H	1,00
3-Cl	0,286±0,013
4-Cl	0,465±0,011
3-CH_3O	0,916±0,035
4-CH_3O	1,72±0,04
4-Br	0,400±0,009
4-CN	0,147±0,006

found that electron-donor substituents accelerate the addition, while electron-acceptor substituents retard it (Table 1); a linear correlation of the relative rate constants with the σ substituent constants [6] was observed ($\rho = -1.22$, $r = 0.979$, and $s_0 = 0.04$).

To obtain more detailed data on the mechanism of the addition and to estimate the relative reactivities of various thiiranes we investigated the kinetics of these reactions by gas-liquid chromatography (GLC) under pseudomonomolecular conditions. The rate constants of the reactions of methylthiirane and thiirane with N-benzylideneethylamine (Ib) in the presence of an excess of the latter are presented in Table 2. Thus on passing from thiirane to methylthiirane the rate of addition decreases by approximately an order of magnitude, while 2,2-dimethylthiirane reacts with azomethine Ib slower by a factor of approximately five than methylthiirane ($k'_1 \approx 10^{-6}$ sec^{-1} at 358°K). These results are, in general, in agreement with the kinetic principles of nucleophilic opening of the thiirane ring by amines [7].

The reaction proved to be extremely sensitive to the steric requirements of the substituent attached to the nitrogen atom. Thus, whereas N-benzylidenemethylamine reacts with thiirane at virtually the same rate as azomethine Ib, the reaction rate decreases by a factor of ∿10 ($k'_1 \approx 5\cdot10^{-7}$ sec^{-1}) on passing to N-benzylideneisopropylamine. In this connection, it may be noted that in the latter case, as well as in the case of N-isopropylideneisopropylamine, we were unable to preparatively isolate the corresponding thiazolidines from the reaction mixtures.

For the addition of methylthiirane to azomethine Ib in the presence of excess episulfide we obtained $k'_1 = 5.9 \pm 0.2$ sec^{-1} (348°K), which differs considerably from the value presented in Table 2. The difference is associated, in all likelihood, mainly with the effect of the medium. We established that the use of alcohol–benzene (1:9), dimethylformamide (DMF), or toluene–DMSO (1:1) as the solvent decreases the rate of addition of thiirane to azomethine Ib by a factor of almost 10.

In order to ascertain the regioselectivity of the addition of unsymmetrically substituted thiiranes to azomethines we obtained 1-ethylamino-2-propanethiol (IV) by regioselective opening of methylthiirane by ethylamine [5, p. 218]. The condensation of aminothiol IV with acetone and benzaldehyde led to the corresponding thiazolidines, which were identical (from the identical character of the IR spectra and the absence of melting-point depressions for mixtures of the derivatives) to the products of the addition of methylthiirane to imines Ia and Ib. This indicates that 5-methyl- and 5,5-dimethyl-substituted thiazolidines, respectively, are formed as a result of the addition of methyl- and 2,2-dimethylthiirane to the azomethines.

With allowance for the data presented in Tables 1 and 2, as well as the structures of the resulting thiazolidines, the addition of thiiranes to azomethines is most simply described by the scheme

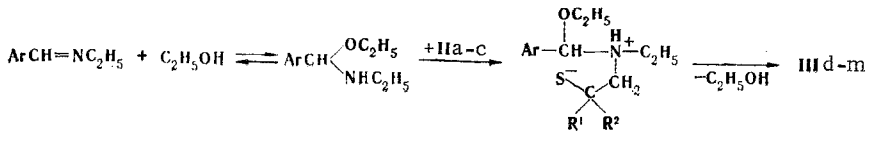
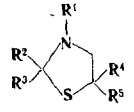


TABLE 2. Activation Parameters for the Addition of Thiiranes to N-Benzylideneethylamine

Reagent	$k'_1 \cdot 10^6$, sec^{-1}						$\Delta G^{\neq}$, kJ/mole	$\Delta H^{\neq}$, kJ/mole	$\Delta S^{\neq}$, J/mole-°K
	333°K	338°K	343°K	348°K	353°K	358°K			
Thiirane	19,4±0,5	28,5±1,0	41,5±1,2	62,2±1,8	—	—	113±2	72,1±1,6	−121±2
Methylthiirane	—	2,83±0,11	—	6,71±0,20	9,51±0,26	13,9±0,4	121±2	77,1±1,8	−124±2

TABLE 3. PMR Spectra of Thiazolidines

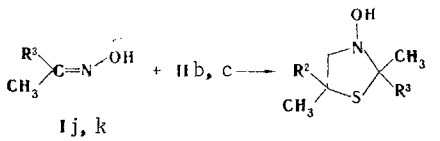


Compound	Solvent	δ, ppm (J, Hz)					
		R^1	R^2	R^3	R^4	R^5	4-H
IIIa	C_2Cl_4	1,08 t ; 2,46 q [a]		1,42 s	2,86 and 3,15 (A_2B_2; 6,3)		
IIIb	C_2Cl_4	2,37; 2,53; 1,06 (ABX_3; $J_{AB}=-12,6$; $J_{AX}=J_{BX}=7,0$)	1,37 s	1,40 s	3,56 m ($J_{45}=5,9$, $J_{4'5}=6,9$)	1,27 d [a]	3,20; 2,66 ($J_{44}=-10,1$)
IIIc	C_2Cl_4	2,49 q ; 1,10 t [a]		1,42 s	1,37 s		2,85 s
IIId-j	C_2Cl_4	1,0—1,1t [a] ; 2,0—3,5 m	4,9—5,1 s	6,5—8,0 m [b]	2,0—3,5 m		
IIIk [c]	C_2Cl_4	0.96; 1,03 t [a] ; 1,9—3,0m	4.78; 4,92 s	7,0—7,6 m	3,3—3,9m	1.26; 1,34 d [a]	1,9—3,0 m
IIIl [c]	C_2Cl_4	0.96; 1,02 t ; 1,9—3,0 m	4.71; 4,82 s	6,5—7,5 m [d]	3,3—3,9m	1.27; 1,37 d [a]	1,9—3,0 m
IIIm	C_2Cl_4	0,95 t [a]; 2,0—3,0m	4,72s	7,0—7,6 m	1,39 s [e]	1,59 s [e]	2,41; 3,15 dd (−9,2)
IIIn [c]	CD_3OD	4,75 (br s)	4,59q [a] and 4,7d [f]	1,42 d [e]; 1,36d [e]	3,85m ($J_{45}=10,1$; $J_{4'5}=6,2$)	1,42; 1,39; 1,36; 1,32 d [a,e]	2,67; 3,56 m ($J_{44}=-12,4$)
IIIo	CCl_4	8,17 (br s)	1.52; 1,53 s		3,96 m ($J_{45}=8,8$; $J_{4'5}=6,5$)	1,34 d [a]	3,04; 3,53 m ($J_{44}=-13,0$)
IIIp	CCl_4	8,18 (br s)	4,57 q [a]	1,50 d [a]	1.52; 1,55 s		3,10; 3,37 dd (−12,0)

[a] J = 7 Hz. [b] The signal of the protons of the methoxy group of IIIg and IIIh is observed at 3.6-3.8 ppm. [c] Mixture of stereoisomers, ~1:1. [d] The signal of the methoxy group is observed at 3.62 ppm. [e] The assignment of the R^3 and R^5 signals is ambiguous. [f] Superimposed on the signal of the OH group.

Since the reaction rate depends markedly on the alcohol concentration, it is reasonable to assume that a product of addition of alcohol to the azomethine is formed initially. The formation of an adduct of this type was established in the case of acetone anil [8]. Judging from the sign and magnitude of the reaction constant, the step that determines the rate of the process as a whole is precisely the step involving opening of the thiirane ring by this intermediate adduct. However, one should not exclude the possibility that other schemes for the formation of thiazolidines such as direct attack on the thiirane ring by the weakly nucleophilic azomethine nitrogen atom of purely aliphatic azomethines, the reactions with which proceed in an aprotic medium, are also realized simultaneously.

We found that aliphatic oximes also react with thiiranes to give thiazolidine derivatives:

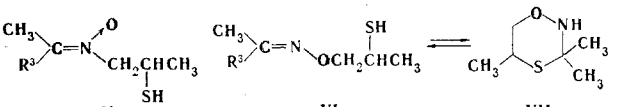


Ij, k

I k $R^3=CH_3$; III o $R^3=CH_3$; p $R^2=CH_3$

However, in a preparative respect the reaction is restricted only to derivatives of aliphatic oximes and methylthiirane. According to our data, benzaldoxime does not undergo reaction with thiiranes; oligomerization predominates in the case of unsubstituted thiirane, while in the case of the unreactive 2,2-dimethylthiirane the yield of N-hydroxythiazolidine is only ∿5%. For this reason, the product of the addition of 2,2-dimethylthiirane to acetaldoxime was not isolated in the individual state, but the presence of 3-hydroxy-2,5,5-trimethylthiazolidine (IIIp) in the distilled preparation was proved from its PMR spectrum (Table 3).

The fact that the reaction of thiiranes with oximes leads to the formation of precisely 3-hydroxythiazolidines is confirmed by the spectral characteristics of the compounds obtained. The presence in the IR spectra of a broad intense ν_{OH} band (3230-3280 cm^{-1}) and the absence of bands of C=N, N–H, and S–H stretching vibrations, as well as the chemical shifts and the spin-spin coupling constants in the PMR spectra (Table 3), repudiate structures of possible isomers of the V-VII type.



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Signals of two stereoisomeric (cis and trans) forms of approximately equal intensities (2-H protons and 5-CH_3 groups) are observed in the spectra of IIIk, l, n, which were obtained from derivatives of unsymmetrical carbonyl compounds Ib, f, j and methylthiirane. This indicates the absence of stereoselectivity in the addition of thiiranes to the azomethine bond.

The constants of spin-spin coupling between the 4-H and 5-H protons of the thiazolidine ring (Table 3) are, in general, quite typical for five-membered heterocycles with heteroatoms in the 1 and 3 positions [9] and, in particular, for thiazolidines [10].

EXPERIMENTAL

The IR spectra of thin layers or 3% solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of 20% solutions of the compounds (Table 3) were obtained with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane as the internal standard. Chromatographic analysis was carried out with a Tsvet-101 chromatograph with a 2 m by 3 mm glass silanized column filled with 5% SE-30 on Inerton AW (0.125-0.16 mm); the vaporizer temperature was 200-230°C, the column temperature was 140-175°C, and the carrier gas was nitrogen (30 ml/min).

N-Arylideneethylamines Ib-i (Tables 4 and 5). A solution of 0.6 mole of ethylamine in 100 ml of ether was added to a solution of 0.5 mole of substituted benzaldehyde in 100 ml of ether. After 2 h, the water was separated, the ether layer was dried with potassium hydroxide or magnesium sulfate, the ether was removed by distillation, and the residue was distilled *in vacuo*.

TABLE 4. N-Arylideneethylamines

Compound	bp, °C (mm)	n_D^{20}	Found, % C	Found, % H	Empirical formula	Calculated, % C	Calculated, % H	Yield, %
Ic	88—90 (6)	1,5528	64,3	6,1	$C_9H_{10}ClN$	64,5	6,0	85
Ie	113—115 (8)	1,5486	73,7	8,0	$C_{10}H_{13}NO$	73,6	8,0	80
Ig	81—82 (1,5)	1,5813	51,0	4,8	$C_9H_{10}BrN$	51,0	4,8	94
Ih	92—94 (12)	1,5164	71,3	6,9	$C_9H_{10}FN$	71,5	6,7	74
Ii	140—145 (12)[a]	—	76,2	6,3	$C_{10}H_{10}N_2$	75,9	6,4	40

[a]This compound had mp 36.5-37.5°C.

TABLE 5. Spectral Characteristics of N-Arylideneethylamines[a]

Compound	δ, ppm (J, Hz) Ar	δ, ppm (J, Hz) CH=N[b]	δ, ppm (J, Hz) CH_2CH_3[c]
Ic	7,0—7,8 m	8,03 t	3,54 q, 1,21 t
Ie	6,7—7,4 m; 3,73 s	8,13 t	3,55 q, 1,23 t
Ig	7,42; 7,50 dd (9)	8,06 t	3,52 q, 1,21 t
Ii	7,66; 7,82 dd (9)	8,28 t	3,66 q, 1,27 t

[a]All of the compounds have a $\nu_{C=N}$ band at 1650-1660 cm^{-1}. [b]J = 1.5 Hz. [c]J = 7 Hz.

TABLE 6. Thiazolidines

Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	Picrate: mp (dec., from alcohol)	found, % C	found, % H	found, % N	found, % S	empirical formula	calculated, % C	calculated, % H	calculated, % N	calculated, % S	Yield, %
IIIa	85—88 (34)	0,9548	1,4947	168—169	41,6	4,9	15,0	8,5	$C_7H_{15}NS \cdot C_6H_3N_3O_7$	41,6	4,9	15,0	8,6	33
IIIb	70—72 (17)	0,9263	1,4830	181—183[a]	48,7	9,3	6,9	15,9	$C_8H_{17}NS \cdot HCl$	49,1	9,3	7,1	16,4	30
IIIc	54—56 (9)	0,9009	1,4682	178—179	44,7	5,6	13,7	7,9	$C_9H_{19}NS \cdot C_6H_3N_3O_7$	44,8	5,5	13,9	8,0	50
IIId	113—114 (3)[b]	1,0764	1,5700	189—191	48,1	4,6	13,2	7,7	$C_{11}H_{15}NS \cdot C_6H_3N_3O_7$	48,3	4,3	13,3	7,6	35
IIIe	145—148 (2)	1,1682	1,5763	188—189	44,6	3,9	12,3	6,8	$C_{11}H_{14}ClNS \cdot C_6H_3N_3O_7$	44,7	3,8	12,3	7,0	30
IIIf	119—122 (1)	1,1651	1,5751	197—199	44,5	3,9	12,3	6,7	$C_{11}H_{14}ClNS \cdot C_6H_3N_3O_7$	44,7	3,8	12,3	7,0	25
IIIg	135—138 (1,5)	1,1058	1,5674	153—154	47,7	4,6	12,3	6,9	$C_{12}H_{17}NOS \cdot C_6H_3N_3O_7$	47,8	4,5	12,4	7,1	53
IIIh	127—132 (1)	1,1067	1,5671	138—140	47,2	4,6	11,9	7,1	$C_{12}H_{17}NOS \cdot C_6H_3N_3O_7$	47,8	4,5	12,4	7,1	32
IIIi	149—151 (2)	1,3674	1,5906	201—203	40,7	3,5	11,2	6,6	$C_{11}H_{14}BrNS \cdot C_6H_3N_3O_7$	40,7	3,4	11,2	6,4	33
IIIj	105—110 (3)	1,1330	1,5494	188—190	46,1	3,9	12,5	7,3	$C_{11}H_{14}FNS \cdot C_6H_3N_3O_7$	46,4	3,9	12,7	7,3	30
IIIk	90—92 (2)	1,0412	1,5546	176—177	49,6	4,6	12,8	7,4	$C_{12}H_{17}NS \cdot C_6H_3N_3O_7$	49,5	4,6	12,8	7,3	30
IIIl	132—136 (1,5)	1,0724	1,5556	117—118	49,2	4,8	12,2	6,9	$C_{13}H_{19}NOS \cdot C_6H_3N_3O_7$	48,9	4,8	12,0	6,9	44
IIIm	83—84 (1)	1,0071	1,5412	136—137	50,3	4,9	12,1	7,1	$C_{13}H_{19}NS \cdot C_6H_3N_3O_7$	50,7	4,9	12,4	7,1	37
IIIn	70—72 (1,5)	—	—	66—67[c]	44,9	8,5	10,2	24,5	$C_5H_{11}NOS$	45,1	8,3	10,5	24,1	15
IIIo	78—82 (2)	1,0623	1,5056	13—15[c]	50,2	9,0	—	—	$C_6H_{13}NOS$	48,9	8,9	—	—	12

[a]The melting point (with decomposition; recrystallized from butanol) and analytical characteristics of the hydrochloride are presented. [b]This compound had bp 117-118°C (3 mm) in [11]. [c]The melting point and analytical characteristics of the free base are presented.

Thiazolidines IIIa-p (Tables 1 and 6). A solution of 0.15 mole of imine I and 0.10-0.12 mole of thiirane II in 100 ml of the solvent was heated in a steel autoclave at 100°C for 15-20 h. The reactions of imine Ia with thiirane and methylthiirane were carried out in benzene, while the reaction with 2,2-dimethylthiirane was carried out in alcohol—benzene (1:3). Alcohol—benzene (1:1) was used in the remaining cases. At the end of the heating period, the solvent was removed by distillation, and the residue was distilled *in vacuo*. The purity of the preparations was monitored by GLC and/or thin-layer chromatography (TLC) on Silufol.

1-Ethylamino-2-propanethiol (IV). A mixture of 15 g (0.20 mole) of methylthiirane, 34 g (0.75 mole) of ethylamine, and 100 ml of benzene was heated in a steel autoclave at 100°C for 4 h, after which the excess ethylamine and solvent were removed by distillation, and the residue was distilled *in vacuo* to give 11 g (46%) of a product with bp 68-70°C (37 mm), d_4^{20} 0.8996, and n_D^{20} 1.4866. IR spectrum: ν_{NH} 3340 and ν_{SH} 2640 cm^{-1}. PMR spectrum

(C_2Cl_4): 1.06 (t, J = 7.1 Hz, ethyl CH_3), 1.26 (d, J = 7.0 Hz, CH_3), 1.37 (broad singlet, NH and SH), and 2.3-3.2 ppm (m, 5H). The picrolonate had mp 227-228°C (dec.). Found: S 8.2%. $C_5H_{13}NS \cdot C_{10}H_8N_4O_5$. Calculated: S 8.4%.

2,2,5-Trimethyl-3-ethylthiazolidine (IIIb). A mixture of 4 g (0.03 mole) of aminothiol IV and 5 ml (0.07 mole) of acetone was refluxed for 10 h, after which the excess acetone was removed by distillation, and the residue was dried with sodium sulfate and distilled to give 3 g (50%) of a product with bp 67-69°C (14 mm) and n_D^{20} 1.4813.

5-Methyl-3-ethyl-2-phenylthiazolidine (IIIk). A mixture of 4 g (0.03 mole) of aminothiol IV, 7 g (0.07 mole) of benzaldehyde, and 50 ml of benzene was refluxed for 10 h in a flask equipped with a Dean–Stark trap. The benzene was then removed by distillation, and the residue was distilled *in vacuo* to give 4 g (50%) of a product with bp 90-92°C (2 mm) and n_D^{20} 1.5547. The picrate had mp 177-178°C (dec., from alcohol). No melting-point depression was observed for a mixture of this picrate with the picrate of the product of the addition of methylthiirane to N-benzylideneethylamine.

Method Used to Carry Out the Competitive Reactions. A 0.0015-mole sample of thiirane was added to a solution containing 0.007 mole each of the competing imines in 4 ml of a mixture of anhydrous alcohol and dry benzene (1:1), and the solution was heated at 75°C for 4 h with subsequent gas-chromatographic determination of the ratio of thiazolidines by the internal-normalization method with calibration with respect to the reaction products (it was demonstrated by control experiments that the thiazolidines are stable under the conditions of the competitive reactions and chromatography). In the case of thiazolidine III, which was formed from imine IIIi but was not isolated preparatively, the k_{CN}/k_H value was obtained as the ratio of the products of the retention times by the heights of the peaks of the corresponding thiazolidines in the reaction mixtures; the calibration coefficient for this method of determination for IIId-j was 1.00 ± 0.03.

Method for the Determination of the Rate Constants for the Addition of Thiiranes to N-Benzylideneethylamine. A 10-ml sample of a solution of the imine in a mixture of dry alcohol and benzene (1:1) (the imine concentration was 2.5 moles/liter; o-nitrobiphenyl was added to the solution as an internal standard) was placed in a reaction vessel, which was hermetically sealed with a rubber stopper and thermostated, and 0.0042 mole of thiirane was introduced into the reaction mixture by means of a syringe. Samples were selected from the reaction mixture by means of a syringe at time intervals that were increased as the reaction proceeded (0.3-1.0 h) and were analyzed by GLC (nine to 11 chromatograms were obtained). The k'_1 values were calculated by the method of least squares from the formula $k'_1 = -[\ln (1 - c_i/c_\infty)]/t_i$ using the thiazolidine concentration found chromatographically for reaction mixtures maintained at 90°C for 24 h as the c_∞ concentration.

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