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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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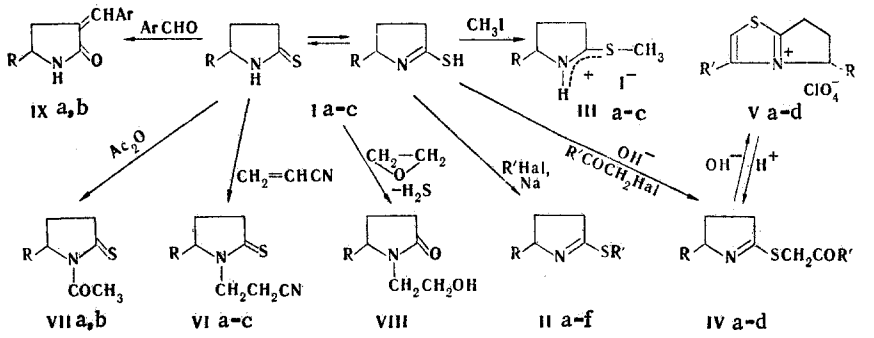


I a $R=C_3H_7$; b $R=C_4H_9$; c $R=i\text{-}C_5H_{11}$; II a $R=C_3H_7$, $R'=CH_3$; b $R=C_4H_9$, $R'=CH_3$; c $R=i\text{-}C_5H_{11}$, $R'=CH_3$; d $R=C_3H_7$, $R'=C_2H_5$; e $R=C_4H_9$, $R'=C_2H_5$; f $R=i\text{-}C_5H_{11}$, $R'=C_2H_5$; III a $R=C_3H_7$; b $R=C_4H_9$; c $R=i\text{-}C_5H_{11}$; IV a $R=C_3H_7$, $R'=CH_3$; b $R=i\text{-}C_5H_{11}$, $R'=CH_3$; c $R=C_3H_7$, $R'=C_6H_5$; d $R=i\text{-}C_5H_{11}$, $R'=C_6H_5$; V a $R=C_3H_7$, $R'=CH_3$; b $R=i\text{-}C_5H_{11}$, $R'=CH_3$; c $R=C_3H_7$, $R'=C_6H_5$; d $R=i\text{-}C_5H_{11}$, $R'=C_6H_5$; VI a $R=C_3H_7$; b $R=C_4H_9$; c $R=i\text{-}C_5H_{11}$; VII a $R=C_3H_7$; b $R=i\text{-}C_5H_{11}$; IX a $R=C_4H_9$, $Ar=C_6H_5$; b $R=C_4H_9$, $Ar=C_6H_4N(CH_3)_2$

and IR spectra of pyrrolidines IIa-f and N-methyl-5-alkyl-2-thioxopyrrolidines synthesized by thionation of N-methyl-5-alkyl-2-pyrrolidines with phosphorus pentasulfide [3].

Onium salts (IIIa-c) are formed when the 5-R-2-thioxopyrrolidines are treated with methyl iodide in the absence of a catalyst. Their structures should evidently be represented in the form of mesomeric structures with a fixed position of the proton and a positive charge that is delocalized between the two heteroatoms and the carbon atom. The IR spectra of salts IIIa-c reflect the contribution of both the N=C bond (band at 1595-1600 cm^{-1}) and the thioamide NH—C=S group (band at 1470-1510 cm^{-1}) to the mesomeric structure; the latter band is less intense than in the case of the starting 2-thioxopyrrolidines Ia-c.

It has been previously assumed that the formation of thiazolium salts (Va-d) proceeds through the formation of keto sulfides [4]. We were able to isolate intermediate 5-R-S-acetonyl(phenacyl)-2-pyrrolines (IVa-d) in the condensation of 5-alkyl-2-thioxopyrrolidines (IIa-c) with chloroacetone or phenacyl bromide in the presence of sodium methoxide; IVa-d are readily converted to the corresponding 2,3-trimethylenethiazolium salts Va-d when they are treated with mineral acids.

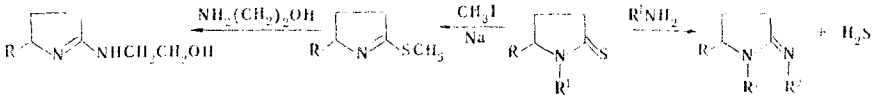
Compounds IVa-d were also obtained by treatment of the thiazolium salts with a 1 N solution of alkali. Absorption bands of C=O (1700 cm^{-1}) and C=N (1640-1660 cm^{-1}) groups appear in the IR spectra of keto sulfides IVa-d. The NMR spectra confirm the presence of a keto sulfide group in IVa-d. The protons of the methylene group attached to the sulfur atom give a signal at δ 2.29 ppm, and a signal of the protons of the methyl group bonded to the carbonyl group is observed at δ 1.94 ppm. The protons of the pyrroline ring show up in the form of a complex multiplet at δ 3.19 ppm.

Compounds Ia-c undergo acetylation and cyanoethylation at the nitrogen atom.

The high reactivities of thioethers [5] make it possible to propose that the reaction takes place initially at the S atom but that subsequent transfer of the cyanoethyl [6] or acetyl group leads to N-substitution products (VIa-c, VIIa,b). The IR spectra of VIa-c contain absorption bands at 2250 (C≡N), 1232 (C=S), and 1545 cm^{-1} (amide II) for the $-\overset{\lceil}{N}-\overset{|}{C}=S$ grouping, whereas the IR spectra of the N-acetyl derivatives (VIIa, b) contain bands at 1700 (C=O), 1234 (C=S), and 1542 cm^{-1} (amide II) for the $-\overset{|}{N}-\overset{|}{C}=S$ grouping.

The hydroxyethylation of Ia-c and their condensation with aromatic aldehydes are accompanied by replacement of the sulfur atom in the thioamide group by oxygen (VIII, XIa, b). 5-Alkyl-N-β-hydroxyethyl derivatives of 2-pyrrolidones (VIII) have been previsouly synthesized by reductive ethanolamination of ethyl esters of γ-keto carboxylic acids [7]. It should be noted that 3-arylidene derivatives (IXa, b) are not formed by direct reaction of pyrrolidones and aromatic aldehydes.

Owing to the amide nature of the carbonyl group, 5-alkyl-2-pyrrolidones do not give derivatives of the hydrazone and oxime type, whereas 5-alkyl-2-thioxopyrrolidines react readily with ethanolamine and hydrazine hydrate to give 2-iminopyrrolidines (Xa-d):



XI a,b X a-d

X a $R=C_3H_7$, $R^1=H$, $R^2=H_2$; b $R=i\text{-}C_5H_{11}$, $R^1=H$, $R^2=NH_2$; c $R=C_3H_7$, $R^1=H$, $R^2=CH_2CH_2OH$; d $R=i\text{-}C_5H_{11}$, $R^1=CH_3$, $R^2=CH_2CH_2OH$; XI a $R=C_3H_7$; b $R=C_6H_{13}$

The absorption of the exocylic C=N bond (1640 cm^{-1}) in the IR spectra of 2-imino-5-R-pyrrolidine (Xc) is identical to the absorption observed for N-methyl-2-imino-5-R-pyrrolidine (Xd). This constitutes evidence that 2-thioxopyrrolidines Ia-c react with aliphatic amines in the thiolactam form. The same fact is confirmed by a comparison of the physical constants of Xa-d obtained by direct reaction of the thioxopyrrolidines with ethanolamine and by nucleophilic substitution of S-methylpyrrolines with the same reagent (XIa, b).

One set of signals — δ 12.05 (1H, s, NH), 3.6 (1H, q, 5-CH), 0.43-2.34 (4H, m, heteroring methylene protons), 0.9-1.4 (protons of the alkyl substituents attached to C_5), and 6.40 ppm (2H, s, NH_2) — is observed in the PMR spectra of Xa, b recorded at room temperature, and this makes it possible to conclude that the investigated compounds exist in the form of one isomer, viz., the syn form, which is stabilized by an intramolecular hydrogen bond (IHB).

The IR spectra of dilute solutions (10^{-3} mole/liter) of 2-imino-5-R-pyrrolidines (Xc,d) constitute evidence in favor of the presence of an IHB, which is formed in the case of a syn orientation of the substituent. Intense absorption bands are observed in the IR spectra in the region of the $\nu_{OH_{assoc}}$ vibrations (3402 cm^{-1}). Absorption bands of a free OH group are absent in all of the spectra.

EXPERIMENTAL

The IR spectra of capillary layers of the liquid compounds and mineral oil and hexachlorobutadiene pastes of the solid compounds were recorded with a UR-20 spectrometer. The NMR spectra were recorded with a BS-477 (Tesla) spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The starting 5-alkyl-2-thioxopyrrolidines were synthesized by the method in [3].

5-Methyl-5-propyl-2-pyrroline (IIa). A solution of 3.1 g (22 mmole) of 5-propyl-2-thioxopyrrolidine in 10 ml of absolute methanol was added to a solution of sodium methoxide (from 15 ml of absolute methanol and 0.45 g of sodium metal), 3.5 g (25 mmole) of methyl iodide was added with stirring, and the reaction mixture was heated on a water bath for 1 h. The precipitate was removed by filtration, the solvent was removed from the filtrate by distillation, and the residue was fractionated in vacuo to give IIa (Table 1).

Compounds IIb-f were synthesized from 5-alkyl-2-thioxopyrrolidines by the method described above (Table 1).

Onium Salts (IIIa-c) of 5-Alkyl-2-thioxopyrrolidines. Excess (40 mmole) methyl iodide was added to a solution of 5-alkyl-2-thioxopyrrolidine (25 mmole) in 20 ml of acetone, and the mixture was allowed to stand at 20°C for 1 h. The precipitated crystals were removed by filtration and dried (Table 1).

Substituted 2,3-Trimethylthiazolium Salts (Va-d). A solution of 20 mmole of 5-alkyl-2-thioxopyrrolidine and 20 mmole of chloroacetone or phenacyl bromide in 10 ml of benzene was heated on a water bath for 20 min, after which the mixture was cooled to 20°C, and the liberated oil was separated, washed with benzene, and dissolved in 20 ml of water. The aqueous solution was refluxed for 10 min, cooled to 20°C, and treated with 20 mmole of $Ba(ClO)_4$ [sic]. The precipitated crystals were recrystallized from alcohol—water (1:3) (Table 1).

TABLE 1. Characteristics of the Compounds Obtained

Compound	bp, °C (mm) or mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IIa	76—77 (4)	61,5	9,6		20,8	$C_8H_{15}NS$	61,2	9,6		20,4	40
IIb	119—120 (4)	63,5	10,1		18,3	$C_9H_{17}NS$	63,2	10,0		18,8	43
IIc	118—120 (4)	65,3	10,1		17,7	$C_{10}H_{19}NS$	64,9	10,4		17,3	40
IId	102—104 (3)			8,1	18,6	$C_9H_{17}NS$			8,2	18,8	41
IIe	104—105 (3)			7,8	17,6	$C_{10}H_{19}NS$			7,6	17,3	42
IIf	110—112 (3)			7,2	16,3	$C_{11}H_{21}NS$			7,0	16,1	41
IIIa	100—102			8,2	11,0	$C_8H_{16}INS$			4,9	11,3	50
IIIb	97—98			4,5	11,0	$C_9H_{18}INS$			4,7	10,7	52
IIIc	99—100			4,6	10,6	$C_9H_{20}INS$			4,6	10,2	50
IVa	112—114	60,5	8,6	7,4	16,6	$C_{10}H_{17}INS$	60,3	8,5	7,0	16,5	43
IVb	114—115	64,0	9,3	6,3	14,7	$C_{12}H_{21}NOS$	63,4	9,4	6,1	14,1	42
IVc	60—62			5,0	12,4	$C_{15}H_{19}NOS$			5,4	12,3	55
IVd	114—116			4,9	11,4	$C_{17}H_{23}NOS$			4,9	11,1	49
Va	82—83			5,0	11,9	$C_{10}H_{16}ClNO_4S$			5,0	11,4	78
Vb	84—85			4,8	10,0	$C_{12}H_{20}ClNO_4S$			4,5	10,4	84
Vc	103—104			4,4	10,1	$C_{15}H_{19}ClNO_4S$			4,1	9,4	90
Vd	98—99			3,4	8,5	$C_{17}H_{22}ClNO_4S$			3,7	8,4	81
VIa	52—53			15,0	16,7	$C_{10}H_{16}N_2S$			14,3	16,3	67
VIb	54—55			13,2	15,6	$C_{11}H_{18}N_2S$			13,3	15,2	75
VIc	58—59			12,8	14,1	$C_{12}H_{20}N_2S$			12,5	14,3	73
VIIa	173—174 (2)	58,6	8,6		17,6	$C_9H_{15}NOS$	58,4	8,2		17,5	75
VIIb	194—197 (3)	62,1	9,1		16,0	$C_{11}H_{19}NOS$	62,0	9,0		15,1	72
IXa	145—147 (2)	78,4	8,1	6,5		$C_{14}H_{17}NO$	78,1	7,9	6,5		54
IXb	152—155 (7)	75,4	9,0	10,5		$C_{17}H_{22}N_2O$	75,0	8,8	10,3		50
Xa	109—110	60,0	10,1	30,0		$C_7H_{15}N_3$	59,6	10,7	29,8		71
Xb	107—108	64,1	11,5	25,0		$C_9H_{19}N_3$	64,0	11,3	24,9		47
Xc	117—118 (2)	59,3	10,0	20,0		$C_7H_{14}N_2O$	59,2	9,9	19,7		
Xd	123—124 (1)	65,6	10,1	15,4		$C_{10}H_{20}N_2O$	65,2	10,8	15,3		49
XIa	112—114	62,6	10,8	15,7		$C_{10}H_{20}N_2O$	62,5	10,8	15,3		63
XIb	160—162	68,4	11,5	13,4		$C_{12}H_{24}N_2O$	62,2	11,3	13,2		62

5-Propyl-S-acetonyl-2-pyrroline (IVa). A) a 3.14-g (0.02 mole) sample of Ia was dissolved in a solution of sodium methoxide (20 ml of absolute methanol and 0.45 g of sodium metal), the solution was cooled to −10°C, 2 ml (0.02 mole) of chloroacetone in 5 ml of methanol was added dropwise, and the mixture was stirred at 0°C for 4 h. It was then allowed to stand at 20°C for 12 h, and the resulting precipitate was removed by filtration and dried.

Compounds IVb-d (Table 1) were similarly obtained.

B) A solution of 1.4 g (5 mmole) of Ia in 15 ml of a 1 N solution of potassium hydroxide was allowed to stand at 20°C for 1 h, and the resulting precipitate was separated and dissolved in 5 ml of acetone. The solution was treated with ice water (10 ml), and the precipitated crystals were removed by filtration and recrystallized from water. No melting-point depression was observed for a mixture of the products obtained by methods A and B.

5-Alkyl-N-cyanoethyl-2-thioxopyrrolidines (VIa-c). A mixture of 20 ml (0.02 mole) of an alcohol solution of the 5-alkyl-2-thioxopyrrolidine and 0.02 mole of acrylonitrile containing 1 ml of triethylamine was refluxed on a water bath for 1 h, after which it was cooled to 20°C and poured over ice (10 g), as a result of which light-colored crystals of VIa-c (Table 1) precipitated.

3-Arylidene-5-R-pyrrolid-2-ones (IXa, b). A mixture of 0.02 mole of the 5-alkyl-2-thioxopyrrolidine and 0.02 mole of the corresponding aromatic aldehyde in 20 ml of acetic anhydride was heated at 140°C for 3-4 h, after which the solvent was removed by distillation, and the residue was fractionated in vacuo to give IXa, b (Table 1).

5-Alkyl-2-iminopyrrolidines (Xa, b). A mixture of 20 ml (0.02 mole) of an alcohol solution of the 5-alkyl-2-thioxopyrrolidine and 0.02 mole of hydrazine hydrate was refluxed on a water bath for 30-60 min, after which it was cooled to 20°C and poured over ice (10 g). The precipitated crystals were separated and dried (Table 1). Compounds Xc, d (Table 1) were similarly obtained.

5-Alkyl-N-(β-ethanolamino)pyrrolines (XIa, b). A 0.22-mole sample of ethanolamine was added with stirring to 10 ml (0.02 mole) of an alcohol solution of the 5-alkyl-S-methylpyrroline, and the mixture was heated for 1 h. The solvent was removed, and the precipitated crystals were separated, washed with ether, and dried (Table 1).

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HETEROATOMIC DERIVATIVES OF AZIRIDINE.

11.* REACTION OF AZIRIDINE WITH TRIALKYLSILANETHIOLS

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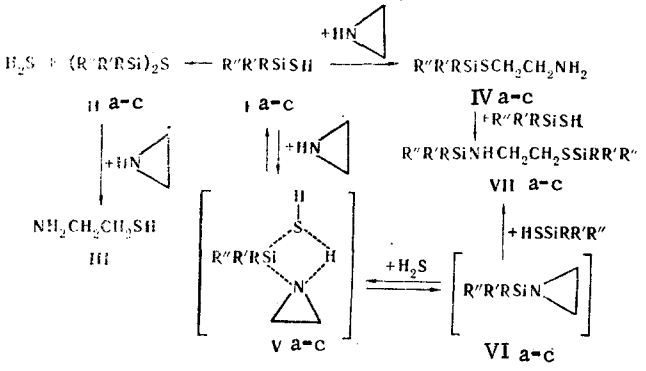
The reaction of aziridine with trialkylsilanethiols in dry tetrahydrofuran (THF) at 55-60°C, which leads to the formation of mixtures of substances [according to the data from the IR and PMR spectra, hexalkyldisilyl sulfides, 2-mercaptoethylamine, trialkyl(2-aminoethylthio)silanes, and 1-trialkylsilylamino-2-trialkylsilylthioethanes], was studied. 2-Mercaptoethylamine and 1-trialkylsilylamino-2-trialkylsilylthioethanes, the structures of which were established on the basis of the IR and PMR spectra, were isolated in pure form.

We have previously obtained N-trialkylsilyl and N-trialkoxysilyl derivatives of 2-aminoethanethiol by the reaction of aziridine with trialkylsilyl- and trialkoxysilylalkanethiols [2]. In order to obtain new types of biologically active organosilicon compounds we accomplished the synthesis of 1-trialkylsilylamino-2-trialkylsilylthioethanes (VIIa-c) by the reaction of aziridine with trialkylsilanethiols.

The reaction of aziridine with trialkylsilanethiols Ia-c proceeds in dry tetrahydrofuran (THF) at 55-60°C in 4 h.



I, II, IV, VII a R = R′ = R″ = C_2H_5; b R = C_2H_5, R′ = R″ = n-C_3H_7; c R = C_2H_5, R′ = R″ = i-C_4H_9

*See [1] for communication 10.

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