RING-CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES.

16.* ARYLIDENE DERIVATIVES OF VICINAL HYDRAZINO THIOLS

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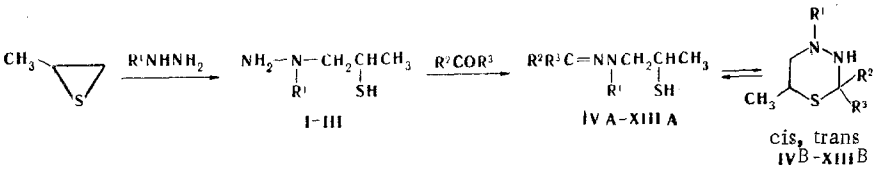
Products of condensation of vicinal hydrazino thiols with aromatic carbonyl compounds, which were found to be mixtures of one acyclic tautomer (a hydrazone) and two stereoisomers with a cyclic form (perhydro-1,3,4-thiadiazine), were obtained. The tautomeric and stereoisomeric equilibria constants were determined by PMR spectroscopy.

It is well known that in ring-chain tautomeric systems — products of the condensation of substituted benzaldehydes with α- and β-amino alcohols [2] or of substituted acetophenones with β-hydrazino alcohols [1] — the equilibrium is shifted to favor the cyclic form as the electron-acceptor character of the substituent in the aromatic ring becomes more pronounced. In the present research we studied arylidene derivatives of vicinal hydrazino thiols in order to evaluate the effect of the polar effects of the substituents, in addition to the steric factor, on the tautomeric equilibrium constant. It has been pointed out that the reaction of 1-(1-methylhydrazino)propane-2-thiol (I) with benzaldehyde and nicotinaldehyde leads, respectively, to a hydrazone [3] and a perhydro-1,3,4-thiaziazine [4]. Trepanier and Krieger [3] observed ring-chain tautomerism only for the hydrochloride of hydrazone IV. However, their conclusion that hydrazone IV in the free base form has a completely chain structure raised some doubts, since it was based only on data from IR and UV spectroscopy without the aid of PMR spectroscopy. Nevertheless, to evaluate the polar effect of substituents we preferred to synthesize a number of arylidene derivatives of hydrazino thiols that contain a substituent larger than the methyl group attached to the nitrogen atom, since this sort of substitution in a series of alkylidene derivatives of hydrazino alcohols leads to a shift in the equilibrium to favor the chain form [5].

Starting hydrazino thiols I-III were obtained from alkylhydrazines and methylthiirane by the method in [3]. Their condensation with carbonyl compounds was carried out under the conditions normally used for such reactions of alkylhydrazines. The physical constants and PMR spectroscopic data for condensation products IV-XIII are presented in Tables 1 and 2.



I R^1=Me; II R^1=Et; III R^1=*n*-Pr; IV R^1=Me, R^2=H, R^3=Ph; V R^1=Et, R^2=H, R^3=4-ClC_6H_4; VI—XI R^1=*n*-Pr, R^2=H, R^3=C_6H_4X (VI X=4-OMe; VII X=H; VIII X=4-F; IX X=4-OMe; X X=4-Cl; XI X=4-NO_2); XII R^1=*n*-Pr, R^2=Me, R^3=Ph; XIII R^1=*n*-Pr, R^2=H, R^3=Me

Ring-chain tautomerism was observed for all of the products of condensation with aromatic carbonyl compounds. The PMR spectra and refractive indexes of these preparations usually change in the course of a few days after their isolation; in addition, reversible changes are observed in the PMR spectra, depending on the temperature of the samples. Compound IV is no exception, so that the conclusion in [3] that only the oepn form is present in this case was actually erroneous. We were able to separate the ring and chain tautomers

*See [1] for Communication 15.

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TABLE 1. Products of Condensation of Vicinal Hydrazino Thiols with Carbonyl Compounds

Compound	bp, °C (mm)	n_D^{20}	d_4^{20} [a]	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	S		C	H	S	
IV	178—182 (10) [b]	1,6000	1,0569				$C_{11}H_{16}N_2S$				88
V	135—136 (1)	1,5781	1,1469	56,2	6,8	13,0	$C_{12}H_{17}ClN_2S$	56,1	6,7	12,5	55
VI	177—187 (3) [c]			63,4	8,3		$C_{14}H_{22}N_2OS$	63,1	8,3		63
VII	123—133 (2)	1,5701	1,0356	66,1	8,3	13,3	$C_{13}H_{20}N_2S$	66,1	8,5	13,6	73
VIII	123—130 (2)	1,5469	1,1042	61,5	7,6	12,8	$C_{13}H_{19}FN_2S$	61,4	7,5	12,6	54
IX	149—157 (2)	1,5668				11,2	$C_{14}H_{22}N_2OS$			12,0	45
X	156—165 (2)	1,5874	1,1199	57,6	7,0	11,8	$C_{13}H_{19}ClN_2S$	57,6	7,1	11,8	47
XIB [d]				55,6	6,8	11,7	$C_{13}H_{29}N_3O_2S$	55,5	6,8	11,4	37
XII	123—134 (2)	1,5465	1,0294			12,5	$C_{14}H_{22}N_2S$			12,8	42
XIII	85—86 (9)	1,4196	0,9590	55,0	10,3	18,3	$C_8H_{18}N_2S$	55,1	10,4	18,4	53

[a]For the freshly distilled preparations. [b]According to the data in [3], this compound had bp 129-131°C (0.5 mm). [c]This compound had mp 24-26°C. [d]This compound had mp 90-92°C.

TABLE 2. PMR Spectra of the Products of Condensation of Vicinal Hydrazino Thiols with Carbonyl Compounds

Compound	δ, ppm						
	R^1	R^2 (c)[a]	R^3	5-H_a	5-H_e	6-H_a	6-CH_3
IVA	2,82 s			1,46 d [b]			1,25 d [b]
↓↑			7,10—7,58 m				
IVB	2,40 s	5,26, 5,44		1,57	3,00	3,26 [c]	1,13 d [b]
VA		7,14					
↓↑			7,20—7,56 m				
VB	1,10 t, 2,59 q [d]	5,22, 5,40		1,71	3,10	3,29 [e]	1,18 d [f]
VIB	0,89 t [b] 1,56 m 2,44 t [b]	5,20, 5,41	6,74, 7,24 dd [g] 3,66 s (OCH_3)	1,67	3,00	3,24 [h]	1,14 d [b]
VIIB	0,88 t [i] 1,58 m 2,44 t [b]	5,24, 5,43	7,20—7,64 m	1,68	2,99	3,22 [j]	1,13 d [b]
VIIIB	0,93 t [b] 1,61 m 2,51 t [b]	5,27, 5,47	6,93—7,76 m	1,75	3,11	3,31 [k]	1,21 d [l]
IXB	0,87 t [d] 1,56 m 2,45 t [b]	5,33, 5,51	6,63—7,41 m, 3,68 s (OCH_3)	1,66	3,01	3,25 [i]	1,12 d [b]
XA	0,90 t [b] 1,54 m 2,37 t [b]	7,05	7,16, 7,32 dd [g]				1,27 d [f]
↓↑							
XB	0,88 t [l] 1,56 m 2,44 t [b]	5,19, 5,36	7,20, 7,36 dd [g]	1,68	3,00	3,23 [n]	1,13 d [f]
XIA	0,90 t [b] 1,65 m 3,34 t [b]	7,15	7,58, 8,12 dd [g]				1,35 d [o]
↓↑							
XIB	0,92 t [b] 1,65 m 2,51 t [b]	5,36, 5,48	7,48, 8,04 dd [g]	1,76	3,10	3,34 [p]	1,20 d [b]
XIIA		1,98					1,13 d [f]
↓↑			7,08—7,80 m				
XIIB	0,82 t [q] 1,60 m 2,42 t [b]	1,53, 1,82					1,07 d [b]
	0,93 t [q] 1,60 m 2,48 t [b]						
XIIIB	0,87 t [l] 1,55 m 2,39 t [b]	4,10—4,50 [r]	1,27 d [b]	1,58	2,98	3,18 [s]	1,09 d [f]

[a]The signal of the cis form is presented first for the cyclic tautomer. [b]J = 7 Hz. [c]J_{5a5e} = −11.9, J_{5a6a} = 10.6, and J_{5e6a} = 3.0 Hz. [d]J = 7.4 Hz. [e]J_{5a5e} = −11.8, J_{5a6a} = 10.5, and J_{5a6e} = 3.0 Hz. [f]J = 6.8 Hz. [g]J = 9.0 Hz. [h]J_{5a5e} = −11.8, J_{5a6a} = 10.6, and J_{5e6a} = 2.8 Hz. [i]J = 7.5 Hz. [j]J_{5a5e} = −11.7, J_{5a6a} = 10.2, and J_{5e6a} = 3.2 Hz. [k]J_{5a5e} = −11.5, J_{5a6a} = 11.5, and J_{5e6a} = 3.0 Hz. [l]J = 7.2 Hz. [m]J_{5a5e} = −11.8, J_{5a6a} = 10.8, and J_{5e6a} = 3.0 Hz. [n]J_{5a5e} = −11.9, J_{5a6a} = 10.7, and J_{5e6a} = 3.1 Hz. [o]J = 6.4 Hz. [p]J_{5a5e} = −12.0, J_{5a6a} = 11.0, and J_{5e6a} = 3.0 Hz. [q]J = 7.3 Hz. [r]Broad (because of coupling with the NH proton) multiple. [s]J_{5a5e} = −11.5, J_{5e6a} = 10.5, and J_{5e6a} = 3.1 Hz.

by means of column chromatography in the case of nitrobenzylidene derivative XI. An intense signal of an azomethine proton and a weaker (by a factor of 10) signal of the 2-H proton of the cyclic tautomer are observed in the PMR spectrum of the chain tautomer immediately after dissolving. Bands at 208 (ε 12000), 260 (ε 12000), and 398 nm (ε 27000) are present in the UV spectrum. The long-wave band apparently corresponds to a π,π* transition

in the conjugated chromophore. Bands at 215 (ε 6000), 272 (ε 7900), and 398 nm (ε 2800) are observed in the UV spectrum of the chain tautomer; the latter band is in all likelihood due to the development in solution of the admixed second tautomer. The chain tautomer is also formed when the cyclic form is dissolved in order to record the PMR spectrum in heated (to 60°C) tetrachloroethylene (its solubility is low at room temperature): The intensity of the signal of the CH=N proton corresponds to a concentration of the open form of ∿20%.

In contrast to the alkylidene derivatives [6], the tautomeric equilibria for the arylidene derivatives of the hydrazino thiols are established extremely slowly (in no less than 6 h, even under acid-catalysis conditions at 90°C). The tautomeric equilibrium constants are presented in Table 3. An increase in the volume of the alkyl substituent attached to the nitrogen atom (a transition form methyl-substituted IV to propyl analog VII) leads to a shift in the equilibrium to favor the ring form. At the same time, simple lengthening of the chain of the substituent (the transition from V to X) has only a slight effect on the equilibrium, and this slight effect is manifested more in the opposite direction. The introduction of a second (methyl) substituent in the 2 position of the cyclic tautomer (compare benzaldehyde derivative VII and acetophenone derivative XII) shifts the equilibrium markedly to favor the ring form. This is explained by the significant decrease in the energy of conjugation of the azomethine grouping with the aromatic ring in the open form as a consequence of steric factors; the increase in the energy of the ring form due to the development of an axial methyl group does not compensate for this decrease. An analogy with the tautomeric transformations of arylidene derivatives of hydrazino alcohols [1] is observed here. However, in the latter case the benzylidene derivatives exist entirely in the chain form. This in turn corresponds to the previously noted shift of the equilibrium to favor the ring form when the oxygen atom is replaced by a sulfur atom [6]. It is important that in a series of alkylidene derivatives of hydrazino alcohols, in which the position of the equilibrium is determined primarily by the steric effects of the substituents, the transition from aldo to keto derivatives is accompanied by a shift of the equilibrium in the opposite direction [7].

It is apparent from the data in Table 3 that in the VI-XI series the dependence of the K_T values on the polar character of substituent X is small and irregular (not even an approximate correlation between log K_T and the σ or σ^+ substituent constants is observed). A possible reason for this consists in the fact that the determination of the tautomeric equilibrium constants was carried out at a temperature close to the isoequilibrium temperature. To verify this assumption one must make measurements at different temperatures; we were unable to do this both because of the slow establishment of equilibrium and because of the slight dependence of K_T at 50 to 90°C. The latter means that the ΔH° value is low. The difference in the enthalpies of the tautomers is usually appreciable in the case of alkylidene derivatives of hydrazino alcohols and hydrazino thiols; the enthalpy of the chain tautomer is higher than that of the ring isomer [2, 6]. The ΔH° value is reduced by the magnitude of the conjugation of the azomethine grouping with the aryl ring in the acylcic tautomer on passing to the benzylidene derivatives, and this also leads to small ΔH° values. It hence follows that the dependence of K_T on the electronic effect of the substituents, which is manifested only through ΔS°, is characterized by a low value of reaction constant ρ.

The presence in the PMR spectra of IV-XI of two singlets with different intensities in the region of the resonance of the 2-H proton of the ring form indicates the existence of perhydro-1,3,4-thiadiazines IVB-XIB in solutions in the form of a mixture of cis and trans isomers that are capable of interconversion through the acyclic tautomer. Since a diequatorial orientation of the substituents in the 2 and 6 positions is more favorable, the fraction of the cis isomer should be higher than that of the equatorial, axial trans isomer. This assignment is confirmed by the vicinal constants of spin-spin splitting of the 5-H and 6-H protons determined for the principal cyclic component, which indicate an axial orientation of the 6-H proton and, consequently, an equatorial orientation of the 6-CH_3 group. In the case of VIIB it was shown that when the temperature is lowered to −45°C (in deuterochloroform), the singlets of the 2-H protons of the ring isomers and the broad NH exchange signal (1.99 ppm) are converted to doublets at 5.36 (2-H of the cis form), 5.61 (2-H of the trans form), and 2.33 ppm (NH) with J = 11.8 Hz. The high values of the spin-spin coupling constants constitute evidence for a diaxial orientation of the NH and 2-H protons in both isomeric forms and, consequently, for an equatorial orientation of the aryl group. Thus the trans isomer probably exists in the preferred 2e,6a conformation. Let us

TABLE 3. Tautomeric (K_T = [A]/[B]) and Stereoisomeric (K_S = [cis]/[trans]) Equilibria Constants of 2-Arylperhydrothiadiazines (in tetrachloroethylene at 90°C)*

Compound	K_T	K_C
IV	2,45	5,1
V	1,27	5,3
VI	1,90	4,4
VII	1,55	4,4
VIII	1,66	4,4
IX	2,02	3,8
X	1,70	4,7
XI	2,70	4,1
XII	0,09	1,6

*The accuracy in the determination of the equilibrium constants was ±10%.

note that, according to data from chromatographic mass spectrometry, the starting hydrazino thiol contains only 4% of the isomer corresponding to alternative opening of the emthylthiirane ring by propylhydrazine [8], so that the signal ascribed to the trans isomer cannot belong to the arylidene derivative of the isomeric hydrazino thiol. In order to confirm the existence of geometrical isomerism in the examined series of compounds we synthesized acetaldehyde XIII, which has a completely cyclic structure. In its PMR spectrum in CCl_4 the signal of the 2-H proton is a poorly resolved multiplet as a consequence of coupling with the NH proton. However, two quartets of the 2-H proton of the cis (4.21 ppm, J = 7.0 Hz) and trans (4.39 ppm, J = 6.9 Hz) isomers with an intensity ratio of 3.8:1 (at 30°C) are observed in the spectrum in CD_3OD. Lowering the temperature to −45°C leads to disappearance of the low intensity signal; it is possible that it becomes invisible because of conversion to two even less intense quartets during "freezing out" of the interconversion of the two conformations (2e,6a and 2a,6e) of the trans isomer.

The existence of two stereoisomers was not observed in the perhydro-1,3,4-oxadiazine series [9]. The development of a trans isomer in the series of sulfur analogs is probably due to lengthening of the C—S bond as compared with the C—O bond, which leads to a decrease in the conformational energies of the substituents in the 2 and 6 positions. The transition to acetophenone derivative XII is, of course, accompanied by an increase in the fraction of the less stable isomer with a ring form. If it is assumed that the conformational energy of the phenyl group is higher than the conformational energy of the methyl group, one should assume that principal stereoisomer XIIB has an equatorial orientation of the 2-C_6H_5 and 6-CH_3 groups.

Thus all of the derivatives of vincinal hydrazino thiols and aromatic carbonyl compounds obtained in this research exist in solutions as tautomeric mixtures of one acylcic tautomer and two stereoisomers with cyclic forms. Judging from the PMR spectrum of a freshly prepared solution, crystalline ring tautomer XIB, which was isolated in individual form, exists only in the cis form in the solid phase.

EXPERIMENTAL

The PMR spectra of 20% solutions of the compounds in CCl_4 were recorded with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The tautomeric equilibrium constants were determined at 90°C from the PMR spectra of solutions in tetrachloroethylene (1 mole/liter) containing 0.1% trifluoroacetic acid as the catalyst with HMDS as the external standard. The establishment of equilibrium was monitored by repeated recording of the spectra. The equilibrium constants in the case of the aldehyde de-

rivatives were evaluated by means of a comparison of the integral intensities of the weak-field part ($\delta > 7$ ppm) and the signals of the 2-H protons or, if this was not possible, by comparison of the signals of the azomethine proton of the acyclic form and the 2-H proton of the cyclic form. The disparity in the results of the measurements made by the two methods did not exceed 2%. In the case of acetophenone derivative XII the composition of the tautomeric mixture was determined from the intensities of the singlet signals of the methyl group. The IR spectra of 5% solutions in CCl_4 or $CHCl_3$ were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol ($4 \cdot 10^{-5}$ mole/liter for the chain tautomer and $1.4 \cdot 10^{-4}$ mole/liter for the cyclic tautomer) were recorded with a Perkin-Elmer 402 spectrophotometer. The purity of preparations I-III and XIII was monitored by gas—liquid chromatography (GLC) with a Tsvet-101 chromatograph with a flame-ionization detector, a 1.8 m × 2 mm glass silanized column filled with 5% SE-30 on Inerton AW (0.125-0.16 mm), nitrogen as the carrier gas, and a column temperature of 150°C. The purity of IV-XII was monitored by thin-layer chromatography on Silufol UV-254 plates [ether—hexane (1:1)]. Preparative column chromatography was carried out on L 100/160 μm silica gel with the same eluent.

1-(1-Methylhydrazino)-2-propanethiol (I) was obtained by the method in [3]. A similar method was used to synthesize 1-(1-ethylhydrazino)-2-propanethiol [II (58%) with bp 70-71°C (10 mm), d_4^{20} 0.9525, and n_D^{20} 1.4850. PMR spectrum: 1.10 (t) and 2.52 (q, J = 7.0 Hz, C_2H_5), 1.24 (d, J = 7.0 Hz, CH_3CS), 2.37 (d, CH_2CS, J = 7.0 Hz), and 3.24 ppm (m, CH). IR spectrum (CCl_4): 1605 (δ_{NH_2}), 2575 (ν_{SH}), and 3215 and 3375 cm^{-1} (ν_{NH}). Found: C 44.7; H 10.5%; MR_D 40.38. $C_5H_{14}N_2S$. Calculated: C 44.7; H 10.5%; MR_D 40.38] and 1-(1-propylhydrazino)-2-propanethiol [III (81%), bp 78-81°C (8 mm), d_4^{20} 0.9324, and n_D^{20} 1.4794. PMR spectrum: 0.92 (t), 1.53 (m), and 2.44 (t, J = 7.0 Hz everywhere, C_3H_7), 1.22 (d, J = 6.7 Hz, CH_3CS), 2.36 (d, J = 6.7 Hz, CH_2CS), and 3.24 ppm (m, CH). IR spectrum: 1590 (δ_{NH_2}), 2560 (ν_{SH}), and 3210 and 3360 cm^{-1} (ν_{NH}). Found: C 49.0; H 10.9; S 21.3%; MR_D 45.11. $C_6H_{16}N_2S$. Calculated: C 48.6; H 10.9; S 21.6%; MR_D 45.03].

4,6-Dimethyl-2-phenylperhydro-1,3,4-thiadiazine (IVB $\rightleftharpoons$ IVA). A mixture of 1.9 g (0.016 mole) of hydrazino thiol I, 1.7 g (0.016 mole) of freshly distilled benzaldehyde, and 60 ml of benzene was refluxed with a Dean—Stark trap until water separation ceased, after which the mixture was distilled in vacuo.

Perhydro-1,3,4-thiadiazines V-X were similarly obtained. In the synthesis of the nitrobenzylidene derivative the residue remaining after removal of the benzene was chromatographed with a column with successive elution of the chain tautomer [XIA (29%) as a dark-red viscous oil] and the ring tautomer [XIB (8%) as yellow crystals].

2,6-Dimethyl-4-propyl-2-phenylperhydro-1,3,4-thiadiazine (XIIB $\rightleftharpoons$ XIIA). A mixture of 6.1 g (0.041 mole) of hydrazino thiol III, 4.9 g (0.041 mole) of acetophenone, and 70 ml of benzene was refluxed with 0.2 g of p-toluenesulfonic acid in an apparatus equipped with a Dean—Stark trap until water separation ceased. The organic layer was washed with water, dried with sodium sulfate, and distilled *in vacuo*.

2,6-Dimethyl-4-propylperhydro-1,3,4-thiadiazine (XIIIB). A 1.3-g (0.029 mole) sample of acetaldehyde was added with stirring and ice cooling in the course of 15 min to a solution of 4.3 g (0.029 mole) of hydrazino thiol III in 30 ml of benzene, after which the mixture was maintained at room temperature for 1 h. It was then refluxed for 1 h, dried with sodium sulfate, and distilled *in vacuo*.

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METHYLATION OF 2-AMINO-Δ^2-THIAZOLIN-4-ONE

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It is shown that the nucleophilicity of the sodium salt of 2-amino-Δ^2-thiazolin-4-one with respect to dimethyl sulfate and methyl iodide is extremely low, regardless of the nature of the solvent. The anomalous (in the 4-thiazolidone series) behavior of this salt in methylation is explained by the low degree of heterolytic dissociation of the O—Na bond. The possible reasons for the inertness of the oxygen atom in the anions of 2-substituted 4-thiazolidones with respect to alkylating agents are discussed.

It is known that 2-substituted 4-thiazolidones are readily alkylated in an alkaline medium to give, as a rule, products of alkylation in the 2 and 3 positions. The ambident character of the anions of 2-oxo- [1], 2-thioxo- [2], and 2-aryliminothiazolidin-4-ones [3] makes it possible to assume that 2-amino-Δ^2-thiazolin-4-one (I) (pseudothiohydantoin) would also display dual reactivity with respect to alkylating agents. The direct alkylation of I has not been reported, although its mono- and dimethyl derivatives, which were obtained from the corresponding thioureas [4], are known.

We were able to obtain the sodium salt (II) of 2-amino-Δ^2-thiazolin-4-one, the IR spectrum of which does not contain carbonyl absorption bands, which constituted evidence for salt formation at the oxygen atom. The signal of the 5-methylene protons of II lies in the same region of the PMR spectrum as in the case of I. This excludes the possible (owing to enolization of the ketomethylene fragment of the molecule) enolate structure of the salt and confirms its lactim structure.

Although the sodium salts of 2-aryliminothiazolidin-4-ones are readily alkylated in ethanol [3], quite unexpectedly the degree of conversion of salt II in the case of methylation with dimethyl sulfate or methyl iodide in various solvents, viz., water, methanol, ethanol, acetone, acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), turned out to be very low (5-10%). Of course, it must be noted that salt II is virtually insoluble in all of the indicated solvents except water and DMSO. According to data from thin-layer chromatography (TLC), four products, the R_f values of which coincide with the R_f values for 2-methylamino-Δ^2-thiazolin-4-one (III), 2-imino-3-methylthiazolidin-4-one (IV), 2,2-dimethylamino-Δ^2-thiazolin-4-one (V), and 2-methylimino-3-methylthiazolidin-4-one (VI), which were obtained by alternative synthesis [4], are present in the reaction mixture. We were able to isolate the products from the reaction mixture in amounts necessary for identification only by means of column chromatography. These products were found to be identical to III-VI. Similarly, methylated derivatives III-VI can be isolated from the reaction mixture from methylation of I with dimethyl sulfate in methanol in the presence of an equivalent amount of sodium methoxide; in both cases the yields are very low ($\sim$5%) and considerably lower than in the methylation under similar conditions of the oxygen analog of I, viz., 2-amino-Δ^2-oxazolin-4-one [5]. In the presence of dibenzo-18-crown-6-ether salt II dissolves in acetonitrile and is methylated by dimethyl sulfate; however, we were unable to separate the products from the crown ether.

The principal reason for the low nucleophilicity of salt II in reactions with methylating agents consists, in our opinion, either in the essentially covalent character of the

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