RING–CHAIN TAUTOMERISM OF S-ACYLALKYLMERCAPTO-SUBSTITUTED AMINOQUINOXALINES

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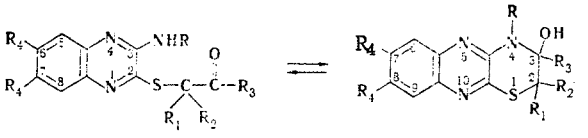
UDC 541.62:547.863'869.2:
543.422.25.4

The ring–chain tautomerism of S-acylalkylmercapto-substituted aminoquinoxalines was studied by means of IR and PMR spectroscopy. It was established that, depending on the substituents, the investigated compounds have open or cyclic structures or exist in the form of mixtures of these forms. Mixtures of diastereomeric forms were detected for two of the investigated compounds.

In the present research we studied the ring–chain tautomerism of 27 S-acylalkylmercapto-substituted aminoquinoxalines (I-XXVII) with the general structure A or B (the various R radicals are presented in Table 1). We have also studied the analogous tautomerism for substituted pyrimidothiazines [1] and S-acylalkylmercapto-substituted imidazoles and annelated imidazole systems [2].

The compounds investigated in the present research can have an open structure and can be represented as 2-acylalkylmercapto-3-aminoquinoxalines (A) or can have a cyclic structure corresponding to 3-hydroxy-3,4-dihydroquinoxalino-1,4-thiazines (B).



A B

A characteristic sign of open form A in the IR spectra is the presence of ν_{CO} bands and, for some compounds, ν_{NH_2} bands; ν_{CO} absorption should be absent in the case of the cyclic form, and ν_{OH} and ν_{NH} absorption should be observed.

It is apparent from Table 2 that all of the investigated $N_{(3)}$-methyl substituted quinoxalines XVIII-XXVI have an open structure in the crystalline state and in solution and that ν_{CO} bands at 1680–1725 cm^{-1} (in $CHCl_3$) are observed in their IR spectra. The spectra of XV and XVII do not contain ν_{CO} bands but do contain ν_{NH} and ν_{OH} absorption; this is in agreement with the cyclic structure of the indicated compounds.

According to the data from the IR spectra of the compounds in solution and in the crystalline state, mixtures of forms A and B with predominance of cyclic form B are observed in the case of IV, VIII, and XII.

Compounds I-III, XIII, XVI, and XXVII exist in the form of mixtures of forms A and B only in solution, and the open form is virtually absent in the crystalline state (Table 2).

The PMR data are in complete agreement with the data from the IR spectra. Thus the affiliation of all N-methyl derivatives XVIII-XXV with open form A was established from the presence in the spectra of these compounds of a doublet of the $N–CH_3$ group due to coupling with the NH proton ($J \approx 4.5$ Hz). In the case of compounds with identical substituents attached to the carbon atom in the $–CR_1R_2$ group, in the spectra of which signals of two nonequivalent protons (I and II, Table 3) or two nonequivalent methyl groups (XVI and XVII) are observed, it was concluded that they exist in cyclic form B.

On the other hand, the presence of a singlet signal of methylene protons in the spectra of VI and VII indicated the open structure of these compounds. Finally, the presence in the

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 0009-3122/79/1501-0102$07.50

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,[a] °C	Radical R[b]			Found, %			Empirical formula	Calc. %			Yield, %
		R_2	R_3	R_4	C	H	S		C	H	S	
I	99	H	CH_2Cl	H	49,7	3,8	11,9	$C_{11}H_{10}ClN_3OS$	49,4	3,8	12.0	87,7
II	100—101	H	CH_2Cl	CH_3	53,0	5,0	10,9	$C_{13}H_{14}ClN_3OS$	52,8	4,8	10,8	77,0
III	71—72	H	CH_3	H	56,8	4,6	13,7	$C_{11}H_{11}N_3OS$	56.6	4.7	13,7	51,7
IV	102—103	H	CH_3	CH_3	59,7	5,8	12,2	$C_{13}H_{15}N_3OS$	59,9	6,0	12,0	41,8
V	152—153	H	$C(CH_3)_3$	H	61.3	6,2	11,7	$C_{14}H_{17}N_3OS$	61,1	6,2	11,6	61,6
VI	142—143	H	$C(CH_3)_3$	CH_3	63,0	6,9	11,0	$C_{16}H_{21}N_3OS$	63,3	7,0	10,6	70,5
VII	134—135	H	C_6H_5	H	65,1	4,6	10,7	$C_{16}H_{13}N_3OS$	65,1	4,4	10,9	67,9
VIII	130—131	H	C_6H_5	CH_3	66,7	5,2	9,9	$C_{18}H_{17}N_3OS$	66,8	5,3	9,9	77.0
IX	94—95	CH_3	CH_3	H	58,4	5,5	12,9	$C_{12}H_{13}N_3OS$	58,3	5,3	13,0	62,8
X	208—209	CH_3	CH_3	CH_3	61,4	5,8	12,0	$C_{14}H_{17}N_3OS$	61,1	6,2	11,7	36,7
XI	165—166	CH_3	C_6H_5	H	65,8	4,7	10.5	$C_{17}H_{15}N_3OS$	66,0	4,9	10.4	81,3
XII	117	CH_3	C_6H_5	CH_3	64,2	6,0	9.1	$C_{19}H_{19}N_3OS+H_2O$	64,2	5,9	9,0	47,3
XIII	108—110	C_6H_5	CH_3	H	62,0	5,2	9,6	$C_{17}H_{15}N_3OS+H_2O$	62,3	5,2	9,8	77,0
XIV	146—147	C_6H_5	C_6H_5	H	71,3	4,6	8,5	$C_{22}H_{17}N_3OS$	71,1	4.6	8.6	93,8
XV	168—169	C_6H_5	C_6H_5	CH_3	72,1	5.3	7.8	$C_{24}H_{21}N_3OS$	72,1	5,3	8.0	63,5
XVI	92—94	CH_3	CH_3	H	59,7	5,8	12,1	$C_{13}H_{15}N_3OS$	59,7	5,8	12,3	68,7
XVII	96—98	CH_3	CH_3	CH_3	62,3	6,7	11,1	$C_{15}H_{19}N_3OS$	62,2	6,6	11,1	61,6
XVIII	163—164	H	C_6H_5	CH_3	67,7	5,9	9,5	$C_{19}H_{19}N_3OS$	67,8	5,7	9,5	79,2
XIX	136—137	H	$C(CH_3)_3$	CH_3	64,3	7,1	10.1	$C_{17}H_{23}N_3OS$	64,3	7,3	10,1	63,5
XX	121—123	CH_3	CH_3	CH_3	62,1	6,6	11,2	$C_{15}H_{19}N_3OS$	62,2	6,6	11,1	60,0
XXI	114—115	CH_3	C_6H_5	H	66,7	5,1	10,1	$C_{18}H_{17}N_3OS$	66,8	5,3	9,9	49.0
XXII	138—139	CH_3	C_6H_5	CH_3	67,9	5,8	8,9	$C_{20}H_{21}N_3OS$	68,3	6,0	9,1	48,0
XXIII	97—98	C_6H_5	CH_3	H	66,7	5,3	9,7	$C_{18}H_{17}N_3OS$	66,8	5.3	9.9	75.4
XXIV	125—126	C_6H_5	C_6H_5	H	71,1	4,8	8,0	$C_{23}H_{19}N_3OS$	71,7	5,0	8,3	79,6
XXV	144—145	C_6H_5	C_6H_5	CH_3	72,7	5,6	7.7	$C_{25}H_{23}N_3OS$	72,6	5.6	7,7	63,8
XXVI	154—155	H	C_6H_4Br	H	51,6	3,4	8,5	$C_{16}H_{12}BrN_3OS$	51,3	3,2	8,6	77,0
XXVII	168—169	H	C_6H_4Br	CH_3	53,5	4,2	8,2	$C_{18}H_{16}BrN_3OS$	53,7	4,0	8,0	67,6

a) The compounds were recrystallized: II, IX, XII, XV-XVIII, XX, and XXII-XXV from hexane; X, XIII, XIV, and XXI from ether; I, III, and IV from cyclohexane; and V-VIII, XI, XIX, XXVI, and XXVII from alcohol. b) R = CH_3 for XVIII-XXV, and R = H for the remaining compounds; R_1 = CH_3 for XVI and XVII, and R_1 = H for the remaining compounds.

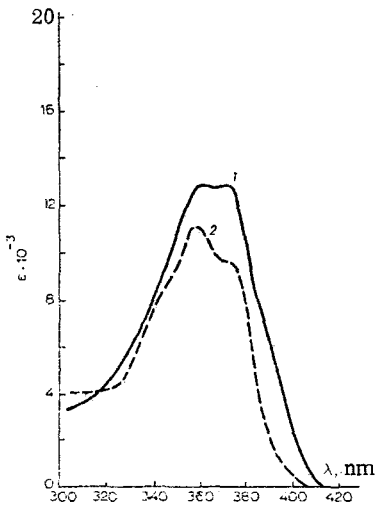

Fig. 1. UV spectra of alcohol solutions of: 1) 2-(tert-butyrylmethylthio)-3-amino-6,7-dimethylquinoxaline (VI); 2) 2-(tert-butyrylmethylthio)-3-aminoquinoxaline (V).

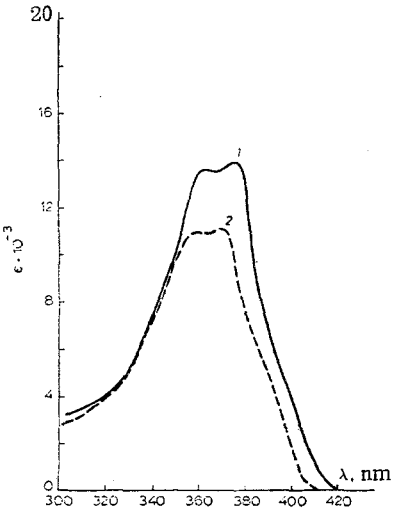

Fig. 2. UV spectra of alcohol solutions of: 1) 2-(benzoylphenylmethylthio)-3-aminoquinoxaline (XIV); 2) 2-(benzoylmethylthio)-3-methylaminoquinoxaline (XXIV).

TABLE 2. Absorption Frequencies (cm^{-1}) of the Functional Groups in the IR Spectra of S-Acylalkylmercapto-Substituted Aminoquinoxalines

Compound	Crystal state		In $CHCl_3$ solution		
	$\nu_{C=O}$	tautomeric form	$\nu_{C=O}$	ν_{NH_2}, ν_{NH}, ν_{OH}	tautomeric form
I	—	B	1700 vvw (in dioxane)	3380 s, 3560 m br	B + A[b]
II	—	B	1730 vvw	3386 m, 3565 w	B + A[b]
III	—	—	1735 w	3410 m, 3500w	B + A[a]
IV	1750w	B + A[a]	1723 w	3404 m, 3520w 3590vw	B + A[a]
V	1705s	A	1715 s	3390 m, 3490 w	A
VI	1717s	A	1715 s	3395 s, 3495m	A
VII	1690s	A	1685 s br	3397 s, 3490 m	A
VIII	1677w, 1689m	B + A	1690 m br	3395 m, 3520 w br, 3600 vw	B + A
IX	—	—	1712 vvw	3400 m, 3520 w	B + A[a]
XI	1655s 1680s	A	1683 s	3395 m, 3495 w	A
XII	1688w	B + A[a]	1682w	3393 m, 3493w, 3585 vw	B + A[c]
XIII	—	B	1720 vvw	3405 m, 3540 w	B + A[b]
XIV	1687s	A	1693 s	3395 m, 3495w	A
XV	—	B	—	3385 m, 3510 w br	B
XVI	—	B	1708 vvw	3402 m, 3510w	B + A[b]
XVII	—	B	—	3406 m, 3512 w br, 3595 s	B
XVIII	1667s	A	1683 s br	3435 s	A
XIX	1710s	A	1715 s	3400 w, 3440 w	A
XX	—	A	1725 s	3439 m	A
XXI	1683 s	A	1682 s	3437 m	A
XXII	1678s	A	1680 s	3440 m	A
XXIII	1705s, 1728m	A	1717 s	3437 m	A
XXIV	1683 s	A	1693 s	3436 m	A
XXV	1680s, 1693m	A	1692 m	3440 m	A
XXVI	1690 s	A	1689 s br	3398 s, 3500 m	A
XXVII	—	B	1691 w	3393 m, 3520 w, 3600 w	B + A (small amount)

a) Very little. b) Traces. c) Form B in pyridine.

spectra of III, IV, and VIII of signals of both equivalent and nonequivalent protons of methylene groups constitutes evidence for the existence of these compounds in the form of mixtures of the open and cyclic tautomeric forms.

It also follows from an examination of the spectra that the signals of the methylene protons are shifted ~1 ppm to weak field in the spectrum of the open form as compared with the cyclic form. The signals of the methyl protons of the S-acyl groups in the open form are also shifted ~0.6 ppm to weak field. The effect of a methyl substituent attached to $N_{(3)}$ (form A) on the chemical shift of the protons of the $-SCH_2-$ group is extremely small, as indicated by the close values of the chemical shifts of the indicated protons in the open forms of VIII and XVIII.

All of this made it possible to establish the affiliation of compounds having various substituents attached to the carbon atom of the $-CR_1R_2-$group with the cyclic (IX, X, XII, XIII, and XV) or open (XI and XIV) forms on the basis of a comparison of the chemical shifts of substituent R_1 = H in the enumerated compounds and the corresponding N-methyl derivatives.

It should be noted that two sets of signals corresponding to two cyclic forms are observed in the spectra of IX and X. This indicates the existence of the compounds in solution in the form of a mixture of diastereomers (in a ratio of ~70:30). When the volume of one of the substituents attached to C_2 or C_3 is increased to the size of the benzene ring, the diastereomeric equilibrium is shifted virtually completely to favor one of the diastereomers.

It is known that the position of the ring–chain tautomeric equilibrium depends on the steric and electronic factors of the structure and on the peculiarities of the intermolecular interactions of the tautomeric forms. The steric factor has the greatest effect on the position of the equilibrium.

TABLE 3. Chemical Shifts of the Protons (δ, ppm) in S-Acylalkylmercapto-Substituted Aminoquinoxalines

Compound	Solvent	Form	CH_3 group of the quinoxaline ring	R_1	R_2	R_3
I	C_5D_5N	B		3,40	3,77	4,18; 4,28
	$CDCl_3$	B		3,13	3,45	3,85; 3,95
II	C_5D_5N	B	2,16	3,38	3,75	4,14; 4,30
	$CDCl_3$	B	2,34	3,07	3,45	3,81; 3,89
III	C_5D_5N	A (⩽10)[a]			4,28	2,33
		B (⩾90)		3,30	3,47	1,87
	$CDCl_3$	A (20)			4,15	2,43
		B (80)		3,01	3,36	1,75
IV	C_5D_5N	B	2,14	3,43	3,22	1,86
	$CDCl_3$	A (⩽15)			4,15	2,4
		B (⩾85)		3,01	3,36	1,75
VI	C_5D_5N	A	2,18		4,62	1,26
VII	C_5D_5N	A			5,03	7,0—8,3
VIII	C_5D_5N	A (15)	2,05		5,05	7,25—8,35
		B (85)	2,18	3,26	3,67	7,25—8,35
	$CDCl_3$	A (40)	2,35		4,75	7,35—8,10
		B (60)	2,39	3,05	3,52	7,35—8,10
IX	C_5D_5N	B		3,67; 3,58	1,44; 1,45	1,8
X	C_5D_5N	B	2,12	3,68	1,47	1,8
	$CDCl_3$	B	2,40	3,70; 3,68	1,47	1,65
XI	$CDCl_3$	A		5,95	1,72	
XII	C_5D_5N	B	2,16	3,96	1,50	7,3—7,9
XIII	C_5D_5N	B		4,90	7,28—7,90	1,64
	$CDCl_3$	B		4,64	7,4—7,70	1,46
XIV	C_5D_5N	A		δ⩾7,0	7,0—8,3	7,0—8,30
	$(CD_3)_2NCDO$	A		7,08	7,08—8,3	7,08—8,30
XV	C_5D_5N	B	2,08	4,95	7,0—7,7	7,0—7,70
	$CDCl_3$	B	2,41	4,78	7,15—7,6	7,15—7,60
XVI	C_5D_5N	B		1,63	1,72	1,93
XVII	C_5D_5N	B	2,16	1,52	1,62	1,82
XVIII[b]	C_5D_5N	A	2,10; 2,17		5,04	7,2—7,5
	$CDCl_3$	A	2,29; 2,37		4,82	7,5—8,05
XX	C_5D_5N	A	2,21	4,86	1,47	2,34
XXI	C_5D_5N	A		5,98	1,63	7,1—7,25
	$CDCl_3$	A		5,91	1,69	7,3—8,17
XXII	C_5D_5N	A	2,15; 2,19	6,05	1,65	7,4—8,32
XXIII	C_5D_5N	A		6,11	7,15—7,79	2,39
	$CDCl_3$	A		5,90	7,3—7,75	2,40
XXIV	C_5D_5N	A				
	$CDCl_3$	A		6,88	7,0—8,1	
XXV	C_5D_5N	A	2,06; 2,16	δ⩾7,1	7,0—8,3	7,0—8,3
	$CDCl_3$	A	2,25; 2,34	6,84	6,9—8,2	6,9—8,2

a) The percentage of the tautomeric form in the mixture is indicated in parentheses. b) For XVIII-XXV, δ_{N-CH_3} 3.05-3.12 ppm.

The effect of the electronic factor is manifested most appreciably in comparison with the tautomeric equilibria of ring-unsubstituted quinoxaline compounds and the corresponding dimethyl derivatives, in which the electron-donor effects of the two methyl groups promote predominance of the cyclic form (compare XXVI and XXVII, VII and VIII, and XI and XII in Tables 2 and 3).

At the same time, the existence of the N—CH_3 substituted compounds (XVIII-XXVI) in the open tautomeric form, in contrast to the analogous N—H derivatives, demonstrates the prevailing influence of the steric effect of the methyl group on the position of the ring—chain tautomeric equilibrium, since one should have expected the formation of the cyclic form be-

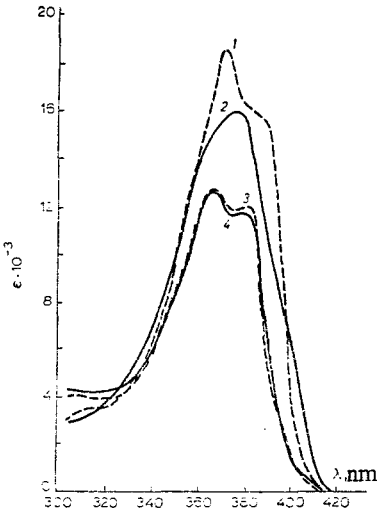

Fig. 3. UV spectra: 2,3-diphenyl-3-hydroxy-7,8-dimethyl-3,4-dihydroquinoxalino-1,4-thiazine (XV): 1) in dioxane; 2) in alcohol; 2-(benzoylphenylmethylthio)-3-methylamino-6,7-dimethylquinoxaline (XXV): 3) in dioxane; 4) in alcohol.

cause of the electron-donor effect of the CH_3 group (the nucleophilicity of the nitrogen atom is increased).

In the half-chair conformation of the dihydrothiazine ring the hybridization of the nitrogen atom bonded to the aromatic ring is close to sp^2. All of the bonds with this atom lie in the plane of the quinoxaline ring, and the free pair of electrons of the nitrogen atom is in maximum conjugation with the π electrons of the quinoxaline ring.

If there is a hydrogen atom attached to the $N_{(4)}$ atom of the thiazine ring, steric hindrance between this atom and the substituents (CH_3, OH) attached to the carbon atom in the 3 position is virtually absent. Replacement of the hydrogen atom by a CH_3 group leads to significant steric hindrance between the methyl group attached to $N_{(4)}$ and the substituents attached to $C_{(3)}$. This should promote opening of the dihydrothiazine ring in the $N-CH_3$ derivatives, and this is actually observed experimentally.

In contrast to imidazothiazolines [2], for which the introduction of a second substituent in the five-membered ring promoted a shift in the equilibrium to favor the open form, the presence of a second substituent [attached to $C_{(2)}$] in the investigated quinoxalinothiazines makes the cyclic form even somewhat preferred over the open form, evidently because of the conformational possibilities of the six-membered ring (see Table 2, VIII and XV and IV and XVII).

As in the case of other previously examined compounds [1, 2], a phenyl substituent attached to the carbon atom of the carbonyl group promotes greater stability of the open forms (Table 3, VII, XI, and XIV). This is evidently associated with the energic advantageousness of the benzoyl system of bonds $C_6H_5-C=O$ and with an increase in the steric effect of the phenyl ring, which hinders cyclization. As a consequence of this latter effect, compounds with a tert-butyl group attached to the carbonyl carbon atom exist only in the open form (Table 2, V and VI).

The crystalline state and the use of pyridine as the solvent promote the existence of the compounds in the cyclic tautomeric form. The effect of pyridine is evidently due to the advantageousness of the formation of intermolecular hydrogen bonds between the hydroxy group and the pyridine nitrogen atom (Table 2, XII; Table 3, III, IV, and VIII). The highly compact character of the molecules of the cyclic form evidently makes a crystal lattice made up of cyclic rather than open molecules energically more advantageous for some of the compounds (Table 2, XII and XXVI).

It is apparent from a comparison of the position of the ring–chain tautomeric equilibria in analogous derivatives of the quinoxalinothiazine and pyrimidothiazine [1] series that in the case of quinoxalinothiazines the equilibrium is shifted to favor the open form as compared with the analogous pyrimidothiazines.

The electron-donor effect of the methyl groups in the quinoxaline ring is manifested in the UV spectra in the form of a bathochromic shift of the long-wave maximum and an increase in its extinction. This is apparent from a comparison of the spectra of the dimethyl derivatives and the corresponding unsubstituted compounds (Fig. 1).

Moreover, a systematic decrease in the extinction of the long-wave absorption as compared with the corresponding NH derivatives is observed in the spectra of the N–CH_3 derivatives of quinoxaline (Fig. 2). This can be explained by the steric effect of the methyl group in substituted N–CH_3 quinoxalines, in which there is steric hindrance between the CH_3 group attached to the nitrogen atom and the S-alkyl substituent. An increase in the extinction of the long-wave maximum and a small bathochromic shift of the latter can be noted for quinoxalinothiazines that have a cyclic structure as compared with the corresponding N-methyl derivatives with an open structure (Fig. 3). The increase in the extinction and the shift of the absorption maximum cannot be explained completely by replacement of themethyl group attached to the nitrogen atom by a hydrogen atom, since the increase in the extinction appreciably exceeds the effects observed in the case of substitution of this type. The cyclic structures probably have somewhat higher intensities of the absorption maxima than the open structures. In addition, these differences are small and cannot be used for evaluation of the ring–chain tautomeric equilibrium in quinoxalinothiazines, as in the case of other previously investigated compounds [1, 2].

EXPERIMENTAL

The IR spectra of mineral oil pastes of the crystalline compounds and solutions of the compounds in $CHCl_3$, pyridine, dioxane, and carbon tetrachloride were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard (δ 0.05); the solvents are indicated in Table 3. The UV spectra of solutions of the compounds in alcohol, a mixture of 90% H_2O and 10% alcohol, and dioxane were obtained with an EPS-3 spectrophotometer.

General Method for the Synthesis of S-Acylmethylmercapto Derivatives of Quinoxaline or 3-Hydroxy-3-alkyl(aryl)-3,4-dihydroquinoxalinothiazines I-XXVII (Table 1). A solution of 5.11 mmole of the corresponding α-halo ketone in 10-15 ml of ethanol was added to a solution of 5.65 mmole of 2-mercapto-3-aminoquinoxaline [3-5] or its N-methyl derivative of 6,7-dimethyl derivatives of quinoxaline in 50 ml of ethanol containing 5.65 mmole of KOH, and the mixture was stirred at 5-10°C for 4-5 h. The potassium chloride (or bromide) was separated, and the alcohol solution was evaporated in vacuo. The residue was triturated with water, and the solid material was removed by filtration, washed successively with alkali solution and water, dried, and recrystallized.

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