CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

10.* ISOMERIC THIAZOLO[4,5-b]QUINOXALINES IN REACTIONS OF N-METHYLQUINOXALINIUM IONS WITH DITHIOCARBAMATES

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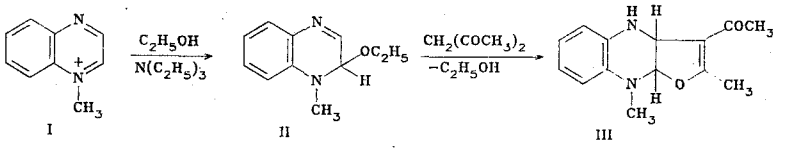
The cyclization of N-methylquinoxalinium iodide with ammonium salts of N-alkyldithiocarbamic acids in DMSO leads to 4-methyl-2,3,3a,4,9,9a-hexahydrothiazolo-[4,5-b]quinoxalines, whereas regioisomeric cycloadducts with a reversed orientation of the thiazole ring are formed in ethanol in the presence of diethylamine.

The reactions of N-alkylquinoxalinium salts with 1,3-bifunctional nucleophiles are among the general methods for the annelation of various heterocycles, viz., furans, pyrroles, imidazoles, etc., with quinoxalines [2]. In the present research we examined the further application of this method, this time for the synthesis of hydrogenated thiazolo[4,5-b]-quinoxalines.

The ability of quinoxalinium salts to undergo double addition of nucleophilic reagents to both C=N bonds of the pyrazine ring lies at the foundation of the synthesis of condensed tetrahydroquinoxalines. As a consequence of the nonequivalence of the 2 and 3 positions in the N-methylquinoxalinium cation (I), generally only one of two possible regioisomeric products of cyclization is formed as a result of reactions with 1,3-bifunctional nucleophiles [2]. It is known that the $C_{(2)}$ carbon atom in N-methylquinoxalinium cation I is considerably more electrophilic than the $C_{(3)}$ atom [1, 3]. However, the orientation of the reagents in the formation of cycloadducts in a number of cases proves to be the opposite of that which one might expect on the basis of the literature data on the reactivities of salts I and 1,3-dinucleophiles. This is precisely what happens, for example, in the cyclization of cation I with β-dicarbonyl compounds [1].



I II III

To explain the reversed orientation of the furan ring in furo[2,3-b]quinoxalines III we proposed [1] a mechanism based on the fact that σ adduct II, which is formed under the reaction conditions (in alcohol in the presence of bases), rather than cation I, undergoes cyclization with β-dicarbonyl compounds. We have previously examined in detail [1] the peculiarities of the formation of σ adducts of the II type and their ability to add nucleophiles to the C=N bond and to replace one nucleophilic residue at the tetragonal $C_{(2)}$ atom by another.

In the present research we obtained further confirmation of the participation of σ adducts of the II type in cyclizations with 1,3-dinucleophiles, the result of which is reversal of the orientation of the annelated five-membered ring.

We showed that ammonium salts IVa,b of N-substituted dithiocarbamic acids react with N-methylquinoxalinium cation I in DMSO to give 3-R-4-methyl-substituted 2,3,3a,4,9,9a-hexa-

*See [1] for communication 9.

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TABLE 1. 4- and 9-Methyl-Substituted 2,3,3a,4,9,9a-Hexahydrothiazolo[4,5-b]quinoxaline-2-thiones

Compound	mp,* °C (dec.)	Found, %				Empirical formula	Calc., %				Mass spectrum, m/z (I ≥ 20%)	ν(NH), cm⁻¹	Yield, %
		C	H	N	S		C	H	N	S			
VIa	121—122	62,1	5,3	12,8	19,8	$C_{17}H_{17}N_3S_2$	62,4	5,2	12,8	19,6	65 (41), 76 (25), 77 (21), 91 (100), 92 (21), 131 (70), 145 (34), 146 (96), 149 (42), 327 (12)	3293	49
VIIIa	174—176	62,7	5,2	13,1	19,6	$C_{17}H_{17}N_3S_2$	62,4	5,2	12,8	19,6	57 (20), 91 (43), 131 (84), 145 (22), 146 (100), 327 (28)	3380	53
VIIIb	195—197	60,1	6,7	13,3	20,0	$C_{16}H_{21}N_3S_2$	60,2	6,6	13,2	20,1		3308	81
VIIIc	131	48,6	3,9	17,8	30,1	$C_{13}H_{12}N_4S_3$	48,7	3,8	17,5	30,0		3347	77

*Recrystallized from ethanol—acetone (5:1).

TABLE 2. ^{13}C NMR Spectra of Thiazolo[4,5-b]quinoxalines VIa and VIIIa,c in Deuterochloroform

Compound	Chemical shifts, δ, ppm				
	$C_{(3a)}$	$C_{(9a)}$	N—CH_3	R	benzene ring
VIa	83,2	56,7	40,6	49,2 (N—CH_2); 126,9; 127,4; 128,2 (phenyl CH)	113,7; 114,8; 119,8; 121,3 (4CH); 133,2; 135,0 (2C—N)
VIIIa	77,6	69,4	36,2	49,7 (N—CH_2); 128,0; 128,4; 129,3 (phenyl CH)	113,2; 115,7; 120,6; 122,3 (4CH); 130,7; 135,0 (2C—N)
VIIIc	81,6	71,0	37,4	115,1; 136,8	114,0; 114,3; 121,4; 121,7 (4CH); 132,8; 133,2 (2C—N)

TABLE 3. ^1H NMR Spectra of Thiazolo[4,5-b]quinoxalines VIa,b and VIIIa-c in d_6-DMSO

Compound	Chemical shifts, δ, ppm						$J_{3a, 9a}$, Hz
	3a-H	9a-H	N—CH_3	R	NH, broad s	aromatic protons	
VIa	5,81 (d)	5,47 (dd)	2,93	4,46 (d, 1H) and 5,20 (d, 1H, J=16 Hz N—CH_2); 7,15—7,40 (m, 5H)	6,47	6,5—6,7 (m, 4H)	5,3
VIb	5,81 (d)	5,30 (dd)	3,17	0,8—2,2 (m, 11H)	6,35	6,5—6,9 (m, 4H)	5,3
VIIIa	5,72 (dd)	6,01 (d)	2,78	4,53 (d, 1H) and 5,32 (d, 1H, J=15 Hz, N—CH_2); 7,33 (s, 5H)	—	6,70 (s, 4H)	7,6
VIIIb	5,88 (dd)	6,04 (d)	2,78	0,9—2,1 (m, 11H)	—	6,70 (s, 4H)	7,0
VIIIc	6,79 (dd)*	6,04 (d)	2,91	7,03 (d, 1H) and 7,59 (d, 1H, J=3,5 Hz)	6,40	6,45—6,90 (m 4H)	8,5

*Data obtained from a solution in deuterochloroform are presented, since the spectrum in d_6-DMSO is uninformative because of overlapping of the signals of the 3a-H and 9a-H protons by the multiplet of the protons of the benzene ring.

hydrothiazolo[4,5-b]quinoxaline-2-thiones VIa,b, whereas the isomeric 3-R-2-methyl-substituted thiazolo[4,5-b]quinoxalines VIIIa,b are formed in alcohol in the presence of diethylamine (Tables 1-3); the formation of only one type of regioisomeric substances is observed in both cases.

Both regioisomeric products (VIa and VIIIa) were obtained with N-benzyl-substituted dithiocarbamate IVa (Table 1). Cycloadduct VIIIb of cation I with N-cyclohexyldithiocarbamate IVb was obtained preparatively (Table 1); regioisomeric adduct VIb is recorded in the ^1H NMR spectra (Table 3), but we could not obtain it in pure form, since it undergoes rearrangement to cycloadduct VIIIb during recrystallization from ethanol. The reason for this is evidently the low thermodynamic stability of 3-R-4-methyl-substituted thiazolo[4,5-b]-quinoxalines, which is due to the steric repulsion between the N-methyl group and bulky substituent R. Probably for the same reason, N-(2-thiazolyl)-substituted dithiocarbamate IVc

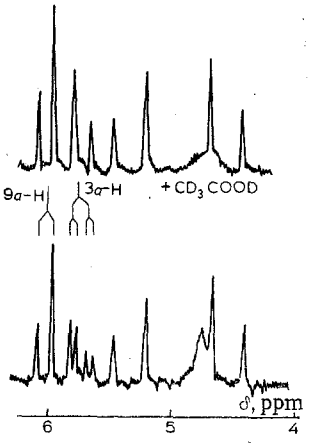


Fig. 1

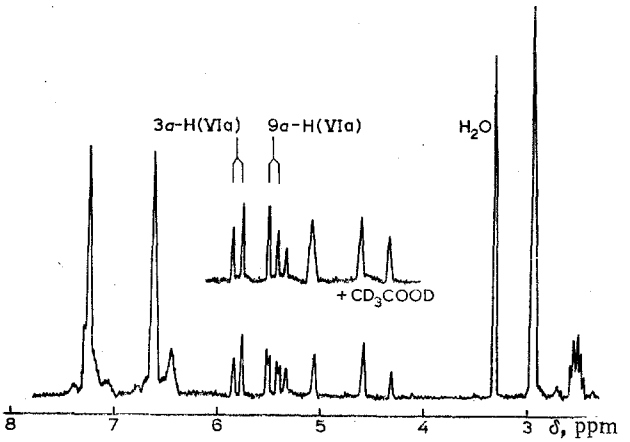
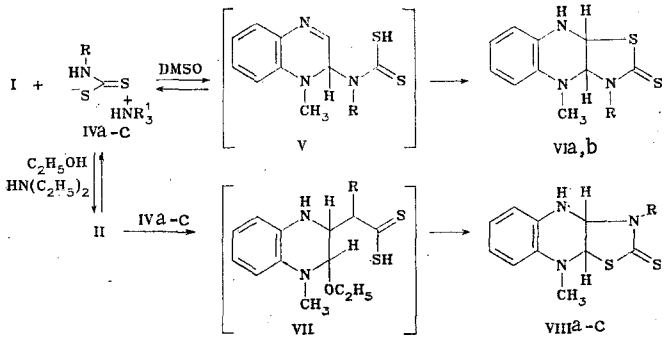


Fig. 2

Fig. 1. Fragment of the ^1H NMR spectrum of the mixture in the reaction of 1-methyl-2-N,N-diethylamino-1,2-dihydroquinoxaline (IX) with ammonium N-benzyldithiocarbamate (1:1) in d_6-DMSO.

Fig. 2. ^1H NMR spectrum of 4-methyl-3-benzyl-2,3,4,4a,9,9a-hexahydrothiazolo[4,5-b]quinoxaline-2-thione (VIa) in d_6-DMSO.

forms the same cyclization product VIIIc (Table 1) with cation I in both DMSO and in ethanol in the presence of diethylamine. The mechanism of the isomerization of thiazolo[4,5-b]-quinoxalines VI to regioisomers VIII is not examined in this paper.*



IV a $R=CH_2C_6H_5$, $R^1=H$; b R= cyclohexyl, $R^1=H$; c R= 2-thiazolyl, $R^1=C_2H_5$; d $R=CH_2C_6H_5$, $R^1=C_2H_5$; VI, VIII a $R=CH_2C_6H_5$; b R= cyclohexyl, c R= 2-thiazolyl

The structures of cyclization products VIa,b and VIIIa-c were confirmed by data from the ^1H and ^{13}C NMR spectra and the mass spectra.

The mass spectra† of isomeric thiazolo[4,5-b]quinoxalines VIa and VIIIa contain M^+ peaks with the same m/z value (327), but the character of the fragmentation differs (Table 1).

The conclusion regarding the orientation of the thiazole ring in VI and VIII was drawn on the basis of data from the ^1H and ^{13}C NMR spectra.

The chemical shifts of the model $C_{(3a)}$ and $C_{(9a)}$ carbon atoms in VI and VIII should differ by ∿17-22 ppm if the effect of the annelated thiazole ring is evaluated approximately by means of the empirical values of the effects of substituents such as NR_2 and SR [4]. One should also take into account the effect of the N-methyl group of the pyrazine ring, which causes a 5-8 ppm shift of the α-carbon atom to weak field, as well as a 2-3 ppm shift of the β-carbon atom to strong field [4]. In complete conformity with this evaulation, the difference in the chemical shifts of the $C_{(3a)}$ and $C_{(9a)}$ atoms in 9-methyl-substituted VIIIa,c is decreased to 8-10 ppm, whereas, on the other hand, it increases to 26.5 ppm in the case of 4-methyl-substituted thiazolo[4,5-b]quinoxaline VIa as a consequence of the counter and concerted effects of the N-methyl group with respect to the effects of the substituents, respectively (Table 2).

*This problem will be considered separately in a future communication.

†We thank N. A. Klyuev for recording the mass spectra.

The N-methyl group affects not only the chemical shifts of the signals of the nodal carbon atoms but also their multiplicities. In addition to the direct constant $^1J_{CH}$ = 166-169 Hz of the $C_{(3a)}$ and $C_{(9a)}$ atoms, long-range constants of spin-spin coupling of the α-carbon atom with the protons of the N-methyl group ($^3J_{CH}$ on the order of 3-4 Hz) appear in the high-resolution ^{13}C NMR spectra of VIa and VIIc, and this makes it possible to draw an unambiguous conclusion regarding the orientation of the thiazole ring. Thus the signal of the $C_{(9a)}$ atom with δ = 71.0 ppm in the ^{13}C NMR spectrum of VIIIc has a long-range $^3J_{CH}$ SSCC with the protons of the methyl group, whereas the more weak-field CH signal with δ = 83.2 ppm experiences splitting by the protons of the N-methyl group in the spectrum of VIa (Table 2).

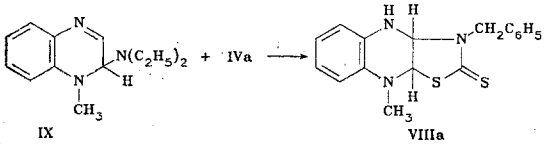
The characteristic features of the ^1H NMR spectra of 9-methyl-substituted thiazolo[4,5-b]quinoxalines VIIIa-c that distinguish them from the isomeric 4-methyl derivatives VIa,b are the substantially higher values of the vicinal constants $^3J_{3a,9a}$ = 7.0-8.5 Hz (Table 3), as well as the differences in the constants between the NH proton and the CH proton of the adjacent nodal atom. In the spectra of VIIIa-c the $^3J_{3a,NH}$ constant has a value on the order of 2 Hz and is displayed distinctly even in the spectra of the reaction mixtures (Fig. 1), whereas in the spectra of VIa,b the $^3J_{9a,NH}$ value does not exceed 1 Hz and is appreciable only in the case of qualitative recording of the spectra (Fig. 2).

The existence of SSCC with NH makes it possible to assign the 3a-H and 9a-H signals in the spectra of VIa,b and VIIIa-c (Table 3).

It is apparent from the data in Table 3 that the chemical shifts of the 9a-H proton in VIIIa-c change only slightly. It is completely natural that the signal of the 3a-H proton attached to the nodal carbon atom closest to it experiences the greater effect of substituent R. The thiazolyl substituent attached to $N_{(3)}$ gives rise to a substantial shift of the signal of the 3a-H proton to weak field, owing to which one can realize an experiment involving recording of its ^{13}C NMR spectrum under conditions of selective suppression of the 9a-H proton at 6.04 ppm. The observed response of the signal of the $C_{(9a)}$ atom at 71.0 ppm confirms the correctness of the assignments made.

At first glance, the assignments of the signals of the 3a-H and 9a-H protons in the spectra of VIa,b do not seem to be completely compatible with the fact that substituent R affects the chemical shifts of the 9a-H proton of the β-carbon atom, whereas the more closely located 3a-H proton resonates at the same δ value of 5.81 ppm (Table 3). However, it should be noted that this effect of substituent R may be the result of not only electronic factors but also steric factors. The steric effects of substituent R in VIa,b are also reflected in the shift of the protons of the N-methyl group (Table 3).

To investigate the reasons for the different specificities of the reactions of cation I with dithiocarbamates IVa-d in DMSO and in ethanol we studied the ^1H NMR spectra of the reaction mixtures. We found that only one type of regioisomeric cyclization products, viz., VIa,b, which were identified from the coincidence of the chemical shifts in comparison with the spectra of the individual compounds in d_6-DMSO (Table 3), is formed immediately when cation I is mixed with ammonium salt IVa,b in solution in DMSO in a ratio of 1:1. However, if dithiocarbamate IVa or IVb dissolved in DMSO in a mixture with an equivalent amount of diethylamine (in a ratio of 1:1:1) is added to a solution of cation I in DMSO, a mixture of isomeric cycloadducts VI and VIII is formed as a result of the reaction. It is apparent from this experiment that the formation of cyclization products VIII with a reversed orientation of the thiazole ring in DMSO solution is associated with the participation in the reaction of an adduct (IX) of cation I with diethylamine; this adduct is formed under the reaction conditions [1]. This conclusion was confirmed completely by an experiment in which dihydroquinoxaline IX, obtained from I iodide and diethylamine [1], rather than cation I, dissolved in DMSO, was subjected to reaction with dithiocarbamate IVa; according to data from the ^1H NMR spectra, only one regioisomer VIIIa with a reversed orientation of the thiazole ring is formed in this case (Fig. 1).



The formation of VIII in an alcohol solution in the presence of diethylamine through the intermediately formed ethoxy complex II under these conditions [1] also becomes clear.

It is assumed from the orientation of the thiazole ring in reaction products VI and VIII that N-addition of N-alkyldithiocarbamates IVa,b is preferable in these reactions to S-addition, i.e., N-adduct V and addition product VII are the most likely intermediates on the way to thiazolo[4,5-b]quinoxalines VI and VIII.

The mechanism examined above satisfactorily explains the different specificities of the cyclization of cation I with ammonium dithiocarbamates IVa,b but does not take into account in any way the effect of the ammonium cation on the reactivities of dithiocarbamates IV. At the same time, experiments show that the nature of the ammonium cation in dithiocarbamates IV also affects the pathway of the cyclizations. Thus, whereas the reaction of cation I with triethylammonium N-benzyldithiocarbamate (IVd) (1:1) in DMSO leads exclusively to cyclization product VIa (as in the reaction with ammonium salt IVa), a mixture of regioisomers VIIIa and VIa in a ratio of 5:2 (according to ^{1}H NMR data) is formed when the reaction is carried out in ethanol in the presence of diethylamine (1:1:1).

The data obtained show that the cyclizations of cation I with dithiocarbamates IV are rather complex reactions, the pathways of which are affected by both the solvent and the nature of the ammonium cation. When such cyclizations are carried out, one should take into account both the participation in them of σ adducts with the solvent or with the base and the possibility of isomerization of some cyclic products to other regioisomeric substances.

EXPERIMENTAL

The ^{1}H NMR spectra of solutions in deuterochloroform and d_6-DMSO were recorded with a Perkin-Elmer R 12B spectrometer (60 MHz) with tetramethylsilane as the internal standard. The ^{13}C NMR spectra of solutions in deuterochloroform were recorded with a Brucker WP 80 spectrometer (20.13 MHz). The chemical shifts were measured with respect to the signal of the solvent (δ = 77.0 ppm) and are presented on the δ scale.

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer.

4-Methyl-3-benzyl-2,3,3a,4,9,9a-hexahydrothiazolo[4,5-b]quinoxaline-2-thione (VIa). A 1.5-g (7.5 mmole) sample of ammonium N-benzyldithiocarbamate was added with stirring at room temperature to a solution of 2.2 g (8.0 mmole) of quinoxalinium (I) methiodide in 10 ml of DMSO. Ethanol (35 ml) was added to the reaction mixture 15 min after the reagents had dissolved, and the resulting precipitate (1.2 g) was removed by filtration and recrystallized from ethanol—acetone (5:1).

The characteristics of VIa are presented in Tables 1-3.

9-Methyl-3-benzyl-2,3,3a,4,9,9a-hexahydrothiazolo[4,5-b]quinoxaline-2-thione (VIIIa). A 2-ml sample of diethylamine was added with stirring at room temperature to a suspension of 1.5 g (7.5 mmole) of ammonium N-benzyldithiocarbamate (IVa) and 2.04 g (7.5 mmole) of quinoxalinium (I) methiodide in 5 ml of ethanol, during which the starting substances dissolved completely. The precipitate (1.3 g) that formed after 15 min was removed by filtration, washed with ethanol, and recrystallized from ethanol—acetone (5:1) (Tables 1-3).

Compound VIIIb was similarly obtained from salt I and dithiocarbamate IVb.

9-Methyl-3-(2-thiazolyl)-2,3,3a,4,9,9a-hexahydrothiazolo[4,5-b]quinoxaline-2-thione (VIIIc). A) A 5-g (18 mmole) sample of triethylammonium N-2(2-thiazolyl)dithiocarbamate in 75 ml of water was added to a suspension of 5 g (18 mmole) of quinoxalinium methiodide in 75 ml of ethanol, and crystals of final product VIIIc began to precipitate immediately from the resulting solution. After 30 min, the precipitate (4.5 g) was removed by filtration and washed well with ethanol. For purification, the substance was dissolved at room temperature in DMF, and 75% aqueous ethanol was added until VIIIc began to crystallize. After 2 h, the precipitated VIIIc was removed by filtration (Tables 1-3).

B) A 1-g (3.6 mmole) sample of triethylammonium N-(2-thiazolyl)dithiocarbamate was added all at once with stirring to a solution of 1 g (3.6 mmole) of quinoxalinium methiodide in 20 ml of DMSO, and the mixture was allowed to stand for 15 min. It was then treated with 75% ethanol until a crystalline precipitate formed. The precipitate (0.9 g) was removed by filtration, washed with ethanol, and dried in a vacuum desiccator over P_2O_5.

The ^{1}H NMR spectra of the compounds obtained by methods A and B coincided completely.

1-Methyl-2-N,N-diethylamine-1,2-dihydroquinoxaline (IX) was obtained by the method described in [1].

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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

11.* REACTIONS OF QUINOXALINIUM SALTS WITH THIOAMIDES — SIMPLE METHOD FOR THE SYNTHESIS OF HYDROGENATED THIAZOLO[4,5-b]QUINOXALINES

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Thioacetamides and thiobenzamides undergo cyclization with N-alkylquinoxalinium salts in the presence of bases to give 4-alkyl-3a,4,9,9a-tetrahydrothiazolo[4,5-b]quinoxalines.

Thiazolo[4,5-b]quinoxaline derivatives have become accessible relatively recently as a result of the development of a number of methods for their synthesis based on the cyclization of 2,3-dichloroquinoxaline with thioamides [2], thioureas [3, 4], thiosemicarbazides [5], and other reagents with a thioamide function [4-7], as well as with ammonium salts of dithiocarbamic acid [7, 8]. All of these bifunctional nucleophiles can be regarded as suitable starting compounds also for the synthesis of hydrogenated thiazolo[4,5-b]quinoxalines as a result of their cyclication with the quinoxalinium cation [9]. However, the reactions of N-alkylquinoxalinium salts with dinucleophiles have their own peculiarities that distinguish them from the cyclizations of 2,3-dichloroquinoxaline. Thus it has been shown [10] that mono- and N,N'-disubstituted thioureas display exclusively the properties of N,N'-bisnucleophiles in reactions with the quinoxalinium cation, which leads to the formation of imidazo[4,5-b]quinoxalines (compare with [3, 4]). Another distinctive feature of the cyclizations of quinoxalinium salts with dinucleophiles is the fact that they can lead to regioisomeric cyclization products. The reasons for the formation of regioisomeric thiazolo[4,5-b]quinoxalines in reactions of N-methylquinoxalinium salts (I) with ammonium salts of dithiocarbamic acids were examined in the preceding communication of this series [1].

The peculiarities of the cyclizations of quinoxalinium salts with thioacetamide and thiobenzamides IIa-c are discussed in the present paper.

*See [1] for communication 10.

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