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].

LITERATURE CITED

1. V. N. Charushin, M. G. Ponizovskii, V. G. Baklykov, G. M. Petrova, L. M. Naumova, N. N. Vereshchagina, E. I. Boreko, and L. V. Korobchenko, in: Advances in the Chemistry of Nitrogen Heterocycles [in Russian], Rostov-on-Don (1983), p. 109.
2. O. N. Chupakhin, in: Advances in the Chemistry of Nitrogen Heterocycles [in Russian], Rostov-on-Don (1983), p. 11.
3. J. W. Bunting and M. G. Meathrel, Can. J. Chem., 50, 917 (1972).
4. F. W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London–New York (1976), p. 37.
5. I. G. Tischenko, O. N. Bubel', and O. A. Grinkevich, Dokl. Akad. Nauk Belorussk. SSR, 24, 819 (1980).

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

V. G. Baklykov, V. N. Charushin, O. N. Chupakhin, and V. N. Drozd

UDC 547.86

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.

S. M. Kirov Ural Polytechnical Institute, Sverdlovsk 620002.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 686-690, May, 1984. Original article submitted July 26, 1983; revision submitted November 22, 1983.

0009-3122/84/2005-0554$08.50

TABLE 1. Thiazolo[4,5-b]quinoxalines IIIa-e

Compound	mp, °C	Found, %				Empirical formula
		C	H	N	S	
IIIa	118—120	60,3	6,0	19,1	14,4	$C_{11}H_{13}N_3S$
IIIb	112—114	61,8	6,7	18,0	13,6	$C_{12}H_{15}N_3S$
IIIc	145—147	60,0	5,8	16,4	12,2	$C_{13}H_{15}N_3OS$
IIId	116—118	68,5	5,4	14,8	11,3	$C_{16}H_{15}N_3S$
IIIe	124—126	61,0	4,5	13,1	10,0	$C_{16}H_{14}ClN_3S$

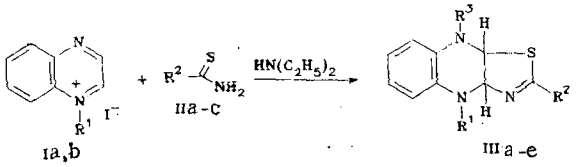
TABLE 1 (continued)

Compound	Calc., %				Mass spectrum, m/z (I ≥ 30%)	Yield, %
	C	H	N	S		
IIIa	60,2	6,0	19,2	14,6	40 (33), 41 (92), 44 (31), 75 (46), 76 (46), 77 (30), 103 (58), 131 (62), 145 (46), 146 (50), 163 (100), 178 (83), 219 (49)	69 (A) 62 (B)
IIIb	61,8	6,5	18,0	13,7	—	50
IIIc	59,7	5,8	16,1	12,3	—	67
IIId	68,3	5,4	14,9	11,4	51 (51), 57 (53), 60 (35), 71 (31), 77 (73), 78 (31), 103 (33), 104 (63), 121 (42), 131 (39), 137 (100), 145 (47), 146 (34), 163 (47), 178 (37), 281 (27)	70
IIIe	60,9	4,5	13,3	10,2	—	67

TABLE 2. ^{1}H NMR Spectra of Thiazolo[4,5-b]quinoxalines IIIa-e in Deuterochloroform

Compound	Chemical shifts of the protons, δ, ppm					SSCC, Hz		
	3a-H	9a-H	R^1	R^2	aromatic protons	$^3J_{3a,9a}$	$^5J_{3a,CH_3}$	$^5J_{9a,CH_3}$
IIIa	5,59 (dq)	5,78 (dq)	3,16 (s, 3H)	2,13 (dd, 3H)	6,4—6,9 (m, 4H)	6,8	1,8	0,5
IIIb	5,65 (m)	5,65 (m)	1,33 (t, 3H) 3,3—4,0 (m, 2H)	2,11 (dd, 3H)	6,4—7,0 (m, 4H)	—	1,2	0,8
IIIc	5,80 (dq)	under the aromatic signals	3,13 (s, 3H)	2,01 (d, 3H)	6,7—7,4 (m, 5H)	8,8	1,7	—
IIId*	5,65 (d)	5,77 (d)	3,20 (s, 3H)	7,2—7,4 (m, 3H) 7,6—7,8 (m, 2H)	6,3—6,8 (m, 4H)	6,8	—	—
IIIe	5,77 (d)	5,90 (d)	3,23 (s, 3H)	7,1—7,8 (m, 4H)	6,3—6,9 (m, 4H)	6,8	—	—

*Recorded in CCl_4, since in $CDCl_3$ the 3a-H and 9a-H protons give one unresolved signal with δ = 5.79 ppm.



I a $R^1=CH_3$; b $R^1=C_2H_5$; II a $R^2=CH_3$; b $R^2=C_6H_5$; c $R^2=C_6H_4$—Cl-p;
III a $R^1=R^2=CH_3$, $R^3=H$; b $R^1=C_2H_5$, $R^2=CH_3$, $R^3=H$; c $R^1=R^2=CH_3$, $R^3=COCH_3$;
d $R^1=CH_3$, $R^2=C_6H_5$, $R^3=H$; e $R^1=CH_3$, $R^2=C_6H_4$—Cl-p, $R^3=H$

The reactions of salts Ia,b with thioacetamide, thiobenzamide, and p-chlorothiobenzamide proceed smoothly in ethanol in the presence of di- or triethylamine to give 4-alkyl-3a,4,-9,9a-tetrahydrothiazolo[4,5-b]quinoxaline derivatives IIIa-e in high yields (Table 1).

The structures of the compounds were established on the basis of data from the ^{1}H and ^{13}C NMR spectra, as well as from the mass spectra.

TABLE 3. ^{13}C NMR Spectra of Thiazolo[4,5-b]quinoxalines IIIa,c,d in Deuterochloroform

Compound	Chemical shifts of the nodal carbon atoms, δ, ppm, and $^1J_{CH}$ direct constants, Hz				Signals of the Remaining carbon atoms
	$C_{(3a)}$	$^1J_{(C_{(3a)}-3a\text{-}H)}$	$C_{(9a)}$	$^1J_{(C_{(9a)}-9a\text{-}H)}$	
IIIa	93,2	—	68,8	—	21,1 (CH_3); 37,8 (N—CH_3); 113,1; 113,5; 119,6; 120,1 (4CH of the benzene ring); 133,9 and 134,0 quat. C—N); 164,8 (C=N)
IIIc	96,8	156,8	68,9	164,4	20,5 and 22,1 (CH_3 and $COCH_3$); 37,6 (N—CH_3); 115,0; 120,0; 124,4; 127,0 (4CH of the benzene ring; ; 141,4 (quat. C—N); 166,4 (C=N); 169,1 ($COCH_3$)
IIId	93,3	154,1	67,7	166,4	37,9 (N—CH_3); 113,1; 113,5; 119,5; 120,0 (4CH of the benzene ring);, 128,0; 128,1; 131,2 (phenyl CH) 133,2; 133,9; 134,3 quat. C—N);. 164,8 (C=N)

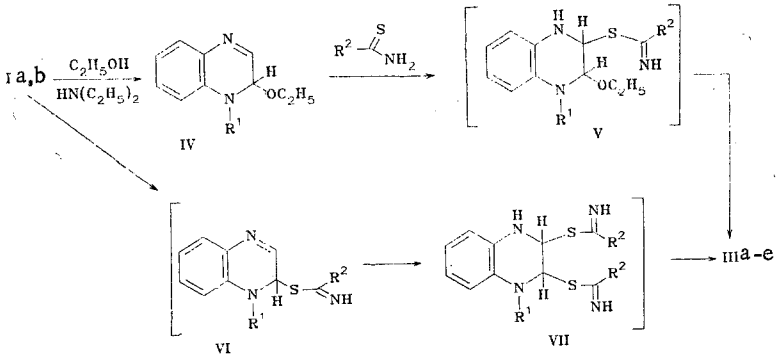
The presence of molecular-ion peaks (M^+) in the mass spectra of IIIa,d and the results of elementary analysis confirm the formation of 1:1 adducts with thioamides (Table 1).

Data from the ^1H NMR spectra (Table 2) indicate annelation of the thiazole ring but do not make it possible to unambiguously establish its orientation relative to the N-alkylpyrazine ring. A characteristic peculiarity of the spectra of cycloadducts IIIa-c is the existence of long-range spin-spin coupling constants (SSCC) between the protons of the methyl group of the thiazole ring and the protons of the nodal 3a-H and 9a-H atoms, as a consequence of which the components of the AB doublets show up in the form of a quartet (3a-H) and a poorly resolved quartet (9a-H) (Table 2). In the absence of coupling with substituent R^2, two distinct doublets of the nodal 3a-H and 9a-H protons with $^3J_{3a,9a} = 6.8$ Hz (Table 2) are observed in the spectra of IIId,e. The vicinal $^3J_{3a,9a}$ constants of IIIa,c-e indicate a cis orientation of the nodal hydrogen atoms in annelation of the thiazole ring [10].

Two signals at 93-97 and 67-70 ppm are observed in the ^{13}C NMR spectra of IIIa,c,d in deuterochloroform in the region of resonance of the methylidyne carbon atoms; on the basis of the literature data [1, 11], the latter should be assigned to the resonance of the $C_{(9a)}$ atom bonded to the sulfur atom of the thiazole ring. The $C_{(3a)}$ atom attached to the C=N bond of the thiazole ring resonates at weaker field and, in addition to the direct constant $^1J_{CH} = 154$-157 Hz, also has a long-range SSCC with the protons of the N-methyl group ($^3J_{CH} \sim 4$ Hz), which indicates that the α-carbon atom of the N-methylpyrazine ring is bonded to the thiazole nitrogen atom. Experiments involving selective proton decoupling carried out for N-acetyl derivative IIIc constitute additional confirmation of the correctness of the assignments made above. The presence of an acceptor group (N—$COCH_3$) has only a slight effect on the shifts of the $C_{(3a)}$ and $C_{(9a)}$ atoms (Table 3) but gives rise to a marked shift of the 9a-H proton to weak field, owing to which one can unambiguously assign the signals of the 3a-H and 9a-H protons in the ^1H NMR spectrum. A response of the signal of the $C_{(3a)}$ atom at 96.8 ppm is observed in the ^{13}C NMR spectrum of IIIc in the case of selective suppression of coupling with the 3a-H proton. Bonding of the 9a-H proton with the $C_{(9a)}$ atom (δ = 68.9 ppm) was confirmed by a similar heteronuclear resonance experiment.

It also follows from the ^1H NMR spectrum of IIIc that $^5J_{3a,CH_3}$ is larger than $^5J_{9a,CH_3}$. Using this difference in the long-range SSCC in the 2-methyl-4,5-dihydrothiazole ring one can assign the signals of the 3a-H and 9a-H protons also for IIIa (Table 2).

The orientation of the thiazole ring in cycloadducts IIIa-e is such that in the case of stepwise cyclization its intermediates should be products of N-addition of the thioamides at the most electrophilic 2 position in cations I. At the same time, it is known that the reactions of thioamides with electrophilic reagents involve primarily the sulfur atom [12]. However, it should be noted here that the formation of condensed tetrahydroquinoxalines with an orientation of the annelated ring that is the opposite of that which one might have expected on the basis of the existing concepts of the reactivities of 1,3 dinucleophiles was observed in cyclizations of salts I with β-diketones [13] and dithiocarbamates [1]. In [1, 3] it was shown that the reason for the reversed orientation of the 1,3-dinucleophilic reagent is the participation in the cyclization of one of the σ adducts of the IV type formed under the reaction conditions rather than cation I. This mechanism also satisfactorily explains the formation of thiazolo[4,5-b]quinoxalines IIIa-e.



The formation of ethoxy complex IV in ethanol in the presence of di- or triethylamine was previously shown in [13]. This is followed by S-addition of the thioamide in the 3-position of adduct IV and intramolecular cyclization based on nucleophilic substitution of the ethoxy group attached to the tetragonal $C_{(2)}$ atom. The indicated mechanism is confirmed by the fact that a cyclization product (IIIa) with the same orientation of the thiazole ring was obtained as a result of the reaction when ethoxy adduct IV rather than cation I was subjected to cyclization with thioamide IIa.

However, it was established by ^{1}H NMR spectroscopy that thiazolo[4,5-b]quinoxalines are formed from cation I and thioamides II not only in an alcohol medium in the presence of bases but also under conditions that exclude the formation of ethoxy σ adduct IV, as, for example in chloroform in the presence of triethylamine. On the basis of the data in [13] it may be assumed that the successive formation of mono- and diadducts VI and VII with subsequent displacement of the thioamide residue from the α position occurs under these conditions. However, attempts to record intermediates VI and VII were unsuccessful as a consequence of the high rates of cyclization. Thus mixing reagents Ia, IIa, and triethylamine in a ratio of 1:1:1 in deuterochloroform at −40°C immediately leads to cyclization product IIIa.

In conclusion, let us note that, in contrast to the reactions of quinoxalinium salts with N-alkyl-substituted dithiocarbamates, in which, depending on the conditions, one can obtain both regioisomeric cycloadducts [1], the cyclizations of salts I with thioamides in the presence of bases lead to the formation of thiazolo[4,5-b]quinoxalines with one only regioorientation.

EXPERIMENTAL

The ^{1}H NMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Perkin-Elmer R-12B (60 MHz) and SKhR 200 (200 MHz) spectrometers with tetramethylsilane as the internal standard.

The ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded with a Bruker WP 80 spectrometer (20.13 MHz).

2,4-Dimethyl-3a,4,9,9a-tetrahydrothiazolo[4,5-b]quinoxaline (IIIa). A) A 3-ml (28.7 mmole) sample of diethylamine was added with stirring at room temperature to a suspension of 1 g (13.3 mmole) of thioacetamide IIa and 3.62 g (13.3 mmole) of quinoxalinium methiodide (Ia) in 8 ml of ethanol, during which the starting substances dissolved completely. The IIIa (2 g) that precipitated after 15-20 min was removed by filtration, washed with ethanol, and recrystallized from ethanol.

Compounds IIIb-e were similarly obtained from the corresponding salts Ia,b and thioamides IIa-c. The characteristics of IIIa-e are presented in Tables 1-3.

B) A 3-ml (28.7 mmole) sample of diethylamine was added to a suspension of 3.62 g (13.3 mmole) of quinoxalinium methiodide (Ia) in dry ether. After stirring for 10-15 min, the diethylamine hydriodide was removed by filtration, and the solvent was evaporated *in vacuo*. The resulting 1-methyl-2-N,N-diethylamino-1,2-dihydroquinoxaline [13] was dissolved in 8 ml of ethanol, thereby converting it to ethoxy adduct IV [13]. A 1-g (13.3 mmole) sample of thioacetamide (IIa) was added to the resulting solution. Compound IIIa began to crystallize 15 min after IIa had dissolved. The crystals of IIIa (1.8 g) were washed with ethanol.

The ^1H NMR spectra of the compounds obtained by methods A and B were identical.

2,4-Dimethyl-9-acetyl-3a,4,9,9a-tetrahydrothiazolo[4,5-b]quinoxaline (IIIc). A 1.68-g (13.7 mmole) sample of acetyl bromide was added with stirring to a solution of 3 g (13.7 mmole) of IIIa in dry benzene. The resulting precipitate was removed by filtration, washed with dry benzene, and dried in a vacuum desiccator over paraffin. The dried precipitate was dissolved in 20 ml of water, and a solution of 1 g of sodium acetate in 20 ml of water was added with stirring. The precipitated IIIc (217 g) was removed by filtration, dried in a vacuum desiccator over P_2O_5, and recrystallized from ethanol (Tables 1-3).

LITERATURE CITED

1. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, G. M. Petrova, and E. O. Sidorov, Khim. Geterotsikl. Soedin., No. 5, 680 (1984).
2. A. K. El-Shafei, H. S. El-Kashef, A. B. Ahmed, and G. Ghattas, Gazz. Chim. Ital., 111, 409 (1981).
3. I. M. Ismail and W. Sauer, Indian J. Chem. Sect. B, 16B, 683 (1978).
4. I. M. Ismail, R. Jacobi, and W. Sauer, Z. Chem., 17, 15 (1977).
5. K. S. Dhaka, J. Mohan, W. K. Chadha, and H. K. Pujari, Indian J. Chem., 12, 966 (1974).
6. H. K. Pujari, Indian J. Chem., Sect. B, 17B, 364 (1979).
7. W. K. Chadha, J. Indian Chem. Soc., 53, 1170 (1976).
8. W. K. Chadha and V. K. Saxena, J. Indian Chem. Soc., 57, 946 (1980).
9. O. N. Chupakhin, in: Advances in the Chemistry of Nitrogen Heterocycles [in Russian], Rostov-on-Don (1983), p. 11.
10. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, N. N. Vereshchagina, L. M. Naumova, and N. N. Sorokin, Khim. Geterotsikl. Soedin., No. 12, 1684 (1983).
11. F. W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London–New York (1976), p. 188.
12. A. V. Bogat-skii, N. G. Luk'yanenko, and T. I. Kirichenko, Khim. Geterotsikl. Soedin., No. 6, 723 (1983).
13. M. G. Ponizovskii, Master's Dissertation Abstract, Sverdlovsk (1983).

MASS-SPECTROMETRIC BEHAVIOR AND PMR SPECTRA OF 9-(2-R-1,3-DIOXAN-5-YL)PURINES

Yu. Yu. Samitov, I. N. Goncharova, N. P. Ramzaeva, and P. B. Terent'ev

UDC 543.51

A trans configuration with an axial orientation of both the purine ring and the furyl ring or the ethoxy group in the 2 position of the dioxane residue was established by PMR spectroscopy for 9-(2-furyl-1,3-dioxan-5-yl)- and 9-(2-ethoxy-2-methyl-1,3-dioxan-5-yl)purine. A comparative analysis of the mass spectra of these compounds makes it possible to confirm conclusions regarding their stereochemistry drawn on the basis of the PMR spectra.

The configurations of 9(1)-(2-substituted-1,3-dioxan-5-yl)purines and -pyrimidines and the conformation of the dioxane ring in these compounds have been previously investigated [1, 2] by NMR spectroscopy with the aid of shift reagents and by X-ray diffraction analysis. Considering the fact that the geometrical configurations of organic compounds have an appreciable effect on the character of dissociative-ionization processes [3, 4], in the present research we investigated the mass-spectrometric behavior of configurational isomers of 6-chloro-9-(2-furyl-1,3-dioxan-5-yl)purine (I) and 6-hydroxy-9-(2-substituted-1,3-dioxan-5-yl)purines (IIa,b and III) and studied their PMR spectra. Compound I was obtained by the reaction of 6-chloro-9-(1,3-dihydroxy-2-propyl)purine with furfural in the presence of

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 691-696, May, 1984. Original article submitted December 1, 1983.

0009-3122/84/2005-0558$08.50