CYCLIZATION OF N-ALKYL AZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

21.* REGIOISOMERIC 1,3,4-THIADIAZINO[5,6-b]QUINOXALINES

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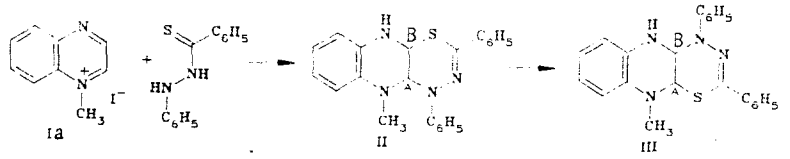
Thiobenzhydrazides undergo cyclization with N-alkyl-quinoxalinium salts to give 5-alkyl-substituted 1,4,4*a*,5,10,10*a*-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxalines, which undergo isomerization to 10-alkyl-substituted thiadiazinoquinoxalines when they are heated in ethanol or in the presence of acids.

We have previously described the cyclization of 1,4-diazinium salts with 1,3- and 1,4-bifunctional reagents containing carbon, oxygen, nitrogen, and sulfur atoms as the anionic centers. As a result of these reactions, we obtained heterocyclic systems in which the pyrazine ring is annelated with five- and six-membered rings: furan, pyrrole, imidazole, pyrazine, thiazole, triazine, and others [2]. The formation of cycloadducts with regioisomeric structures was noted in a study of the reactions of quinoxalinium cations with 1,3-N,S-dinucleophiles such as thioamides and ammonium salts of dithiocarbamic acids [3], and transformations of some regioisomers to others under the influence of acids were also observed [4]. An unusual orientation of the thiazole ring in thiazolo[4,5-b]quinoxalines formed under kinetic control conditions was also noted in [4, 5], since the sulfur atom, which is more nucleophilic in thioamides, adds to the carbon atom in the β position of the N-alkylpyrazine ring rather than in the α position during cyclization.

To study the peculiarities of annelation to the pyrazine ring of six-membered sulfur containing heterocycles, in the present research we investigated the reactions of quinoxalinium salts with thiobenzoic acid hydrazides.

1-Phenylthiobenzhydrazide reacts with N-methylquinoxalinium iodide (Ia) at 20°C both in ethanol in the presence of diethylamine and in an aprotic medium (DMSO, triethylamine) to give 5-methyl-2,4-diphenyl-1,4,4*a*,5,10,10*a*-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (II) (Tables 1-3). When heated in ethanol or when catalytic amounts of acids are added, II undergoes isomerization to thiadiazino[5,6-b]quinoxaline III with an inverted orientation of the thiadiazine ring.



Side reactions involving dimerization and oxidation by cations Ia,b, which ultimately lead to a diphenyl-sym-tetrazine, as in the reactions of thiobenzhydrazide with alkyl halides in alkaline media [6], were observed in the reaction of thiobenzhydrazide with N-alkylquinoxalinium iodides Ia,b in ethanol in the presence of diethylamine. In order to eliminate the oxidative action of salts Ia,b the reactions of thiobenzhydrazide were carried out with adducts (IVa,b) of the quinoxalinium cations with diethylamine. In this case we were able to realize cyclization, as a result of which we obtained thiadiazinoquinoxalines Va,b (Tables 1-3).

The orientation of the thiadiazine ring in Va,b was established on the basis of the multiplicities of the signals of the A-H and B-H protons in the PMR spectra (Table 2). The signals of the A-H protons of thiadiazino[5,6-b]quinoxalines Va,b show up in the form of doublets

*See [1] for Communication 20.

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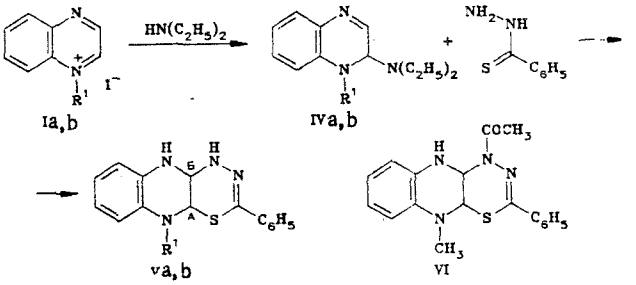


I, IV, V a $R^1=CH_3$; b $R^1=C_2H_5$

at 5.62 and 5.52 ppm, while the stronger-field signals of the B-H protons (4.88 and 4.70 ppm) have the form of broad doublets due to coupling with the protons of the NH groups; this is possible only when the mutual orientation of the fused heterorings is such that the sulfur atom of the thiadiazine ring is bonded to the α-carbon atom of the pyrazine ring. The introduction of an acetyl group into the 4 position of the thiadiazine ring in Va caused a marked shift of the signal of the B-H proton in the PMR spectrum of acetyl derivative VI* to weak field to 6.38 ppm but did not change the multiplicites of the signals of the A-H and B-H protons; this is in agreement with the structures. The conclusion regarding the regioorientation of the thiadiazine ring is also confirmed by the ^{13}C NMR spectra of Va,b and VI in d_6-DMSO (Table 3). The nodal $C_{(A)}$ atoms, which experience the effect of the more electronegative sulfur atom, resonate at weaker field (61.6-63.3 ppm) had have larger $^1J_{(C-H)}$ constants (164-166 Hz) as compared with the signals of the $C_{(B)}$ atoms: 54.6-54.8 ppm and 155-160 Hz (Table 3). The signals of the $C_{(A)}$ atom also have constants of spin–spin coupling with the protons of the N-methyl group, viz., $^3J_{(C-H)}$ (~4 Hz); this makes it possible to not only unambiguously assign the signals of the nodal carbon atoms in the ^{13}C NMR spectra but also to establish the character of the fusion of the heterorings. An experiment on selective decoupling, which was carried out for VI, is an additional confirmation of the assignments made. In the case of irradiation with a frequency corresponding to the resonance of the A-H proton, merging to a singlet of the signal of the $C_{(A)}$ atom at 61.2 ppm is observed in the ^{13}C NMR spectrum of VI. Coupling of the B-H proton with the $C_{(B)}$ atom, which resonates at 50.7 ppm, was confirmed by a similar $^{13}C-^1H$ heteronuclear resonance experiment.

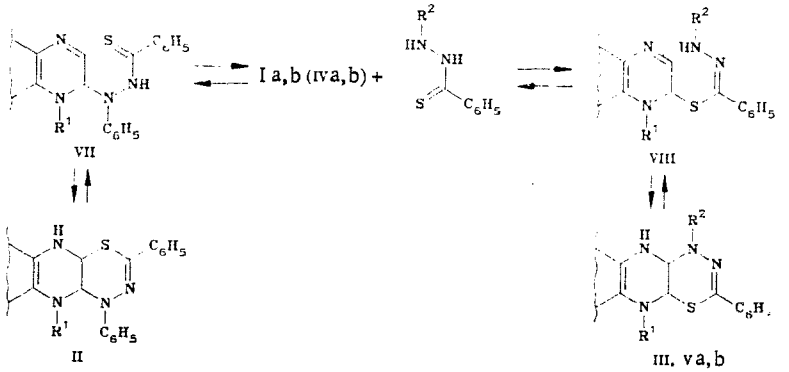
The closeness of the chemical shifts of the protons (5.84 and 5.88 ppm for A-H; 5.70 and 5.57 ppm for B-H) and the nodal carbon atoms [56.5 and 56.7 ppm for $C_{(B)}$; 61.1 and 61.2 ppm for $C_{(A)}$] in the ^1H and ^{13}C NMR spectra of thiadiazino[5,6-b]quinoxalines II and III (Tables 2 and 3), respectively, does not make it possible to form an opinion regarding regioorientation of the condensed heterorings. A conclusion regarding their structures was drawn on the basis of the proton-coupled ^{13}C NMR spectra. In the ^{13}C NMR spectrum of II the signal of the $C_{(A)}$ atom at 61.1 ppm has a smaller constant [$^1J_{(C_A-HA)}$ = 156 Hz] than the $C_{(B)}$ atom at 56.5 ppm [$^1J_{(C_B-H_B)}$ = 164 Hz]; upon comparison with the ^{13}C NMR spectra of Va,b and VI, this indicates that the weaker-field signal belongs to the carbon atom bonded to two nitrogen atoms (Table 3). In the ^{13}C NMR spectrum of III, on the other hand, the stronger-field signal of the $C_{(A)}$ atom has a greater $^1J_{(C_A-HA)}$ constant, which indicates the regioisomeric structure of III (Table 3).

There are other peculiarities that indirectly confirm the conclusions regarding the regioorientation of these cycloadducts in the PMR spectra of II and III. Thus the chemical shift of the protons of the N–CH_3 group at 2.55 ppm in the PMR spectrum of II is at anomalously low field with respect to the spectrum of III (2.94 ppm); this is explained by the effect of the anisotropic field of the phenyl ring, which gives rise to a shift to strong field of the signal of the protons of the methyl group of II.

The formation of regioisomeric thiadiazino[5,6-b]quinoxalines II, III, and Va,b can be explained by means of concepts regarding the ring-chain isomerism of their probable intermediates, viz., dihydroquinoxalines VII and VIII [7].

The ambident character of thiobenzhydrazides permits the formation in the first step of products of N- and S-addition to the quinoxalinium salts, viz., dihydroqyinoxalines VII and VIII, respectively. As a consequence of the high nucleophilicity of the sulfur atom, N-adducts VII undergo rapid intramolecular cyclization; this is in agreement with the experimental fact

*The structure of VI was also confirmed by x-ray diffraction analysis; a separate communication will be published.



that dihydroquinoxalines of the VII type cannot be recorded in the PMR spectra even at −40°C. Thus under kinetic-control conditions the equilibrium is shifted toward the formation of cycloadducts of the II type. Under acidic-catalysis conditions or at increased temperatures, when the reversibility of the cyclizations becomes an important factor, the equilibrium is shifted toward the more thermodynamically stable thiadiazinoquinoxaline III. The formation of Va,b from N-adducts IVa,b is probably associated with the fact that S-addition of thiobenzhydrazide, which leads to intermediate VIII, proves to be dominant in the competitive N- or S-displacement of a diethylamine residue in adducts IVa,b.

Thus the same principles as in the cyclizations of thioamides with 1,4-diazinium salts were established in the annelation of sulfur-containing six-membered heterorings to N-alkylquinoxalinium salts: In the products formed in the kinetically controlled step the orientation of the sulfur-containing ring being annelated is such that the sulfur atom is bonded in the β position of the pyrazine ring, and the nitrogen atom is bonded with the α-carbon atom.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were recorded with Perkin–Elmer R-12B

TABLE 1. Characteristics of Regioisomeric 1,3,4-Thiadiazino-[5,6-b]quinoxalines

Compound	mp, °C (with dec.)	IR spectrum (NH) cm^{-1}	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
II	140—141	3420	71,1	5,5	15,0	8,5	$C_{22}H_{20}N_4S$	70,9	5,4	15.0	8,6	85
III	143—144	3415	71,2	5,3	14,8	8,6	$C_{22}H_{20}N_4S$	70,9	5,4	15,0	8,6	90
Va	129—130	3339	65,0	5,6	18,8	10,7	$C_{16}H_{16}N_4S$	64,8	5,4	18,9	10,8	62
Vb	121—122	3349	65,6	6,1	17,9	10,3	$C_{17}H_{18}N_4S$	65,8	5,8	18,1	10,3	62
VI	164—166	—	63,7	5,4	17,0	9,4	$C_{18}H_{18}N_4OS$	63,9	5,4	16,6	9,5	76

TABLE 2. PMR Spectra of Regioisomeric 1,3,4-Thiadiazino[5,6-b]-quinoxalines

Compound	Chemical shifts, δ, ppm					^3J (H_A–H_B), Hz
	A-H	B-H	N–R'	aromatic protons	signals of the remaining protons	
II	5,84 d	5,70 br d	2,55 s (3H)	6,59 s (4H); 6,8—7,9 m (11H)	Signal of the NH proton is overlapped by the aromatic multiplet	3,0
III	5,88 d	5,57 br d	2,94 s (3H)	6,52 s (4H); 6,8—7,8 m (10H)	6,15 br s (1H, 5-H)	3,0
Va	5,62 d	4,88 br d	2,92 s (3H)	6,53 s (4H); 7,2—7,8 m (5H)	5,62 br s (1H) and 7,87 br s (1H) (4-H and 5-H)	3,5
Vb	5,52 d	4,70 br d	1,20 t (3H); 3,37 q (2H)	6,48 s (4H); 7,1—7,7 m (5H)	5,56 br s (1H) and 7,80 br s (1H) (4-H and 5-H)	3,0
VI	5,58 d	6,38 br d	2,97 s (3H)	6,58 s (4H); 7,2—7,8 m (5H)	2,38 s (3H, $COCH_3$), 6,22 br s (1H, 5H)	3,0

TABLE 3. ^{13}C NMR Spectra of Regioisomeric 1,3,4-Thiadiazino-[5,6-b]quinoxalines

Compound	Chemical shifts of the nodal carbon atoms, δ, ppm, and SSCC, Hz				
	$C_{(A)}$	$J(C_A-H_A)$ *	$C_{(B)}$	$J(C_{(B)}-H_{(B)})$	signals of the remaining carbon atoms
II	61,1	156	56,5	164	32,5 ($N-CH_3$); 112,6; 114,3; 115,3; 118,3; 119,9; 120,0; 123,4; 128,6; 129,3; 129,5; 130,0; 132,1; 134,9; 142,4; 147,1 ($C_{(2)}=N$)
III	61,2	165	56,7	155	37,0 ($N-CH_3$); 112,8; 113,7; 116,2; 117,7; 120,4; 121,4; 126,1; 128,5; 129,1; 129,9; 133,9; 137,0; 137,1; 147,1 ($C_{(2)}=N$)
Va	63,3	166	54,8	156	36,6 ($N-CH_3$); 112,6; 113,0; 117,4; 120,2; 124,8; 128,3; 128,7; 129,6; 134,0; 137,3
Vb	61,1	164	54,6	155	13,0 и 44,1 ($N-C_2H_5$); 112,2; 113,6; 117,5; 119,3; 124,7; 128,2; 128,6; 133,8; 137,3
VI	61,2	167	50,7	160	22,9 ($COCH_3$); 37,0 ($N-CH_3$); 112,9; 113,6; 118,1; 120,6; 125,7; 128,7; 129,9; 130,4; 132,8; 136,3; 143,3 ($C_{(2)}=N$); 172,1 ($COCH_3$)

*Coupling with the protons of the N-alkyl group with $^3J_{(C-H)}$ values of 3-4 Hz is also manifested in the hyperfine structure (hfs) of the signal of the C_A atom.

(60 MHz) and Brucker WP-80 (80 MHz) spectrometers with tetramethylsilane (TMS) and hexamethyldisiloxane (HMDS) as the internal standards. The ^{13}C NMR spectra of solutions in d_6-DMSO were recorded with Brucker WH-90 (22.62 MHz) and Varian FT-80A (20.13 MHz) spectrometers. The chemical shifts were measured with respect to the signal of the solvent (d_6-DMSO, 39.6 ppm).

The quinoxaline base was synthesized from o-phenylenediamine by the method in [8]. Quaternary salt Ia was obtained by dissolving quinoxaline in a threefold excess of methyl iodide and separation of the crystals of the salt after 70-100 h at 20°C. N-Ethylquinoxalinium iodide (Ib) was obtained from a mixture of ethyl iodide with DMSO and the quinoxaline base. The thiobenzhydrazide and phenylthiobenzhydrazide were synthesized from dithiobenzoic acid by the method in [9].

The characteristics of the compounds obtained are presented in Tables 1-3.

5-Methyl-2,4-diphenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (II). A 1-g (4.4 mmole) sample of 1-phenylthiobenzhydrazide and 1 ml of diethylamine were added with stirring to a suspension of 1.19 g (4.4 mmole) of N-methylquinoxalinium iodide (Ia) in 2 ml of ethanol. The starting substances dissolved completely. The II that precipitated after 10 min was removed by filtration, washed thoroughly with small portions of ethanol and ether, and air dried.

10-Methyl-2,4-diphenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (III). A 1-g (2.7 mmole) sample of II was dissolved in refluxing ethanol. The crystals of III that precipitated after the solution was cooled were removed by filtration and air dried.

10-Methyl-2-phenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (Va). A 2.5-ml sample of diethylamine was added to a suspension of 2.68 g (9.8 mmole) of quinoxalinium iodide Ia in dry ether, after which the mixture was stirred for 10-15 min, and the diethylamine hydriodide was removed by filtration. The filtrate was evaporated in vacuo, and the resulting 1-methyl-2-(N,N-diethylamino)-1,2-dihydroquinoxaline was dissolved in 7 ml of ethanol. A 1.5 g (9.8 mmole) sample of thiobenzhydrazide was added to the solution. Crystallization commenced 10 min after the latter had dissolved. The precipitated Va was removed by filtration, washed with ethanol, and recrystallized from ethanol.

1,3,4-Thiadiazino[5,6-b]quinoxaline Vb was similarly obtained from thiobenzhydrazide and the Ib cation.

4-Acetyl-10-methyl-2-phenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (VI). A suspension of 2 g (6.7 mmole) of Va in 5 ml of acetic anhydride containing 5 ml of triethylamine was heated on a water bath at 50°C until Va had dissolved completely. After 30 min, the reaction mass was poured over ice, and the precipitated VI was removed by filtration and recrystallized from ethanol.

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