EXPERIMENTAL

The low-resolution and high-resolution mass spectra of I-V were taken on an MKh-1320 mass spectrometer with direct sample inlet. The ionizing electron energy was 70 eV. The resolution was 9000-10,000. The ion source temperature was 20-25°C. The DADI spectra and metastable defocusing spectra were taken on a Varian MAT-311 mass spectrometer at 70 eV. The compounds studied were synthesized according to our previous procedure [7]. The purity and individuality of the compound samples were monitored by gas–liquid chromatography and liquid chromatography.

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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BINUCLEOPHILES.

8.* ANNELLATION OF THE IMIDAZOLE RING WITH PYRAZINES AND QUINOXALINES

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Monosubstituted and N,N'-disubstituted thioureas enter into cyclization with pyrazinium and quinoxalinium ion to form imidazo[4,5-b]-annellated pyrazines and quinoxalines.

Heteroaromatic cations containing a pyrazine fragment are capable of undergoing cyclization with various 1,3-bifunctional nucleophilic reagents (enamines [2], β-diketones [3, 4], amides of β-keto acids [1], α-substituted acetimidic esters [5]). These reactions make it possible to obtain condensed heterocyclic systems based on the tetrahydroquinoxaline ring with annellated furan [3, 4] and pyrrole [1, 5] rings or a carbocyclic fragment [2]. In the present work we are reporting on the annellation of the imidazole ring to pyrazines and quinoxalines.

As a rule derivatives of imidazo[4,5-b]pyrazine and imidazo[4,5-b]quinoxaline are obtained by cyclizations of 2,3-diaminopyrazines (or quinoxalines) [6-8]. We have established that derivatives of imidazo[4,5-b]pyrazine and imidazo[4,5-b]quinoxaline are formed in the reactions of 2,3-dimethoxycarbonyl-N-ethylpyrazinium fluoroborate (Ia) and N-alkylquinoxalinium iodides (Ib, c) with monosubstituted and N,N'-disubstituted thioureas (IIb-f) (Scheme, Table 1).

*For Communication 7, see [1].

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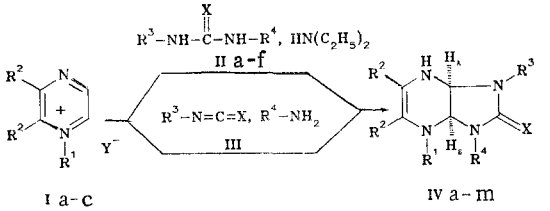
TABLE 1. Characteristics of Imidazo[4,5-b]pyrazines (IVa-c) and Imidazo[4,5-b]quinoxalines (IVd-m)

Compound	mp, *	R_f	Found, %				Mol. formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
IVa	182—183	0,58	54,6	5,4	—	8,6	$C_{17}H_{20}N_4O_4S$	54,3	5,3	—	8,5	72
IVb	180—181	0,60	53,9	5,9	—	7,7	$C_{19}H_{24}N_4O_5S$	54,3	5,7	—	7,6	57
IVc	183—185	0,87	61,0	5,4	12,5	—	$C_{23}H_{24}N_4O_4S$	61,0	5,4	12,4	7,1	90
IVd	183—184	0,58	64,4	5,5	18,8	10,9	$C_{16}H_{16}N_4S$	64,8	5,4	18,9	10,8	87
IVe	197—199	0,39	68,5	5,7	19,9	—	$C_{16}H_{16}N_4O$	68,6	5,8	20,0	—	78
IVf	177—179	0,79	65,6	6,0	18,0	—	$C_{17}H_{18}N_4S$	65,8	5,8	18,0	—	93
IVg	200—202	0,47	69,3	6,2	19,2	—	$C_{17}H_{18}N_4O$	69,4	6,2	19,1	—	83
IVh	210—212	0,83	65,9	5,8	18,2	—	$C_{17}H_{18}N_4S$	65,8	5,8	18,0	—	86
IVi	198—200	0,85	66,2	6,3	17,3	9,9	$C_{18}H_{20}N_4S$	66,6	6,2	17,3	9,9	92
IVj	194—195	0,82	70,7	5,5	14,9	—	$C_{22}H_{20}N_4S$	70,9	5,4	15,0	—	90
IVk	175—177	0,87	71,7	5,9	14,3	8,0	$C_{23}H_{22}N_4S$	71,5	5,7	14,5	8,3	96
IVl	215—216	0,82	66,7	5,6	—	7,4	$C_{24}H_{24}N_4O_2S$	66,7	5,6	—	7,4	82
IVm	172—174	0,85	68,3	6,1	—	6,9	$C_{26}H_{28}N_4O_2S$	67,9	6,1	—	7,0	73

*Compounds (IVa, b) were recrystallized from aqueous ethanol (1:1), compounds (IVc, d, j, l, m) from ethanol, (IVh, i) from a mixture of ethanol and acetone, and (IVg, e, f, k) from acetone.



I a-c IV a-m

Ia $R^1=C_2H_5$, $R^2=COOCH_3$, Y=BF_4; Ib $R^1=CH_3$, R^2=benzo, Y=I; Ic $R^1=C_2H_5$, R^2=benzo Y=I; IIa—d $R^3=C_6H_5$, IIe $R^3=C_6H_4$—OCH_3-*p*, IIf $R^3=C_6H_4$—OC_2H_5-*p*; IIa, b R^4=H, IIc $R^4=CH_3$, IId $R^4=C_6H_5$, IIe $R^4=C_6H_4$—OCH_3-*p*, IIf $R^4=C_6H_4$—OC_2H_5-*p*; IIa X=O, IIb—f X=S; III R^4=H, CH_3; IV a—c, f, g, i, k $R^1=C_2H_5$; IVd, e, h, j, l, m $R^1=CH_3$; IVa—c $R^2=COOCH_3$; IVd-m R^2=benzo; IVa, c, d—k $R^3=C_6H_5$; IVb, m $R^3=C_6H_4$—OC_2H_5-*p*; IVl $R^3=C_6H_4$—OCH_3-*p*; IV a, b, d-g R^4=H; IVc, j, k $R^4=C_6H_5$; IVh i $R^4=CH_3$; IVl $R^4=C_6H_4$—OCH_3-*p*; IVm $R^4=C_6H_4$—OC_2H_5-*p*; IVa-d, f, h—m X=S; IVe, g X=O

The reactions of the salts (Ia-c) with the thioureas (IIb-f) take place in ethanol in the presence of an excess of diethylamine at room temperature.

Another version of the synthesis of compounds (IV) was developed by means of which it is possible to bring phenyl isothiocyanate into reaction with salts (I) in the presence of primary amines (III), by-passing the isolation of the intermediately formed thioureas (method B, see the experimental section).

The N,N'-disubstituted thioureas can exist in various tautomeric forms and can exhibit the characteristic both of N,N'-bifunctional and N,S-bifunctional nucleophiles. Thus, methods for the synthesis both of imidazoles [9] and of thiazoles [10] on the basis of cyclizations with thioureas are well known.

At the same time, in a fairly large series of experiments on the cyclization of the salts (Ia-c) with thioureas (IIb-f) we have not once been able to record the formation of the corresponding condensed thiazoles. The data from UV and ^1H and ^{13}C NMR spectroscopy discussed below show that closure of the imidazole ring occurs in all cases.

The annellation of the imidazole ring is demonstrated primarily by the chemical shifts of the methine carbon atom C_A and C_B in the region of 72-79 ppm (Table 2) and also by the absorption of the carbon atom of the C=S bond in the characteristic region of thioureas at 179-180 ppm (Table 2) [11]. The difference in the chemical shifts of the C_A and C_B carbon atoms for compounds (IVd, h, m) amounts to only 3-5 ppm, which corresponds to the expected effect of the N-methyl group on the downfield shift of the α-carbon [11]. During the formation of a thiazole ring a larger difference would be expected in the shifts

TABLE 2. The ^{13}C NMR Spectra of Compounds (IVd, h, m) in DMSO-d_6 (δ, ppm)

Compound	CA	CB	N—CH_3	Benzene rings	C=S
IVd	72,7*	75,7*	34,8	112,6; 115,2; 119,5; 120,3; 127,0; 128,4; 128,8; 133,4; 136,2; 137,7	180,2
IVh	73,5*	77,8*	33,9 37,6	113,3; 114,8; 120,0; 126,9; 128,4; 128,7; 134,4; 135,5; 138,3	179,8
IVm	74,2	78,9	37,5	113,4; 114,5; 115,0; 120,1; 129,8; 129,9; 130,7; 132,6; 134,7; 135,6; 157,6	180,1

*The assignment of the signals may be reversed.

of the bridgehead carbon atom, and more upfield resonance would be expected for the methine carbon atom situated between the nitrogen and the sulfur atoms, as observed in the ^{13}C NMR spectra of hydrogenated thiazolo[4,5-b]quinoxalines.*

The closure of the imidazole ring in the reactions with thioureas is also confirmed by the fact that the reactions of the salts (Ib, c) with N-phenylurea (IIa) give cyclic adducts (IVe, g), the electronic spectra of which are extremely similar to those for the thio analogs (IVd, f), while the ^1H NMR spectra have extremely close characteristics (Table 3). Thus, the electronic spectrum of (IVe) in ethanol contains three absorption bands with λ_{max} (log ε) 214 (4.62), 242 (4.25) and 297 nm (3.54), while the absorption maxima of compound (IVd) are at 219 (4.64), 242 (4.35), and 297 nm (3.70).

The conclusion about the orientation of the unsymmetrical thioureas was made on the basis of the effect of the substituents R^3 and R^4 on the chemical shifts of the protons H_A and H_B and of the N-alkyl group of the pyrazine ring (Table 3). The shift of the proton H_A changes very little and remains in the range of 5.75-6.02 ppm for the whole series of imidazo[4,5-b]-quinoxalines (IVd-m) (Table 3), since the C_A carbon atom is always attached to the N-arylamide fragment. In addition, in the ^1H NMR spectra of the cyclic ureas (IVe, g) ($R^3 = C_6H_5$, R^4 = H, X = O) in DMSO-d_6 spin—spin coupling shows up clearly between the H_B proton and the proton of the amide group and is removed with exchange by deuterium, indicating conclusively that the $C_{(2)}$ atom of the pyrazine ring is attached to the unsubstituted end of the phenylurea (Fig. 1). In the transition from monophenyl-substituted imidazo[4,5-b]quinoxalines (IVe, f) (R^4 = H) to the diphenyl derivatives (IVj, k) ($R^4 = C_6H_5$) the signal of the H_B proton undergoes a fairly large downfield shift, i.e., from 5.43-5.53 to 6.25-6.28 ppm (Table 3). Here the signal for the protons of the N-alkyl group of the pyrazine ring, which lie in the region of the anisotropic field of the benzene ring, is shifted upfield from 2.87 (IVd) to 2.45 ppm (IVj) for the N-methyl and from 1.16 (IVf) to 0.85 ppm (IVk) for the triplet signal of the methyl protons in the N-ethyl group (Table 3). The diaryl derivatives (IVℓ, m) have similar values for the chemical shifts of the H_A, H_B, and N—CH_3 protons to those for compound (IVj) (Table 3).

The chemical shifts of the H_B proton and, particularly, the N-alkyl group are extremely sensitive to the substituent R^4 and not only to the aryl substituent. The substitution of R^4 = H (IVd, f) by a methyl group leads to a downfield shift both of the signal for the H_B proton and of the signal for the N-alkyl group in compounds (IVh, i) (Table 3).

The vicinal constants J_{AB} of 8.6-9.5 Hz for compounds (IVd-m) indicate the cis orientation for the hydrogen atoms H_A and H_B. Similar values for the constants J_{AB} of 9-10 Hz were observed for furo[2,3-b]-annellated quinoxalines [3, 4] and furo[3,2-b]-annellated quinolines [12], in which the cis orientation of the hydrogen atom during fusion of the heterocycles was confirmed by x-ray crystallographic analysis. In the case of the trans orientation of the H_A and H_B hydrogen in compounds (IV) small values must be expected for J_{AB}, as observed, for example, in trans-substituted 4,5-diamino-4,5-dihydroimidazoles, which have

*The chemical shifts of the bridgehead carbon atoms $C_{(3a)}$ and $C_{(9a)}$ in the ^{13}C NMR spectrum of 2,4-dimethyl-9-acetyl-3a,4,9,9a-tetrahydrothiazolo[4,5-b]quinoxaline in DMSO-d_6 are 96.9 and 68.9 ppm respectively. The annellation of the thiazole ring with the quinoxaline ring will be considered in the next communication.

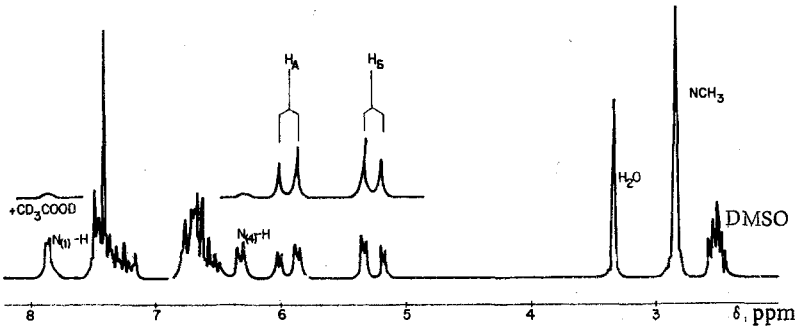


Fig. 1. The ^1H NMR spectrum of 9-methyl-3-phenyl-2, 3,3a,4,9,9a-hexahydro-1H-imidazo[4,5-b]quinoxalin-2-one (IVe) in DMSO-d_6.

TABLE 3. The ^1H NMR Spectra of Imidazo[4,5-b]pyrazines (IVa-c) in Deuterochloroform and Imidazo[4,5-b]quinoxalines (IVd-m) in DMSO-d_6

Compound	Chemical shifts, δ, ppm							SSCC, Hz	
	H_A, dd	H_B, d	R^1	R^2	R^3	R^4	$N_{(4)}$–H	H_AH_B	H_AH_4
IVa	5,69	5,20	3,19 (q, 2H), 1,17 (t, 3H)	3,57 (s, 3H), 3,85 (s, 3H)	7,1—7,5 (m, 5H)	8,00 (bs)	4,36	7,8	2,8
IVb	5,58	5,19	3,19 (q, 2H), 1,16 (t, 3H)	3,63 (s, 3H), 3,84 (s, 3H)	6,89 (d, 2H), 7,12 (d, 2H)	8,04 (bs)	4,32	7,8	2,7
IVc	5,69	5,69	2,2—3,1 (m, 2H), 0,90 (t, 3H)	3,69 (s, 3H), 3,82 (s, 3H)	7,2—7,7 (m, 10H)		4,40	—	—
IVd	5,95	5,43	2,87 (s, 3H)	6,4—7,0 (m, 4H)	7,1—7,8 (m, 5H)	9,44 (bs)	6,36	9,2	2,7
IVe	5,94	5,27	2,84 (s, 3H)	6,4—6,9 (m, 4H)	7,0—7,6 (m, 5H)	7,86 (bs)	6,32	8,6	2,3
IVf	5,93	5,53	1,16 (t, 3H), 2,8—3,8 (m, 2H)	6,4—6,9 (m, 4H)	7,1—7,7 (m, 5H)	9,38 (bs)	6,32	9,0	2,8
IVg	5,83	5,28	1,18 (t, 3H), 2,7—3,7	6,3—6,8 (m, 4H)	7,0—7,6 (m, 5H)	7,68 (bs)	6,18	9,0	2,7
IVh	5,80	5,50	3,15 (s, 3H)	6,3—6,8 (m, 4H)	7,0—7,6 (m 5H)	3,15 (s, 3H)	6,14	9,1	2,0
IVi	5,75	5,60	1,11 (t, 3H), 2,9—4,0 (m, 2H)	6,4—7,0 (m, 4H)	7,0—7,6 (m, 5H)	3,08 (s, 3H)	6,15	9,0	2,0
IVj	6,02	6,25	2,45 (s, 3H)	6,4—7,0 (m, 4H)	7,2—7,7 (m, 10H)		6,40	8,9	2,0
IVk	6,00	6,28	0,85 (t, 3H), 2,4—3,2 (m, 2H)	6,5—7,0 (m, 4H)	7,1—7,8 (m, 10H)		6,35	9,5	2,0
IVl	5,92	6,18	2,52 (s, 3H)	6,4—7,6 (m, 12H), 3,85 (s, 6H)			6,40	9,0	2,0
IVm	5,97	6,25	2,53 (s, 3H)	6,5—7,6 (m, 12H), 4,16 (q, 4H), 1,36 (t, 6H)			6,50	9,2	2,0

$J_{4,5}$ values between 1.0 and 3.6 Hz, depending on the substituents [13, 14].

The same relationships are observed in the ^1H NMR spectra of the imidazo[4,5-b]pyrazines (IVa-c). Thus, monosubstituted and N,N'-disubstituted thioureas react with quaternary pyrazinium and quinoxalinium salts as N,N'-bis-nucleophiles. In reactions with monoaryl-substituted thioureas the unsubstituted thioamide group is combined into the cations (Ia-c) with the more electrophilic $C_{(2)}$ atom.

EXPERIMENTAL

The UV spectra were recorded in ethanol on a Specord UV-vis instrument. The ^1H and ^{13}C NMR spectra were recorded in deuterochloroform and DMSO-d_6 on Perkin—Elmer R12B (60 MHz) and Varian FT-80A instruments with TMS or HMDS as internal standard. The purity was monitored by chromatography on Silufol UV-254 plates in 6:3:1 chloroform—ethyl acetate—ethanol system, and they were detected by development with iodine vapor. The melting points were determined on a Boetius Bench.

The quinoxaline and its quaternary salts were obtained as described earlier [1]. Dimethyl 2,3-pyrazinedicarboxylate was obtained according to [15].

N-Ethyl-2,3-dimethoxycarbonylpyrazinium Fluoroborate. A 3.8-g sample (20 mmole) of triethyloxonium fluoroborate was dissolved in 22 ml of dry dichloroethane, a solution of 3.2 g (16.3 mmole) of dimethyl pyrazinedicarboxylate in 17 ml of dry dichloroethane was added, and the mixture was heated to boiling. After 2 h the solvent was evaporated, ethanol was added to the residue, and the product was rubbed until a crystalline precipitate had formed. The precipitate was separated and washed with ethanol and with ether. The yield was 3.9 g (80%); mp 98-99°C (from a 2:1 mixture of benzene and ethanol). Found, %: C 38.3; H 4.5. $C_{10}H_{13}BF_4N_2O_4$. Calculated, %: C 38.4; H 4.4.

7-Ethyl-3-phenyl-5,6-dimethoxycarbonyl-2,3,3a,4,7,7a-hexahydro-1H-imidazo[4,5-b]pyrazine-2-thione (IVa). To a suspension of 0.4 g (1.3 mmole) of N-ethyl-2,3-dimethoxycarbonylpyrazinium fluoroborate and 0.2 g (1.3 mmole) of N-phenylthiourea in 5 ml of ethanol we added dropwise 0.5 ml (4.7 mmole) of diethylamine. The mixture was heated until the reagents had completely dissolved (40-50°C) and kept at this temperature for 15 min. After 2 h the solvent was evaporated, 10 ml of water was added to the residue, and the mixture was left overnight. The extract was decanted, a new portion of water was added to the residue, and the mixture was rubbed until a crystalline precipitate had formed. The precipitated compound (IVa) was filtered off and recrystallized from aqueous ethanol. The yield was 0.35 g (70%); mp 182-183°C. Found, %: C 54.6; H 5.4. $C_{17}H_{20}N_4O_4S$. Calculated, %: C 54.3; H 5.3.

The reactions of the cation (Ia) with N-(p-ethoxyphenyl)thiourea and N,N'-diphenylthiourea were carried out similarly, and compounds (IVb, c) were obtained. The characteristics of compounds (IVa-c) are given in Tables 1 and 3.

1,9-Dimethyl-3-phenyl-2,3,3a,4,9,9a-hexahydro-1H-imidazo[4,5-b]quinoxaline-2-thione (IVh). A. To a suspension of 3.27 g (12 mmole) of N-methylquinoxalinium iodide in 6 ml of ethanol at 20-25°C, while stirring, we added 2 g (12 mmole) of N-phenyl-N'-methylthiourea and 3.2 ml (31 mmole) of diethylamine. Here a colorless solution was formed initially and then a precipitate of compound (IVh), which was separated and crystallized from a a mixture of ethanol and acetone. The yield of (IVh) was 3.2 g (82%), and the product formed colorless crystals; mp 211-212°C. R_f 0.83. Found, %: C 65.9; H 5.8; N 18.2. $C_{17}H_{18}N_4S$. Calculated, %: C 65.8; H 5.8; N 18.1.

Compounds (IVe, f, i-m) were obtained by method A.

B. To a suspension of 2 g (7.2 mmole) of N-methylquinoxalinium iodide in 5 ml of ethanol, while stirring, we added 1 g (7.3 mmole) of phenyl isothiocyanate. A stream of methylamine was passed into the obtained mixture for 10-15 min until the reagent had completely dissolved and the solution was colorless. The bubbling of methylamine was continued for a further 5 min. In this time an abundant precipitate of compound (IVh) formed. It was separated and recrystallized from a mixture of ethanol and acetone. The yield was 1.2 g (52%), and the product formed colorless crystals; mp 211-212°C. R_f 0.83.

The ^1H NMR spectra of compound (IVh) obtained by methods A and B were identical (Table 3). Compound (IVd) was also obtained by both methods. The characteristics of the compounds are given in Tables 1-3.

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