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REACTIONS OF N-ALKYLAZINIUM CATIONS.

2.* REACTION OF QUINOXALINIUM SALTS WITH MALONODINITRILE AND CYANOACETIC ESTER

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UDC 547.863

N-Alkylquinoxalinium salts react with malonodinitrile and cyanoacetic ester carbanions to give addition products, which, due to favorably disposed CN groups and active CH centers, subsequently undergo intramolecular cyclization with the formation of a five-membered ring.

N-Alkylazinium cations are capable of readily adding carbanions and heteroatomic anions, as well as uncharged anionoid nucleophiles, to give the corresponding dihydro compounds [2]. The N-alkylquinoxalinium cation, which has a tendency to add two molecules of a nucleophilic reagent [3-5] to give tetrahydroquinoxaline derivatives, occupies a special position among these cations. The reaction of quinoxalinium salts (I) with enamines was investigated in [6], and an unusual cyclization reaction, at the basis of which also lies the ability of the quinoxalinium cation to undergo diaddition, was observed. In the present research we studied the reaction of quinoxalinium salt I with derivatives of cyanoacetic acid, viz., the ester and nitrile, which, according to the literature data, have rather high CH activity that is sufficient for participation in reactions even with less electrophilic azinium cations such as the quinolinium cation [7].

We established that, depending on the reaction conditions, the formation of several products is possible with malonodinitrile. The slow addition of a base to a mixture of quinoxalinium salt I with a twofold excess of malonodinitrile in ethanol at room temperature (method A, see the experimental section) leads to an exothermic reaction that is ac-

*See [1] for Communication 1.

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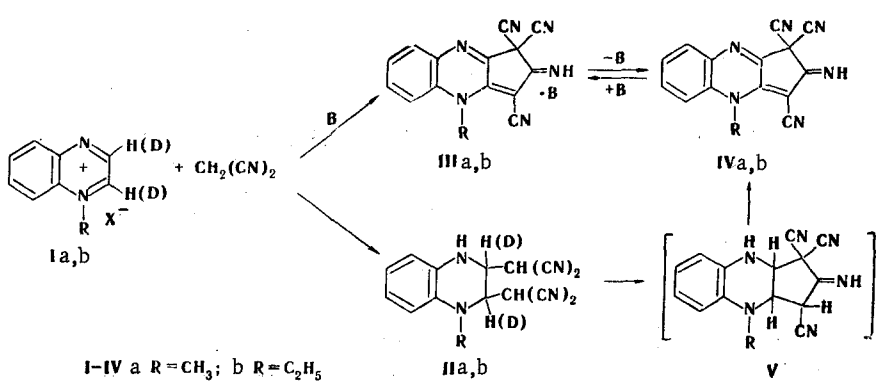
TABLE 1. Quinoxalines II-IV and VII

Compound	mp, °C	R_f	IR spectrum. NH	IR spectrum. C≡N	Electronic spectrum in ethanol, λmax, nm (log ε)	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
IIa	133	0,77[a]	3406	2262	309 (3,89)[b]	65,4	4,5	29,8	$C_{15}H_{12}N_6$	65,2	4,3	30,4	63
IIb	136	0,76[a]	3415, 3400	2263	311 (3,72)[b]	66,3	4,9	29,1	$C_{16}H_{14}N_6$	66,2	4,8	29,0	65
IIIa	>330[c]	0,76[d]	—	2200	239 (4,36), 253 (4,67), 452 (4,62), 473 (4,55)	66,5	5,8	28,0	$C_{15}H_8N_6 \cdot HN(C_2H_5)_2$	66,1	5,5	28,4	76
IIIb	>330[c]	0,76[d]	—	2205	239 (4,37), 253 (4,71), 451 (4,71), 478 (4,64)	66,6	5,8	27,3	$C_{16}H_{10}N_6 \cdot HN(C_2H_5)_2$	66,8	5,8	27,3	70
IIIc	>330[c]	0,76[d]	—	2200	237 (4,84), 277 (4,31), 455 (4,74), 481 (4,64)	67,4	6,0	25,8	$C_{15}H_8N_6 \cdot N(C_2H_5)_3$	67,6	6,2	26,3	—
IVa	>330	0,76[d]	—	2220	238 (4,62), 254 (4,20), 269 (4,15), 457 (4,61), 481 (4,51)	65,9	3,0	30,9	$C_{15}H_8N_6$	66,2	2,9	30,9	—
IVb	>330	0,76[d]	—	2223	238 (4,79), 253 (4,39), 269 (4,34), 455 (4,79), 481 (4,69)	66,8	3,7	29,4	$C_{16}H_{10}N_6$	67,1	3,5	29,4	—
VII	175	0,77[e]	3360, 3332, 3426	2250	221 (4,59), 258 (4,14), 277 (4,14)	61,7	6,1	—	$C_{19}H_{22}N_4O_4$	61,6	6,0	—	27

[a]In benzene—ethanol (2:1). [b]In dioxane. [c]An amine is split out at temperatures above 200°C and during chromatography on Silufol plates. [d]In chloroform—ethanol—amyl acetate (1:1:1). [e]In ethanol.

companied by dissolving of the starting salt and simultaneous precipitation of colorless crystals, which were identified as products (IIa, b) of the addition of two malonodinitrile

Scheme



residues (Table 1). The PMR spectrum of IIa in deuteroacetone is presented in Fig. 1. The chemical shift of the protons of the methyl group (δ 3.34 ppm) and the narrow multiplet of protons of the benzene ring centered at δ 6.85 ppm are characteristic for tetrahydroquinoxaline derivatives [3]. The 2-H and 3-H protons of the heteroring and the protons of the two CH groups of the substituents give a complex multiplet at 4.5-5.0 ppm. The use of the 2,3-d_2-quinoxalinium salt in the reaction simplified this part of the spectrum to two broad singlets of $CH(CN)_2$ protons (Fig. 1). The signals of two CH groups (δ 25.9 and 28.0 ppm) and four nitrile groups (112.7, 112.7, 112.75, and 113.1 ppm) of the substituents in the ^{13}C NMR spectrum of IIb and the chemical shifts of the carbon atoms of the pyrazine ring (δ 52.7 and 58.1 ppm) are in complete agreement with structure II. The mass spectra of diaddition products IIa, b contain peaks of their molecular ions.

The formation of IIa, b in solution in ethanol also occurs at lower temperatures (up to −80°C); lowering the temperature increases their yields and purity. Water can also be used as the solvent, and diethyl- and triethylamines, cycloalkylamines, and primary aliphatic amines can be used as the base.

TABLE 2. High-Resolution Mass Spectrum of IVb

Fragmentation pathway and ions	Relative intensity, %	Empirical composition		
		formula	determined	calculated
$M^{+\cdot}$	95,6	$C_{16}H_{10}N_6$	286,1007	286,0966
1. $[M-C_2H_5]^+$	17,9	$C_{14}H_8N_6$	257,0527	257,0575
$[(M-C_2H_5)-CN]^+$	55,8	$C_{13}H_8N_5$	231,0515	231,0545
$[(M-C_2H_5-CN)-CN]^+$	25,2	$C_{12}H_8N_4$	205,0503	205,0514
2. $[M-C_2H_4]^+$	97,1	$C_{14}H_6N_6$	258,0650	258,0653
$[(M-C_2H_4)-CN]^+$	16,9	$C_{13}H_6N_5$	232,0615	232,0623
$[(M-C_2H_4-CN)-CN]^+$	26,5	$C_{12}H_6N_4$	206,0533	206,0592
3. $[M-HCN]^{+\cdot}$	32,2	$C_{15}H_9N_5$	259,0825	259,0858

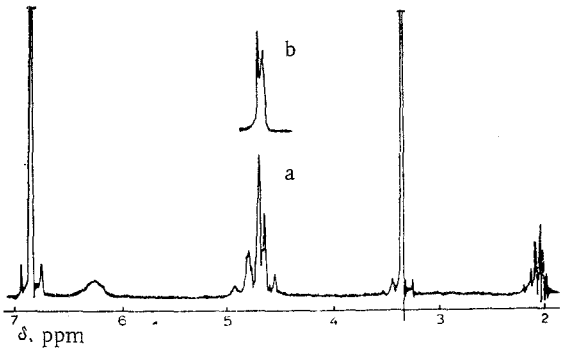


Fig. 1. PMR spectra of IIa in deuteroacetone (a) and its 2,3-d_2-substituted derivative (b).

A change in the reaction conditions leads to a different result. The rapid addition of a base to the same suspension of salt I and malonodinitrile in ethanol at room temperature (method B, see the experimental section) leads to a solution, from which deeply colored crystals precipitate with time; cyclopentenoquinoxaline structures IVa, b should be assigned to these crystals on the basis of the IR, ^1H and ^{13}C NMR, and mass spectra. Compounds IVa, b usually precipitate from solutions in the form of complexes (IIIa, b) with a molecule of the base (Table 1). The PMR spectrum of complex IIIa contains, in addition to signals of diethylamine, only a signal of protons of a methyl group at δ 4.28 ppm and a multiplet of aromatic protons at 7.4-8.0 ppm, the chemical shifts of which are in good agreement with formula III. A great deal of information is provided by the ^{13}C NMR spectrum, which contains a number of characteristic signals: the carbon atom of the iminium bond (δ 172.2 ppm) and the carbon atom of the C=N bond of the quinoxaline ring (δ 159.4 ppm) [8] resonate at a weak field, and we assigned the signal at δ 71.6 ppm to the carbon atom of a cyclopentene ring bonded to two nitrile groups. The complex nature of IIIa-c is confirmed by their formation in the presence of not only secondary amines (IIIa, b) but also a tertiary amine (IIIc), as well as by their ability to split out a molecule of the base upon heating. Complexes IIIa, b are once again formed when the amines are added to ethanol solutions of IVa, b. Complexing with the amine imparts a blue coloration to crystals of IIIa-c and lowers the frequency of the stretching vibrations of the C≡N bond by ∿20 cm^{-1} with respect to crystals of IV. The electronic spectra of very dilute ethanol solutions of III and IV in the visible region are very similar (Table 1), and this may indicate dissociation of complexes IIIa-c in solution. An additional confirmation of the correctness of structures III and IV is provided by an examination of their mass spectra. The mass spectra of IIIb and IVb have identical molecular masses and differ only in the low-mass region due to superimposition of ions formed from diethylamine. The high-resolution mass spectrum of IVb is presented in Table 2. The composition of the M^+ ion and the principal pathways of fragmentation of IVb associated with detachment of an alkyl substituent attached to the nitrogen atom and elimination of CN and HCN (Table 2) confirm its structure.

On the basis of the literature data on intramolecular cyclization with the participation of nitrile groupings [9-11], it might have been assumed that III and IV develop as a result of intramolecular cyclization of the initially formed diadduct II. A study of the

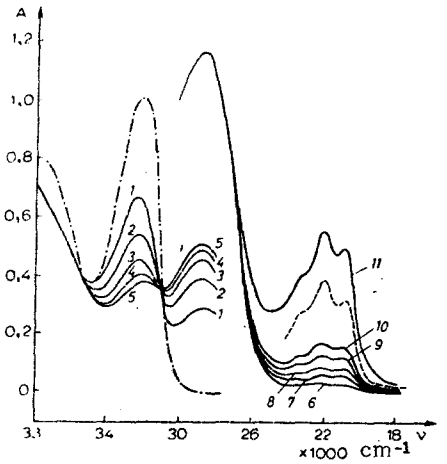


Fig. 2

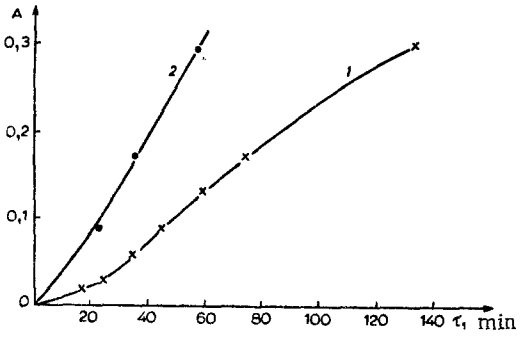


Fig. 3

Fig. 2. Change in the electronic spectra of a solution of IIb in ethanol (C_0 = 10^{-3} mole/liter) in the UV (l = 0.2 cm) and visible (l = 0.5 cm) regions. Curves 1-5 were recorded at minute intervals in the course of the first 5 min immediately after dissolving, while curves 6-11 were recorded after 25, 35, 45, 60, 75, and 315 min, respectively. The spectrum of IVb is shown by the dash line, and the spectrum of IIb in dioxane (C = 10^{-3} mole/liter, l = 0.2 cm) is shown by the dot-and-dash line.

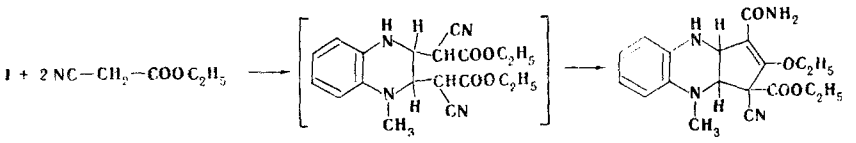
Fig. 3. Kinetic curves of the formation of IVb from diadduct IIb in ethanol at room temperature: 1) C_0 (IIb) = 10^{-3} mole/liter, l = 0.5 cm; 2) the same with the addition of diethylamine (10^{-3} mole/liter).

electronic spectra of ethanol solutions of II showed that IIa, b are, in fact, converted in ethanol solution with time to products IVa, b; this is established from the coincidence of the absorption bands in the visible region (Fig. 2). The pronounced S-shaped character of the kinetic curve of the accumulation of IVb (Fig. 3) recorded from the increase in the absorption intensity at λ_{max} 450 nm constitutes evidence that an intermediate that most likely has structure V precedes it. Precisely the formation of intermediate V also determines the character of the change in the electronic spectra in the initial period of the reactions (Fig. 2), during which final product IVb is not yet recorded in the spectra. In the first 10 min one observes a decrease in the absorption intensity of starting IIb at λ_{max} 311 nm with a simultaneous increase in the concentration of intermediate V with λ_{max} 348 nm. In this period, during which the IVb concentration is negligibly small, the system is a virtually two-component system, and a limited isobestic point [12], which corresponds to the IIb → V transformation, is observed at λ 322 nm (Fig. 2). Superimposition of the absorption of final product IVb in the UV region subsequently complicates the picture. The addition of an equimolar amount of diethylamine to a solution of IIb in ethanol gives rise to the rapid II → V transformation (Fig. 2) and ultimately accelerates the formation of reaction product IIIb (Fig. 3). This fact explains the different reaction pathways as a function of the rate of addition of the base. Excess amine created by the rapid addition of the base (method B) is also responsible for rapid cyclization of diadducts II to III.

A product of addition of two CH residues of active VI is also evidently initially formed in the reaction of iodide I with cyanoacetic ester; however, we were able to isolate only the product of its subsequent cyclization (VII) from the reaction mass.

The structure of VII was established on the basis of data from the IR, PMR, and mass spectra. The tetrahydroquinoxaline fragment is characterized in the PMR spectra by a narrow multiplet of aromatic protons at 6.6-6.9 ppm, a singlet of an N–CH_3 group at δ 3.03 ppm, and two doublets of 2-H and 3-H protons at 4.28 and 4.59 ppm with J = 5.6 Hz. The broad signal of an NH proton at 4.0-4.7 ppm which readily undergoes deuterium exchange vanishes when deuteromethanol is added, in contrast to the signal of the two amine protons at δ 5.95 ppm which undergo only slow exchange when CD_3COOD is added. The IR spectrum of VII contains absorption bands of NH and amide NH_2 (3360, 3332, and 3426 cm^{-1}), ester C=O (1741 cm^{-1}), amide (1688 cm^{-1}, amide I), and C≡N (2250 cm^{-1}) stretching vibrations. The presence

of a molecular-ion peak in the spectrum of VII and the character of its fragmentation also confirm its structure.



VI VII

The results constitute evidence that when residues that are capable of subsequent transformations are introduced in the quinoxaline ring, one should reckon with the possibility of their intramolecular cyclization. This property of the products of diaddition to quinoxaline can be used for the synthesis of new heterocyclic systems based on it.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Perkin–Elmer R-12B spectrometer (60 MHz) with tetramethylsilane as the internal standard. The ^{13}C NMR spectra were recorded with a Varian WP-80 spectrometer (20.115 MHz); the chemical shifts of the ^{13}C nuclei were measured relative to the signal of the solvent and are presented on the δ scale in parts per million. The electronic spectra were recorded with a Specord UV-vis spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Varian Mat-311 spectrometer; the samples were introduced directly into the ion source, and the accelerating voltage was 3 kV, the ionization energy was 70 eV, and the cathode emission current was 300 μA. The precise values of the masses of the individual ions were determined with a Jeol high-resolution mass spectrometer with a resolution of $M/\Delta M = 20{,}000$ with PFK as the standard. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol plates.

Reaction of Quinoxalinium Salts with Malonodinitrile. A) A solution of 1.44 g (0.022 mole) of malonodinitrile in 12 ml of ethanol was added at room temperature to a suspension of 3 g (0.011 mole) of N-methylquinoxalinium iodide in 15 ml of ethanol, after which 2.3 ml (0.022 mole) of diethylamine was added slowly dropwise with stirring. Warming up of the reaction mixture, dissolving of the starting salt, and the formation of a colorless crystalline precipitate were observed as the diethylamine was added. The precipitated 1-methyl-2,3-bis(dicyanomethyl)-1,2,3,4-tetrahydroquinoxaline (IIa) [1.9 g (63%)] was removed by filtration and was purified as rapidly as possible by reprecipitation. For this, IIa was dissolved in the minimum amount of acetic anhydride, the solution was shaken two to three times with a fivefold volume of water, the aqueous layer was removed, and 70% aqueous ethanol was added to the residual solution until the crystals were precipitated completely. The precipitate was separated, washed with ethanol, and dried at 60°C. Compound IIb was similarly obtained. Data for IIa, b are presented in Table 1.

Mass spectra, m/e ($J \geqslant 20\%$). Compound IIa: 38 (30), 39 (38), 65 (26), 66 (100), 76 (26), 77 (43), 80 (22), 92 (26), 102 (22), 103 (30), 104 (21), 107 (35), 122 (36), 130 (20), 131 (37), 132 (24), 133 (21), 145 (89), 146 (41), 184 (23), 276 (29). Compound IIb: 38 (97), 39 (100), 40 (26), 50 (23), 51 (26), 64 (31), 65 (38), 66 (98), 76 (33), 77 (43), 103 (38), 104 (31), 130 (35), 131 (84), 159 (79), 160 (77), 290 (2).

^{13}C NMR spectrum of IIb in acetone, δ: 13.1 (CH_3); 25.9 and 28.0 (2 CH); 45.8 (N–CH_2); 52.7 and 58.1 (carbon atoms of the pyrazine ring); 112.7 (2 CN); 112.75 (CN); 113.1 (CN); 113.9, 116.1, 120.6, 121.0 (4 CH of the benzo ring); 129.4 ppm (2 C–N of the benzo ring).

B) A 0.48-g (7.2 mmole) sample of malonodinitrile was added at room temperature to a suspension of 1 g (3.6 mmole) of N-methylquinoxalinium iodide in 5 ml of ethanol, after which 0.75 ml (0.080 mole) of diethylamine was added all at once. The solution was allowed to stand at room temperature for 24 h, after which the precipitated crystals of IIIa were separated, washed with ethanol, and dried to give 0.47 g of red-brown needles. Another 0.5 g of IIIa was isolated from the reaction solution after 2 days for an overall yield of 76%. Compounds IIIb and IIIc were similarly obtained; triethylamine was used as the base in the latter case. The principal characteristics of IIIa-c are presented in Table 1.

^{13}C NMR spectrum of IIIa in dimethyl sulfoxide (DMSO), δ: 11.1 [$HN(CN_2CH_3)_2$]; 35.5 (NCH_3); 39.2 [$HN(CH_2CH_3)_2$]; 71.6 [$C(CN)_2$]; 114.6 [$C(CN)_2$]; 116.6 (CN); 124.2 (C=C); 125.7 126.2, 127.2, 128.2 (4 CH of the benzo ring); 137.8 and 140.9 (2 C–N of the benzo ring); 159.4 (C=N of the pyrazine ring); 172.2 ppm (C=NH).

Conversion of Complexes IIIa-c to IV. The conversion was carried out at 220-250°C for 30 min. The characteristics of IVa and IVb are presented in Table 1. The corresponding complexes were regenerated in the case of recrystallization of IV from ethanol with the addition of the amines.

Reaction of N-Methylquinoxalinium Iodide with Cyanoacetic Ester. A 3-ml (0.025 mole) sample of cyanoacetic ester was added to a suspension of 3 g (0.011 mole) of iodide I in 12 ml of ethanol, after which 3 ml (0.040 mole) of diethylamine was added with stirring. After 15 min, 100 ml of water was added to the resulting solution, during which a resinous precipitate formed. The aqueous alcohol solution was decanted, and the residue was treated with ether, removed by filtration, and recrystallized from ethanol to give 1.1 g (27%) of colorless crystals of VII with mp 175°C. PMR spectrum in deuterochloroform, ppm: 1.33 t (OCH_2CH_3), 1.40 t (OCH_2CH_3), 3.03 s (NCH_3), 4.28 d (2-H, J = 5.6 Hz), 4.29 q (OCH_2CH_3), 4.46 q (OCH_2CH_3), 4.59 d (3-H), 5.95 ($O{=}C{-}NH_2$), 6.6-6.9 m (4H of the benzene ring). Mass spectrum, m/e (J ⩾ 10% of the maximum peak): 65 (15), 77 (22), 92 (22), 94 (16), 104 (11), 119 (25), 121 (19), 131 (44), 132 (11), 133 (65), 145 (34), 146 (26), 184 (14), 185 (16), 208 (14), 209 (17), 223 (39), 224 (15), 250 (16), 251 (100), 252 (27), 263 (11), 278 (12), 280 (13), 295 (41), 296 (13), 297 (13), 324 (23), 370 (79), 371 (16).

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