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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BISNUCLEOPHILES. 5.* CYCLIC ADDUCTS AND RECYCLIZATION PRODUCTS IN THE REACTIONS OF BENZODIAZINIUM CATIONS WITH IMIDO ESTERS

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The reaction of imido esters that contain an active methylene group with four isomeric benzodiazinium cations, viz., the 1-methylquinoxalinium, 2-methylcinnolinium, 3-methylquinazolinium, and 2-methylphthalazinium cations, was investigated. The 1-methylquinoxalinium cation reacts with imido esters via a scheme involving anionic [3⁻ +2]-cycloaddition to form tetrahydropyrrolo[2,3-b]quinoxalines. The 2-methylcinnolinium cation forms an adduct with an annelated pyrrole ring. Under the influence of imido esters, the 3-methylquinazolinium cation undergoes recyclization to a 2,3-disubstituted quinoline. The 2-methylphthalazinium cation is inert in this reaction.

The research of Strauss on reactions involving so-called "meta bridging" of polynitroaromatic compounds with bisnucleophilic reagents, which leads to complex polycyclic systems in one step [2-6], compelled us to investigate the possibility of the participation of highly π-deficient N-alkylazinium cations in such cyclizations. The observed ortho cyclization of quinoxalinium salts (I) with enamines of ketones [7] has been extended to other 1,3-bisnucleophilic reagents, viz., β-diketons and their esters [8] and amide [9], as well as to other azinium cations that contain a pyrazine fragment [1]. The formation of a five-membered ring, which leads to [2,3-b]-annelated tetrahydropyrazines, was observed in all of these reactions [1,7-9].

In the present research we investigated the reactions of yet another type of bisnucleophilic reagent, viz., CH-active imido esters, with four isomeric benzodiazepinium cations, viz., 1-methylquinoxalinium (I), 2-methylcinnolinium (II), 3-methylquinazolinium (III), and 2-methylphthalazinium (IV) cations. If one starts from the analogies with the reactions of aromatic polynitro compounds, due to the different orientations of the aza groups in this

*See [1] for Communication 4.

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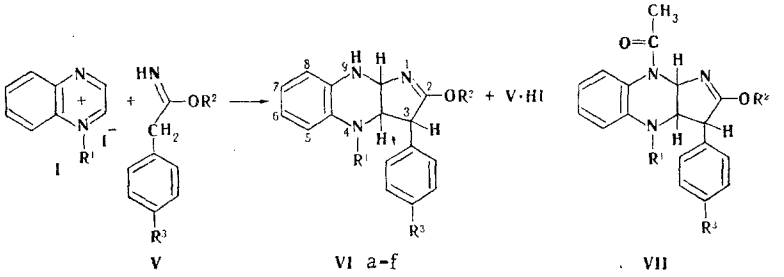
TABLE 1. Characteristics of the Synthesized VIa-f and VII

Compound	R^1	R^2	R^3	mp, °C	R_f*	PMR spectra in deuteroacetone δ, ppm 3-H	3a-H	9a-H	$J_{3a,9a}$, Hz	Found, % C	H	N	Empirical formula	Calc., % C	H	N	Yield, %
VIa	CH_3	C_2H_5	NO_2	182—184	0,43	4,16	4,28	5,62	7,0	64,6	5,7	15,8	$C_{19}H_{20}N_4O_3$	64,8	5,7	15,9	87
VIb	C_2H_5	C_2H_5	NO_2	163—165	0,31	4,09	4,40	5,44	7,0	65,5	6,1	15,5	$C_{20}H_{22}N_4O_3$	65,6	6,1	15,3	80
VIc	CH_3	CH_3	NO_2	186	0,44	4,11	4,28	5,65	7,1	64,2	5,6	16,6	$C_{18}H_{18}N_4O_3$	63,9	5,4	16,6	83
VId	C_2H_5	CH_3	NO_2	192—193	0,49	4,10	4,40	5,52	7,0	64,8	5,9	16,0	$C_{19}H_{20}N_4O_3$	64,8	5,7	15,9	51
VIe	CH_3	C_2H_5	H	187	0,47	3,94	4,15	5,55	7,0	74,6	7,0	13,7	$C_{19}H_{21}N_4O$	74,2	6,9	13,7	86
VIf	C_2H_5	C_2H_5	H	159—161	0,35	3,90	4,26	5,42	6,8	74,9	7,4	12,9	$C_{20}H_{23}N_3O$	74,7	7,2	13,1	90
VII	CH_3	C_2H_5	H	164—166	0,37	3,85	4,27	6,93	8,2	72,2	6,7	11,9	$C_{21}H_{23}N_3O_2$	72,2	6,6	12,0	77

*On Silufol plates [elution with ethanol—chloroform (1:20)].

series of azinium cations one might have expected the formation of all types of cycloadducts, viz., ortho, meta, and para, which would make it possible to establish the general principles of such cyclizations.

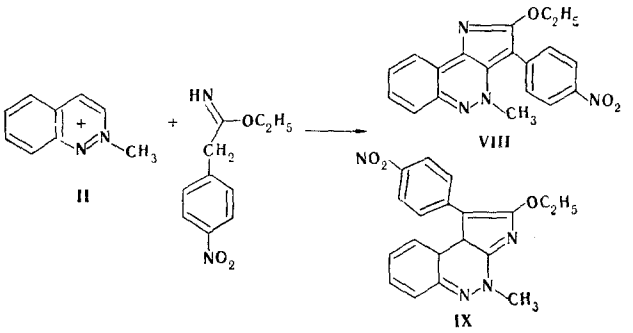


The experiments showed that each of the I-IV cations has its own peculiarities in its reaction with imido esters. Quaternary quinoxalinium salts I react with imido esters V in the cold to give 3a,4,9,9a-tetrahydro-cis-3H-pyrrolo[2,3-b]quinoxalines (VIa-f). A twofold excess of the imido ester is necessary for the reaction. (One molecule of the imido ester acts as a proton acceptor.)

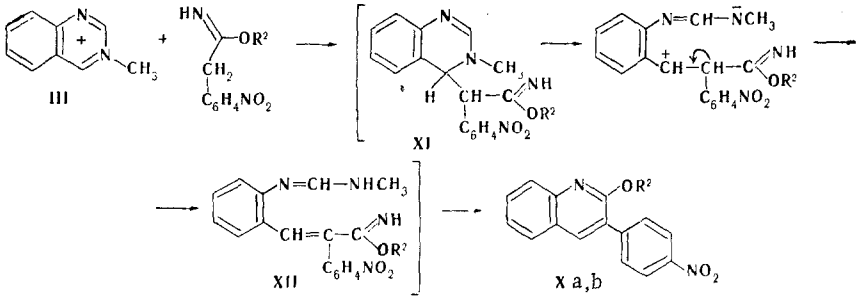
The individuality of VIa-f was confirmed by thin-layer chromatography (TLC) and spectral data (Table 1). The electronic spectra contain absorption bands at 260 and 300-310 nm that are characteristic for compounds with a tetrahydroquinoxaline structure [10]. The stretching vibrations of an imine bond show up distinctly in the IR spectra. The orientation of the pyrrole ring relative to the unsymmetrical pyrazine ring is determined by the chemical shifts and the multiplicity of the signals of the 3a-H and 9a-H protons in the PMR spectra. The weaker-field signal of the 9a-H proton, which is attached to a carbon atom between two heteroatoms, is split by the NH group. Acetylation of the imino group eliminates this effect and gives rise to a significant shift of the signal of the 9a-H proton to weak field (∿1.4 ppm), whereas the signal of the 3a-H proton is shifted only 0.12 ppm (compare VIe and VII in Table 1). The $^3J_{3a,9a}$ values indicate a cis orientation of the 3a-H and 9a-H protons [7].

The high yields of individual VIa-f make it possible to speak of pronounced regio- and stereoselectivity of the reaction, which is in good agreement with a scheme involving anionic [3⁻ +2]-cycloaddition [11] of the 4π system of the aza-allyl anion to the π bond of the pyrazinium cation.

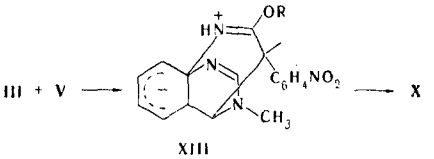
The reaction of cinnolinium cation II with ethyl p-nitrophenylacetimidate was carried out under the same conditions, i.e., in ethanol at 20°C. One of the alternative structures — VII or IX — can be assigned to the reaction product on the basis of the results of elementary analysis and the ^1H and ^{13}C NMR and mass spectra.



The result of the reaction of imido ester V with quinazolinium cation III was somewhat unexpected. The signal of the protons of the N-methyl group of the quinazoline was absent in the PMR spectra of the products of the reaction of cation III with alkyl p-phenylacetimidates V, and only the signals of nine aromatic protons and the OR group were present. The results of elementary analysis, as well as the mass spectrum of Xb, corresponded to the compositions $C_{16}H_{12}N_2O_3$ (for Xa) and $C_{17}H_{14}N_2O_3$ (for Xb). A definitive conclusion regarding the structure of Xa,b was drawn on the basis of the ^{13}C NMR spectra, which completely confirmed that these compounds were 2,3-substituted quinolines. The chemical shifts of the signals of the unsubstituted C_4 atom at δ 138.47 and 138.44 ppm for Xa,b, respectively, exclude the alternative isoquinoline structure. (The shift of the signal of the C_1 atom in the spectrum of isoquinoline is 153.1 ppm [12].) The transformation of the quinazolinium salts to quinoline derivatives X can be represented by a scheme that assumes the addition of the imido ester carbanion to the C_4 atom of cation III, opening of the heteroring at the N_3-C_4 bond of dihydro compound XI, and subsequent intramolecular cyclization of azomethine XII. This scheme is based on literature analogies. Thus the recyclization of pteridines to pyrido[2,3-b]pyrazines under the influence of CH-active compounds proceeds with opening of the pyrimidine ring at the N_3-C_4 bond to give intermediate XII [13].



Pyrimidine and quinazoline derivatives readily undergo recyclization under the influence of various nucleophiles [14, 15]. In particular, the transformation of quaternary pyrimidine salts to pyridine derivatives under the influence of carbanions, in which, just as in the case under consideration the C_2-N-CH_3 fragment is replaced by two carbon atoms, has been described [15]. Another cyclization pathway that includes meta-bonded adduct XIII, is also possible.



meta-Bonded adducts have already been considered as possible intermediates in the recyclizations of pyrimidines under the influence of bisnucleophilic reagents [17]. The possibility that cycloadducts XIII can also be intermediates in the transformation of salts III to quinolines X or exist in equilibrium with the starting substances is not excluded. The absence of experimental data as to which of the nitrogen atoms (the 1-N-quinazoline or imido ester nitrogen atom) is included in the quinoline ring makes it impossible to exclude this recyclization pathway and form a preference for one of the schemes.

The N-methylphthalazinium cation (IV) is inactive in the reaction with imido ester V not only at room temperature but also when the components are heated. Starting salt IV was

isolated in quantitative yield from the reaction mixture after refluxing in ethanol for 2 h. Further heating of the reaction mixture leads to hydrolysis of the imido ester.

Thus the character of the reaction of benzodiazinium cations with bisnuelcophiles depends on the relative orientation of the aza groups, and the presence of two ortho-oriented carbon atoms in diazinium cations is evidently the most favorable situation for the occurrence of the cyclization reaction.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The ^1H and ^{13}C NMR spectra of solutions in deuterochloroform and deuteroacetone were recorded with Perkin-Elmer R12B, Bruker HX-90 (^{13}C, 22.63 MHz), and Varian XL-200 (^{13}C, 50.3 MHz) spectrometers with hexamethyldisiloxane and tetramethylsilane as the internal standards. The mass spectra were recorded with a Varian MAT311-A spectrometer by electron impact with direct introduction of the samples into the ionization region.

The benzodiazine bases and their quaternary salts I-IV were synthesized by known methods: quinoxaline [18], cinnoline [19], quinazoline [20], and phthalazine [21]. The quaternization of quinazoline with methyl iodide gave a mixture of 1-N- and 3-N-methylquinazolinium iodides in a ratio of 1:5; the mixture was subjected to reaction with the imido esters without separation. The yields and structures of the reaction products constitute evidence that the 3-N-methylquinazolinium cation undergoes reaction with the imido ester. (The literature also contains information regarding the high activity of the 3-N-methylquinazolinium cation in reactions with nucleophilic reagents [22].) Imido esters V were obtained by the method in [23].

2-Ethoxy-4-methyl-3-(p-nitrophenyl)-3a,4,9,9a-tetrahydro-cis-3H-pyrrolo[2,3-b]quinoxaline (VIa). A 1.5-g (7.2 mmole) sample of ethyl α-(p-nitrophenyl)acetimidate V was added to a stirred suspension of 1 g (3.6 mmole) of N-methylquinoxalinium iodide in 5 ml of ethanol, and the precipitate that formed from the dark-red solution was removed by filtration and washed on the filter with ethanol to give 1.1 g (87%) of orange prisms with mp 182-184°C (from ethanol). IR spectrum: 3383 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 220 (4.54), 263 (4.15), and 303 nm (3.89). PMR spectrum [$(CD_3)_2CO$, TMS]: 1.08 (t, 3H, CH_3), 2.78 (s, 3H, N-CH_3), 4.15 (q, 2H, CH_2), 4.16 (d, 3-H), 4.28 (dd, 3a-H, $J_{3a-H,9a-H}$ = 4.5 Hz), 5.62 (dd, 9a-H, $J_{3a-H,9a-H}$ = 7.0 Hz), 5.79 (s, NH), 6.5-6.9 (M, 4H, aromatic), and 7.61 and 8.35 ppm (d, 4H, p-$C_6H_4NO_2$). ^{13}C NMR spectrum ($CDCl_3$, TMS): 13.60 (CH_3), 36.91 (N-CH_3), 53.97 (O-CH-CH_3), 64.25 (3a-CH), 72.68 (9a-CH); 111.90, 114.51, 119.27, 119.91 (4CH, aromatic); 124.0, 128.45 (4CH, p-$C_6H_4NO_2$); 133.94 (4a-C); 134.64 (4'C); 146.92 (8a-C and 1'-C); 170.65 (N-C-OC_2H_5). Found: C 64.6; H 5.7; N 15.8%. $C_{19}H_{20}N_4O_3$. Calculated: C 64.8; H 5.7; N 15.9%. Compounds VIb-f were similarly obtained (see Table 1).

2-Ethoxy-4-methyl-3-phenyl-9-acetyl-3a,4,9,9a-t-trahydro-cis-3H-pyrrolo[2,3-b]quinoxaline (VIIa). A suspension of 2 g (6.5 mmole) of VIe in 5 ml of acetic anhydride was heated cautiously to 70°C, after which it was cooled, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 1.75 g (77%) of a product with mp 164-166°C. IR spectrum: 1647 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 220 (4.39), 253 (4.06), and 295 nm (3.55). PMR spectrum ($CDCl_3$, TMS), δ: 1.0 (t, 3H, CH_3), 2.14 (s, 3H, $COCH_3$), 2.85 (s, 3H, N-CH_3), 3.85 (d, 3-H), 4.07 (q, 2H, O-CH_2), 4.27 (dd, 3a-H, $J_{3a-H,9a-H}$ = 3.1 Hz), 6.93 (d, 9a-H, $J_{3a-H,9a-H}$ = 8.2 Hz). 6.8-7.1 (m, 4H, aromatic), and 7.1-7.6 ppm (m, 5H, C_6H_5). Found: C 72.2; H 6.7; N 11.9%. $C_{21}H_{23}N_3O_2$. Calculated: C 72.2; H 6.6; N 12.0%.

Product of Cyclization of the 2-N-Methylcinnolinium Ion with Ethyl α-(p-Nitrophenyl)-acetimidate (VIII or IX). A 0.15-g (0.72 mmole) of ethyl α-(p-nitrophenyl)acetimidate V was added to a stirred suspension of 0.1 g (0.36 mmole) of 2-N-methylcinnolinium iodide in 1.5 ml of ethanol. After 10 min, a precipitate began to form from the resulting dark-green solution. Stirring was continued for another 5 h until the green coloration vanished. The bright-orange precipitate was removed by filtration and recrystallized from ethanol to give 6.06 g (68%) of a product with mp 206-208°C. UV spectrum, λ_{max} (log ε): 234 (3.07), 385 (2.79), and 472 nm (2.69). PMR spectrum ($CDCl_3$, TMS): 1.52 (t, 3H, CH_3), 4.72 (s, 3H, N-CH_3), 4.76 (q, 2H, O-CH_2), 7.37-8.2 (m, 4H, aromatic), and 7.96 and 8.41 nm (d, 4H, p-$C_6H_4NO_2$). ^{13}C NMR spectrum ($CDCl_3$, TMS): 4.8 (CH_3), 34.3 (N-CH_3), 55.4 (O-CH-CH_3); 112.6, 117.4, 117.8 (4CH, aromatic); 113.6 and 119.9 (4CH, p-$C_6H_4NO_2$); 91.0, 110.2, 116.3, 131.6, 132.0,

135.4, 136.9 (9a-, 11a-, 3-, 5a-, 4'-, 3a-, and 1'-carbon atoms); 159.0 ppm (2-C). Found: C 66.0; H 4.7; N 16.2%; M^+ 348. $C_{19}H_{16}N_4O_3$. Calculated: C 65.5; H 4.6; N 16.1%; M 348.

2-Methoxy-3-(p-nitrophenyl)quinoline (Xa). A 1-g (3.6 mmole) sample of N-methylquinazolinium iodide and 1.4 g (7.2 mmole) of methyl α-(p-nitrophenyl)acetimidate V were stirred in 5 ml of methanol for 15 min, after which the mixture was allowed to stand at 20°C. The Xa that precipitated from the orange solution after 2.5 h was removed by filtration and recrystallized from ethanol to give 0.19 g (22%) of colorless needles with mp 139-141°C. UV spectrum, λ_{max} (log ε): 207 (4.69), 265 (4.14), and 315 nm (4.28). PMR spectrum ($CDCl_3$, TMS): 4.17 (s, 3H, $O-CH_3$), 7.5-8.1 (m, 4H, aromatic), 8.0 (s, 4-H), and 8.12 and 8.44 ppm (d, 4H, $p-C_6H_4NO_2$). ^{13}C NMR spectrum ($CDCl_3$, TMS), δ: 53.62 (OCH_3); 123.19, 130.04 (4CH, $p-C_6H_4NO_2$); 123.76 (3-C); 124.52, 126.92, 127.55, 130.04 (4-CH, aromatic); 124.98 (4a-C); 138.47 (4-CH); 143.32 (4'C); 146.29 (8a-C); 147.06 (1'-C); 159.01 ppm (2-C). Found: C 68.2; H 4.4; N 10.2%. $C_{16}H_{12}N_2O_3$. Calculated: C 68.5; H 4.3; N 10.0%.

2-Ethoxy-3-(p-nitrophenyl)quinoline (Xb). This compound, with mp 135-136°C, was similarly obtained in 24% yield. UV spectrum, λ_{max} (log ε): 205 (4.65), 265 (4.13), and 315 nm (4.22). PMR spectrum ($CDCl_3$, TMS): 1.45 (t, 3H, CH_3), 4.64 (q, 2H, $O-CH_2$), 7.3-8.1 (m, 4H, aromatic), 7.92 (s, 4-H), and 8.0 and 8.36 ppm (d, 4H, $p-C_6H_4NO_2$). ^{13}C NMR spectrum ($CDCl_3$, TMS): 14.24 (CH_3); 62.08 ($O-CH_2-CH_3$); 123.3, 130.04 (4CH, $p-C_6H_4NO_2$); 123.92 (3-C); 124.34, 126.89, 127.52, 130.04 (4CH, aromatic); 124.89 (4a-C); 138.44 (4-CH); 143.47 (4'-C); 146.39 (8a-C); 147.0 (1'-C); 158.44 ppm (2-C). Found: C 69.3; H 9.7; N 9.7%; M^+ 294. $C_{17}H_{14}N_2O_3$. Calculated: C 69.4; H 4.8; N 9.5%. M 294.

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