CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BISNUCLEOPHILES.

7.* REACTIONS OF QUINOXALINIUM SALTS WITH α-SUBSTITUTED ACETAMIDES

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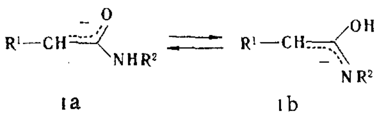
Acetamides that contain acceptor substituents in the α position react with quinoxalinium salts to give cis-hexahydropyrrolo[2,3-b]quinoxalin-2-ones. Acetic acid arylamides are inert under these conditions.

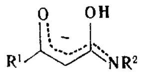
The reactions of 1,3-ambident nucleophiles with o-bifunctional azines are among the direct methods for the annelation of five-membered heterorings to azines. Classical representatives of ambident nucleophiles are enolate anions, in the reactions of which with azaheterocycles annelation of the furan ring is possible. Thus the reactions of halo- and nitro-substituted pyridines [2, 3] and pyrazines [4], as well as unsubstituted pteridine [5], with derivatives of β-dicarbonyl compounds leads to the formation of a furan ring. Furo[2,3-b]quinoxaline derivatives are also formed in the reactions of enolates of β-diketones or esters of β-keto acids with quinoxalinium salts and their aza and benzo analogs [6-8].

In the present research we investigated the reactions of quinoxalinium salts with amides of β-keto acids and p-nitrophenylacetamide in the presence of bases.

The anions of α-substituted acetamides can be represented in prototropically tautomeric forms of enolate anion Ia and 1-azaallylic anion Ib and, consequently, may display the properties of both C,O- and C,N-ambident nucleophiles. It is known that α-substituted acetamides, viz., malondiamide and cyano-, acetyl-, and phenylacetamides are capable of acting as C,N-ambident nucleophiles that cause transformation of pyrimidines to pyridine derivatives [9, 10]. A more complex situation arises in the case of mesomeric anions (II) of β-keto acid amides, which can exist in various tautomeric forms and configurations [11].



Ia Ib



II

TABLE 1. Characteristics of the Synthesized Va-j

Compound	mp,* °C	R_f	Found, %			Empirical formula	Calc., %			Yield,† %
			C	H	N		C	H	N	
Va	151—152	0,66	68,5	6,2	11,8	$C_{20}H_{21}N_3O_3$	68,4	6,0	12,0	88
Vb	145	0,62	69,1	6,4	11,5	$C_{21}H_{23}N_3O_3$	69,0	6,3	11,5	69
Vc	102	0,64	—	—	12,6	$C_{20}H_{21}N_3O_2$	71,6	6,3	12,5	78
Vd	123—125	0,44	71,3	6,3	12,6	$C_{20}H_{21}N_3O_2$	71,6	6,3	12,5	34
Ve	142—144	0,33	64,4	5,2	12,0	$C_{19}H_{18}ClN_3O_2$	64,1	5,1	11,8	90
Vf	139—141	0,47	65,3	5,5	11,2	$C_{20}H_{20}ClN_3O_2$	65,0	5,5	11,4	86
Vg	160—162	0,31	70,7	5,9	12,9	$C_{19}H_{19}N_3O_2$	71,0	6,0	13,1	94
Vh	149—151	0,39	71,3	6,2	13,1	$C_{20}H_{21}N_3O_2$	71,6	6,3	12,5	79
Vi	152	—	68,7	4,8	10,3	$C_{24}H_{20}ClN_3O_2$	69,0	4,8	10,1	86
Vj	184	—	69,5	5,2	9,7	$C_{25}H_{22}ClN_3O_2$	69,5	5,1	9,7	95

*All of the substances were recrystallized from ethanol.

†By method A (see the experimental section).

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*See [1] for communication 6.

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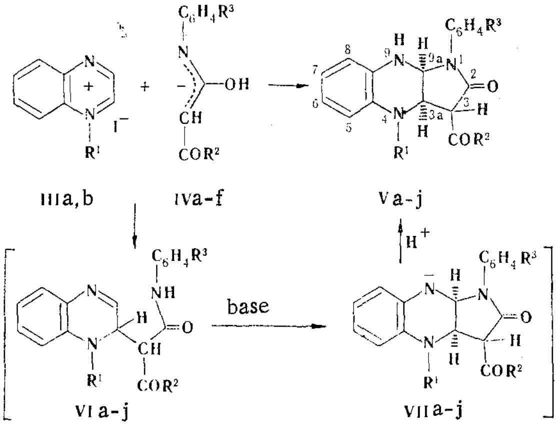
TABLE 2. IR, UV, and PMR Spectra of Hexahydropyrrolo[2,3-b]quinoxalin-2-ones V

Compound	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	PMR spectrum			
				δ, ppm			$J_{3a,9a}$, Hz
	ν_{CO}	ν_{NH}		3-H	3a-H	9a-H	
Va	1678, 1720	3337	220 (4,55); 258 (3,75); 303 (3,53)	3,75	5,02	5,67	8,4
Vb	1694, 1725	3370	221 (4,43); 263 (3,72); 304 (3,47)	3,76	5,08	5,59	8,2
Vc	1682, 1720	3336	220 (4,46); 255 (3,69); 304 (3,50)	3,80	5,04	5,58	9,4
Vd	1696, 1703	3392	221 (4,55); 304 (3,63)	3,74	4,94	5,66	8,2
Ve	1698, 1720	3398	221 (4,52); 304 (3,65)	3,76	4,86	5,62	7,9
Vf	1698, 1720	3395	222 (4,51); 306 (3,63)	3,78	4,93	5,54	7,8
Vg	1698, 1720	3396	222 (4,51); 304 (3,63)	3,80	4,92	5,70	8,0
Vh	1698, 1716	3392	223 (4,49); 306 (3,59)	3,78	4,95	5,52	7,8
Vi	1662, 1712	3365	222 (4,48); 251 (4,36); 299 (3,60)	4,70	5,09	5,78	8,2
Vj	1667, 1715	3372	223 (4,48); 251 (4,38); 306 (3,56)	4,76	5,15	5,73	8,2

However, we have established that the reactions of quinoxalinium salts with anilides (IV) of benzoyl- and acetoxyacetic acids proceed selectively at the C,N centers of the mesomeric anion and lead exclusively to the formation of pyrroloannelated quinoxalines Va-j (Table 1).

The reaction proceeds in ethanol at room temperature in the presence of excess diethylamine. It also takes place with sodium salts of β-keto acid amides; however, this method is preparatively less convenient, since the yields of V in this case are almost halved.



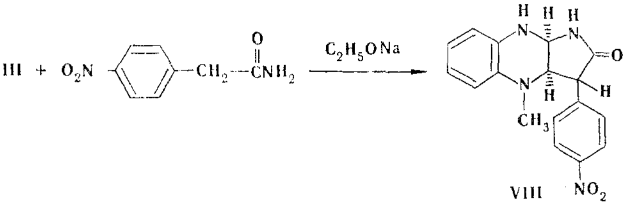
III a $R^1=CH_3$, b $R^1=C_2H_5$; IVa—e $R^2=CH_3$, a $R^3=o\text{-}OCH_3$, b $R^3=o\text{-}CH_3$, c $R^3=p\text{-}CH_3$, d $R^3=p\text{-}Cl$, e $R^3=H$, f $R^2=C_6H_5$, $R^3=p\text{-}Cl$; V, VI, VII a,c,d,e,g,i $R^1=CH_3$, b,f,h,j $R^1=C_2H_5$, a-h $R^2=CH_3$, i,j $R^2=C_6H_5$, a,b $R^3=o\text{-}OCH_3$, c $R^3=o\text{-}CH_3$, d $R^3=p\text{-}CH_3$, e,f,i,j $R^3=p\text{-}Cl$, g, h $R^3=H$

The individuality of the reaction products was confirmed by thin-layer chromatography (TLC) and spectral (IR, UV, and PMR) data (Table 2).

Stretching vibrations of an NH group and two CO groups appear in the IR spectra of cycloadducts Va-j. The absorption at 1670-1690 cm^{-1} should be assigned to the vibrations of a ring carbonyl group, while the absorption at 1710-1725 cm^{-1} should be assigned to a carbonyl group in a side chain. The characteristics of the IR spectra of V are in good agreement with the literature data from spectroscopy of hydrogenated pyrrolo[2,3-b]quinoxalines [12, 13]. The UV spectra of V are typical for tetrahydroquinoxalines [14].

Analysis of the PMR spectra of V makes it possible to establish the mutual orientation of the pyrrole and tetrahydropyrazine fragments in hexahydropyrrolo[2,3-b]quinoxalin-2-ones V. The protons of the nodal carbon atoms (3a-H and 9a-H) absorb at ~5 ppm (doublet of doublets) and 5.7 ppm, respectively (Table 2). The signal of the weaker-field 9a-H proton is a poorly resolved doublet of doublets, which is converted to a doublet upon deuteration of the proton of the NH group. These data exclude the alternative orientation of the pyrrole ring relative to the unsymmetrical tetrahydropyrazine derivative. The $J_{3a,9a}$ constants for coupling between the vicinally oriented 3a-H and 9a-H protons amount to 7.7-9.4 Hz and may correspond, according to the Karplus relationship [15], to dihedral angles 0-25° or 120-180°. According to Williamson and Johnson [16], small constants correspond to angles close to 0°, and the $H{-}C_{3a}{-}C_{9a}{-}H$ dihedral angle is consequently ∿0-25°, which corresponds to a cisoid orientation of the 3a-H and 9a-H protons. Close values of the $J_{3a,9a}$ constants were also observed for furo[2,3-b]quinoxalines, in which the cis orientation or the 3a-H and 9a-H protons was confirmed by x-ray diffraction analysis [7]. Thus the cyclization of salts III with amides IV proceeds not only regioselectively but also stereoselectively to give cis cycloadducts V.

p-Nitrophenylacetamide also successfully undergoes cyclization with the cation of III in the presence of sodium ethoxide, although it is inactive in the presence of diethylamine.



VIII

The PMR spectrum of the reaction product, viz., 4-methyl-3-(p-nitrophenyl)-2,3,3a,4,-9,9a-hexahydro-1H-pyrrolo[2,3-b]quinoxalin-2-one (VIII), is similar to the spectra of cycloadducts V. Evidence in favor of the presented regioorientation of the pyrrole ring relative to the tetrahydropyrazine ring is provided by the fact that exchange of the proton attached to the $N_{(9)}$ atom by deuterium when deuteromethanol is added eliminates splitting of the weaker-field signal of the 9a-H proton located at the carbon atom between the two heteroatoms; the amide $N_{(1)}{-}H$ proton does not undergo exchange under these conditions. Yet another argument in favor of the given orientation is the strong-field (as compared with cycloadducts V) shift of the signal of the $N{-}CH_3$ group, which lies in the zone of shielding of the ring anisotropic current of the phenyl ring in the 3 position.

The presence of acceptor groupings in the α position of acetamides is a necessary condition for cyclization. Acetic acid anilides do not react with salts III.

Thus acid amides that contain an active α-methylene group undergo cyclization with the quinoxalinium cation, thus displaying the properties of C,N-ambident nucleophiles. We have already discussed the possible mechanisms of such cyclizations, viz., a concerted mechanism of the $[3^- + 2]$-anionic cycloaddition type with redistribution of the 6π electrons in the cyclic transition state [7, 17], and a stepwise mechanism with successive addition of the anionic ends of the bisnucleophile at the $C_{(2)}$ and $C_{(3)}$ positions of the quinoxalinium salt [6, 7].

Anions IV can be regarded as analogs of 1-azaallylic anionic systems, the participation of which in 1,3-anionic cycloaddition to quinoxalinium salts was discussed in [17]. The cyclization of salts III with amides IV proceeds regiospecifically and, in conformity with the cis principle, makes it possible to regard this reaction as proceeding via 1,3-anionic cycloaddition.

However, the possibility that cis adducts V are formed in a stepwise reaction under the condition that the VI → VII cyclization takes place more rapidly than rotation about the C—C bond in adduct VI or because the stereoisomers of cycloadducts V with a trans orientation of the 3a-H and 9a-H hydrogen atoms simply do not exist because of the extremely high ring strain is not excluded.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform or suspensions in mineral oil were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in deuterochloroform and d_6-DMSO were recorded with a Perkin-Elmer R 12 B spectrometer (60 MHz) with tetramethylsilane and hexamethyldisiloxane as the internal standards. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates; the substances were eluted with ethanol—chloroform (1:20) and were detected by development in iodine vapors.

The quinoxaline base was obtained by the method in [18], and quaternary quinoxalinium salts III were obtained by the method in [1]. The β-keto acid anilides were synthesized from the β-keto acid ethyl esters and aromatic amines by the method in [19]. The sodium salts of the β-keto acid anilides were obtained by reaction of the anilides with sodium ethoxide in absolute ethanol.

4-Methyl-1-(o-methoxyphenyl)-3-acetyl-cis-2,3,3a,4,9,9a-hexahydropyrrolo[2,3-b]quinoxalin-2-one (Va). A) A 0.746-g (3.6 mmole) sample of acetoacetic acid o-anisidide and 1 ml of diethylamine were added with stirring to a suspension of 1 g (3.6 mmole) of N-methylquinoxalinium iodide in 5 ml of ethanol, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 1.12 g (88%) of colorless crystals with mp 151-152°C. IR spectrum: 1678, 1720 (CO); 3337 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 220 (4.55), 258 (3.75), and 303 nm (3.53). PMR spectrum ($CDCl_3$, TMS): 2.48 (s, 3H, $COCH_3$), 2.85 (s, 3H, NCH_3), 3.75 (d, 3-H, $^3J_{3,3a}$ = 5.2 Hz), 3.87 (s, 3H, OCH_3), 4.35 (NH), 5.02 (d, 3a-H, $^3J_{3a,9a}$ = 8.4 Hz), 5.67 (broad d, 9a-H), and 6.6-7.0 ppm (m, 8H, aromatic). Found: C 68.5; H 6.2; N 11.8%. $C_{20}H_{21}N_3O_3$. Calculated: C 68.4; H 6.0; N 12.0%.

B) A 0.412-g (1.5 mmole) sample of N-methylquinoxalinium iodide was added to a solution of 0.36 g (1.5 mmole) of the sodium salt of acetoacetic acid o-anisidide in 2 ml of absolute ethanol, and the mixture was allowed to stand for 24 h for crystallization. The resulting precipitate was removed by filtration and recrystallized from ethanol to give 0.22 g (42%) of a product with mp 151-152°C. The PMR spectra of the samples of Va obtained by methods A and B coincided completely.

The other 1-aryl-cis-2,3,3a,4,9,9a-hexahydropyrrolo[2,3-b]quinoxalin-2-ones Vb-j were similarly obtained by method A; data on them are presented in Tables 1 and 2.

4-Methyl-3-(p-nitrophenyl)-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[2,3-b]quinoxalin-2-one (VIII). A 0.08-g (3.6 mmole) sample of sodium was dissolved in 15 ml of absolute ethanol, 0.476 g (3.6 mmole) of p-nitrophenylacetamide and 1 g (3.6 mmole) of N-methylquinoxalinium iodide were added, the resulting solution was poured with stirring into 150 ml of water, and the mixture was allowed to stand for 15 h for crystallization. The precipitate was removed by filtration, recrystallized from ethanol, and dried *in vacuo* at 100°C for 5 h to give 0.82 g (66%) of orange needles with mp 198-199°C. IR spectrum: 1503, 1515, 1598, 1605, 1698, 1704, 3105, 3130, 3165, and 3328 cm^{-1}. UV spectrum, λ_{max} (log ε): 222 (4.57), 265 (4.10), and 303 nm (3.89). PMR spectrum (d_6-DMSO, hexamethyldisiloxane): 2.60 (s, 3H, NCH_3), 3.75 (d, 3-H, $^3J_{3,3a}$ = 7.2 Hz), 4.48 (dd, 3a-H, $^3J_{3a,9a}$ = 7.8 Hz), 5.20 (broad d, 9a-H), 6.22 $[N_{(9)}–H]$, 6.6-7.1 (m, 4H, aromatic), 7.96 and 8.64 (d, 4H, p-C_6H_4–NO_2), 9.10 ppm $[N_{(1)}–H]$. Found: C 63.1; H 5.0; N 17.7%. $C_{17}H_{16}N_4O_3$. Calculated: C 63.0; H 5.0; N 17.3%.

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SYNTHESIS OF 2-ARYLOXY-4,6-BIS(4-CARBOXYPHENYL)-sym-TRIAZINES AND THEIR CHLORIDES

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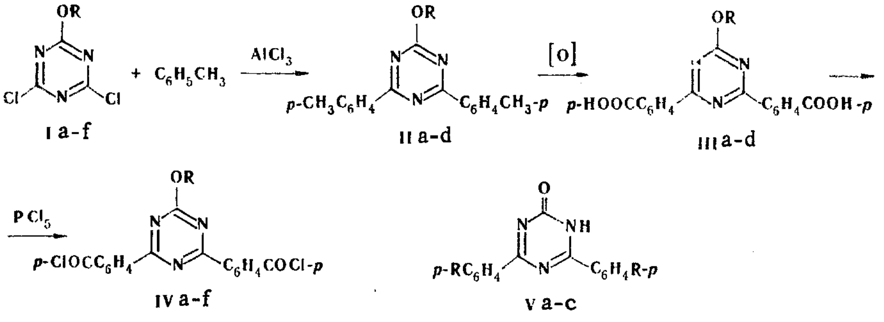
The peculiarities of the reaction of some substituted (in the benzene ring) 2,4-dichloro-6-aryloxy-sym-triazines with toluene under the conditions of the Friedel–Crafts reaction were investigated. Methods for the synthesis of 2-arloxy-4,6-bis(4-carboxyphenyl)-sym-triazines and their chlorides were developed. Cleavage of the ether bond to give a dihydro-sym-triazine structure occurs in the case of 2,4-dichloro-6-benzyloxy-sym-triazine.

We have previously [1] synthesized 2-phenoxy-4,6-bis(4-carboxyphenyl)-sym-triazine and have demonstrated the promising character of its use in the synthesis of heat-resistant polymers. A number of intermediates in the synthesis of such triazine-containing acids were described, and the peculiarities of the reaction of cyanuric acid chloride and its monosubstituted derivatives with toluene under the conditions of the Friedel–Crafts reaction were investigated [2]; it was shown that 2-phenoxy-4,6-bis(4-methylphenyl)-sym-triazine is formed in high yield.

In the present research we investigated the peculiarities of the reaction of toluene with aryloxy-substituted derivatives of dichloro-sym-triazine by the Friedel–Crafts reaction as a function of the structure of the substituent in the benzene ring, as well as the possibilities of the synthesis of sym-triazine-containing carboxylic acids and their chlorides on the basis of the compounds obtained:



I a $R=2\text{-}CH_3C_6H_4$, b $R=3\text{-}CH_3C_6H_4$, c $R=3\text{-}ClC_6H_4$, d $R=4\text{-}BrC_6H_4$, e $R=4\text{-}NO_2C_6H_4$, f $R=CH_2C_6H_5$, II a $R=2\text{-}CH_3C_6H_4$, b $R=3\text{-}CH_3C_6H_4$, c $R=3\text{-}ClC_6H_4$, d $R=4\text{-}BrC_6H_4$; III a $R=2\text{-}HOOCC_6H_4$, b $R=3\text{-}HOOCC_6H_4$, c $R=3\text{-}ClC_6H_4$, d $R=BrC_6H_4$; IV a $R=2\text{-}ClOCC_6H_4$, b $R=3\text{-}ClOCC_6H_4$, c $R=3\text{-}ClC_6H_4$, d $R=4\text{-}BrC_6H_4$; V a $R=CH_3$; b $R=COOH$, c $R=COCl$

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