CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BISNUCLEOPHILES.

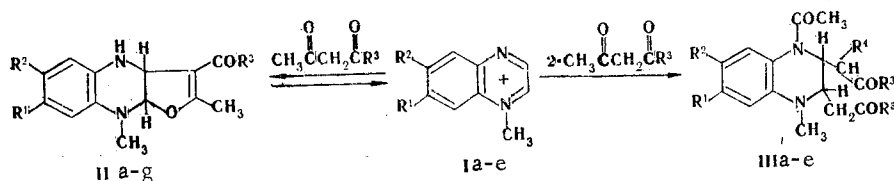## 6.* CYCLOELIMINATION OF TETRAHYDRO-endo-FURO[2,3-b]QUINOXALINES
LEADING TO 2,3-DISUBSTITUTED TETRAHYDROQUINOXALINES

M. G. Ponizovskii, O. N. Chupakhin,   UDC 547.863.13.16'722.3.07:543.422.539.26
V. N. Charushin, and G. G. Aleksandrov

The reaction of an N-methylquinoxalinium salt with a β-diketone under thermodynam-
ic-control conditions leads to 2,3-disubstituted tetrahydroquinoxaline via cyclo-
elimination of the initially formed tetrahydro-endo-furo[2,3-b]quinoxaline.

The initial products in anionic cycloaddition are usually endo adducts, which then may
undergo rearrangement to the more stable exo isomers [2]. This phenomenon has also been not-
ed in the reactions of the quinoxalinium anion (I) with azoallyl analogs [3]. Similar cyclo-
addition of oxoallyl anions to cations Ia-e leads to 3a,4,9,9a-tetrahydro-endo-furo[2,3-b]-
quinoxalines IIa-g [4]. In the present research we proposed to investigate the possibility
of isomerization of these endo adducts II to the exo isomers.

I a $R^1=R^2=H$, b $R^1=Cl$, $R^2=H$, c $R^1=H$, $R^2=Cl$, d $R^1=Br$, $R^2=H$, e $R^1=H$, $R^2=Br$;
II a $R^1=R^2=H$, $R^3=CH_3$, b $R^1=Cl$, $R^2=H$, $R^3=CH_3$, c $R^1=H$, $R^2=Cl$, $R^3=CH_3$, d $R^1=Br$,
$R^2=H$, $R^3=CH_3$, e $R^1=H$, $R^2=Br$, $R^3=CH_3$, f $R^1=R^2=H$, $R^3=OC_2H_5$, g $R^1=R^2=H$,
$R^3=C_6H_5$; III a $R^1=R^2=H$, $R^3=CH_3$, $R^4=COCH_3$, b $R^1=Cl$, $R^2=H$, $R^3=CH_3$, $R^4=COCH_3$,
c $R^1=Br$, $R^2=H$, $R^3=CH_3$, $R^4=COCH_3$, d $R^1=R^2=H$, $R^3=C_6H_5$, $R^4=H$, e $R^1=R^2=H$,
$R^3=CH_3$, $R^4=OC_2H_5$

The reaction of N-methylquinoxalinium iodide (Ia) with 2 mole of acetylacetone in the
presence of 2 moles of diethylamine at increased temperatures unexpectedly led to the forma-
tion of IIIa, the elementary composition and molecular mass (M^+ 334) of which correspond to
the formula $C_{19}H_{24}N_2O_4$. An analysis of the PMR spectrum of the compound obtained, in which
the four acetyl groups and one N-methyl group are clearly distinguishable, indicates unam-
biguously that two molecules of acetylacetone add to the quinoxalininium cation to give the
tetrahydroquinoxaline structure. The 2a-H proton shows up in the PMR spectrum as a doublet
of triplets and, in addition to coupling with the protons of the methylene group ($^3J_{2a,CH_2}$ =
6.5 Hz) has a constant of spin—spin coupling (SSC) with the 3a-H proton of the pyrazine ring
($^3J_{2a,3a}$ = 2.0 Hz). The proton of the CH group of the β-diketone residue gives a doublet with
$^3J_{CH,3a}$ = 10.5 Hz. The suppression of the signal of the 3a-H proton in the spectrum of IIIa
leads to conversion of the multiplet signal of the 2a-H proton at 3.87 ppm to a triplet and
conversion of the doublet signal of the methylidyne group at 3.65 ppm to a singlet. One should,
however, take into account the fact that the PMR spectra of IIIa are very sensitive to temper-
ature changes as a result of the flexible structure of the molecule, and $^3J_{2a,3a}$, $^3J_{2a,CH_2}$,
and $^3J_{3a,CH}$ thus reflect the average value of the constant of SSC between the corresponding
protons. Individual IIIb and IIIc were isolated when mixtures of 6- and 7-halo substituted
quinoxaline cations Ib,c and Id,e were subjected to the reaction. The similarity between the
spectra of these substances and the spectra of unsubstituted IIIa, particularly the closeness
of the SSCC, indicates their similar structures. However, a different orientation of the ali-

---

phatic residues relative to the pyrazine ring, as well as a different position of the halogen, can also be proposed.

To clarify this we carried out the x-ray diffraction analysis of IIIb. The structure was decoded by the direct method of least squares within the fully matrix anisotropic (Cl)—isotropic approximation up to R = 0.12. Refinement of the coordinates of all of the atoms of the structure within the anisotropic approximation did not give good results, since anomalously large B_{ij} values (temperature factors) were found for the terminal atoms of the acetyl groups; this is due to the existence of the compounds in the form of several conformers that differ with respect to rotation of the acetyl groups. This gives rise to divergence in the determination of the bond lengths (0.02-0.05 Å) and the bond angles (2-3 deg). The final coordinates of the atoms and their temperature factors are presented in Table 3.

The structure of the IIIb molecule is shown in Fig. 2 (see Tables 1 and 2, respectively, for the bond lengths and bond angles). In the tetrahydroquinoxaline ring the N(1), C(1), C(2), and N(2) atoms deviate from the plane of the benzene ring by 0.18, 0.27, 0.73 and 0.02 Å, respectively; this is in agreement with a distorted twisted boat conformation. A substantial difference is observed in the configurations of the nitrogen atoms: At the N(1) atom the sum of the bond angles is 360°C, as compared with 355° at the N(2) atom. The disruption of the trigonal-planar configuration of the N(2) atom is due to the greater steric overloading of the N(2)—C(2) fragment than in the case of the N(1)—C(1) fragment. The bulky substituents at the C(1) and C(2) atoms are evidently responsible not only for the transoid configuration of the molecule about the C(1)—C(2) bond [the C(4)C(1)C(2)C(7) torsion angle is 169.1°] but also for the overall form of the tetrahydroquinoxaline ring, for which one must expect [5]

TABLE 1. Bond Lengths (d, Å) for IIIb (numbering of atoms given in Fig. 2)

Bond	d	Bond	d
Cl—C(17)	1,78 (2)	C(4)—C(5)	1,52
O(1)—C(5)	1,21	C(5)—C(6)	1,57
O(2)—C(8)	1,19	C(7)—C(8)	1,57
O(3)—C(10)	1,22	C(7)—C(10)	1,55
O(4)—C(12)	1,20	C(8)—C(9)	1,53
N(1)—C(1)	1,45	C(10)—C(11)	1,46
N(1)—C(3)	1,51	C(12)—C(13)	1,35
N(1)—C(15)	1,33	C(14)—C(15)	1,41
N(2)—C(2)	1,44	C(14)—C(19)	1,37
N(2)—C(12)	1,50	C(15)—C(16)	1,39
N(2)—C(14)	1,45	C(16)—C(17)	1,38
C(1)—C(2)	1,50	C(17)—C(18)	1,35
C(1)—C(4)	1,62	C(18)—C(19)	1,44
C(2)—C(7)	1,68		

TABLE 2. Bond Angles (ω, deg) for IIIb

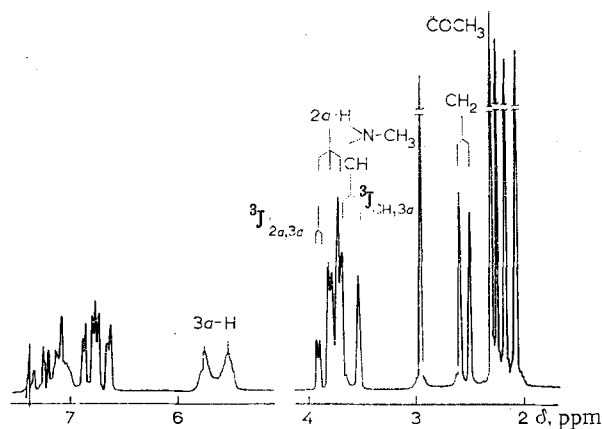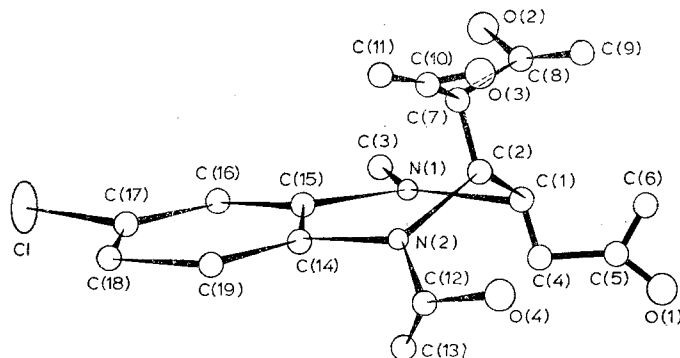| Angle	ω	Angle	ω
N(1)C(1)C(2)	115	N(2)C(12)O(4)	118
N(1)C(1)C(4)	112	O(4)C(12)C(13)	120
C(2)C(1)C(4)	106	N(2)C(14)C(15)	119
C(1)C(2)N(1)	112	N(2)C(14)C(19)	118
N(2)C(2)C(7)	109	C(15)C(14)C(19)	123
C(1)C(2)C(7)	117	N(1)C(15)C(14)	120
C(1)C(4)C(5)	115	N(1)C(15)C(16)	122
C(4)C(5)C(6)	117	C(14)C(15)C(16)	118
C(1)C(5)C(4)	118	C(15)C(16)C(17)	119
O(1)C(5)C(6)	124	ClC(17)C(16)	117
C(2)C(7)C(6)	105	C(16)C(17)C(18)	125
C(2)C(7)C(10)	98	ClC(17)C(18)	118
C(8)C(7)C(10)	123	C(17)C(18)C(19)	117
C(7)C(8)C(9)	132	C(14)C(19)C(18)	118
O(2)C(8)C(7)	110	C(1)N(1)C(3)	116
C(2)C(8)C(10)	117	C(1)N(1)C(15)	123
O(3)C(10)C(7)	114	C(3)N(1)C(15)	121
C(7)C(10)C(11)	117	C(2)N(2)C(14)	114
C(3)C(10)C(11)	123	C(2)N(2)C(12)	117
N(2)C(12)C(13)	122	C(12)N(2)C(14)	124

Fig. 1. PMR spectrum of compound IIIa in deuterochloroform.

Fig. 2. Structure of the compound IIIb molecule.

TABLE 3. Coordinates of the Atoms ($\times 10^3$; $\cdot 10^4$ for Cl) and Their Temperature Factors

Atom	x	y	z	$B_{iso} \times 10$
Cl	1091 (3)	679 (6)	250 (0)	*
O(1)	503 (1)	769 (3)	330 (3)	92 (8)
O(2)	423 (1)	555 (3)	18 (3)	85 (7)
O(3)	298 (1)	931 (2)	113 (2)	77 (7)
O(4)	300 (1)	910 (2)	384 (2)	53 (7)
N(1)	351 (1)	391 (2)	267 (2)	31 (5)
N(2)	274 (1)	678 (2)	294 (2)	53 (7)
C(1)	393 (1)	539 (2)	275 (2)	32 (8)
C(2)	347 (1)	681 (2)	246 (2)	30 (6)
C(3)	395 (1)	242 (2)	250 (3)	40 (6)
C(4)	422 (2)	571 (3)	391 (3)	53 (9)
C(5)	470 (1)	718 (3)	405 (3)	54 (9)
C(6)	485 (2)	778 (5)	517 (4)	96 (5)
C(7)	332 (1)	663 (3)	119 (2)	40 (6)
C(8)	413 (2)	670 (4)	69 (3)	93 (9)
C(9)	470 (2)	805 (4)	62 (4)	69 (9)
C(10)	272 (2)	797 (3)	106 (2)	39 (7)
C(11)	206 (2)	759 (4)	45 (3)	74 (9)
C(12)	262 (4)	791 (3)	382 (3)	76 (9)
C(13)	210 (1)	765 (3)	455 (2)	34 (6)
C(14)	234 (1)	530 (2)	281 (2)	41 (6)
C(15)	276 (1)	387 (2)	272 (2)	26 (6)
C(16)	236 (1)	246 (2)	261 (2)	24 (5)
C(17)	158 (1)	252 (2)	252 (2)	36 (8)
C(18)	117 (1)	388 (2)	256 (3)	52 (8)
C(19)	157 (1)	534 (2)	275 (2)	43 (9)

*Anisotropic temperature factor of the Cl atom in the form $T = \exp[-\frac{1}{4}(B_{11}h^2a*^2 + B_{22}k^2b*^2 + B_{33}l^2c*^2 + 2B_{12}hka*b* + 2B_{13}hlb*c* + 2B_{23}klb*c*)]$; $B_{11} = 3.6$ (2); $B_{22} = 4.0$ (2); $B_{33} = 9.0$ (4); $B_{12} = 1.8$ (2); $B_{13} = -0.2$ (2); $B_{23} = 0.3$ (3).

half-chair conformations with the C(1) and C(2) atoms located on different sides of the N(1)C(15)C(14)N(2) plane but at the same distance from it. The principal geometrical parameters of the molecule are in agreement with the standard values [6].

The reaction of benzoylacetone with cation Ia differs in certain respects from the reactions examined above: Detachment of the acetyl residues from both of the β-diketone molecules that undergo the reaction occurs in the formation of IIId, as compared with the detachment of one of the β-diketone molecules as in the formation of IIIa-c.

The problem as to whether the formation of II and III takes place via parallel or consecutive processes was solved by PMR spectroscopy. According to the data from the PMR spectra,
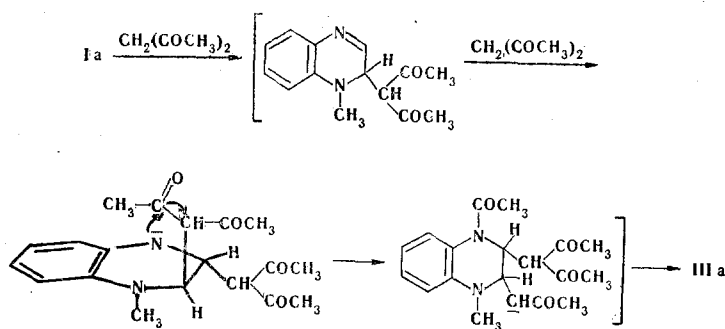
TABLE 4. Characteristics of Compound III

Compound	mp, °C	PMR spectrum chemical shift, ppm			SSCC, Hz $J_{2a,3a}$	UV spectrum λ_{max}, nm (log ε)	IR spectrum, cm⁻¹	Mass spectrum, m/z (I ≥ 40%)	¹³C NMR spectrum, ppm	Found, %			Empirical formula	Calc., %		
		NCH₃	2a-H	3a-H						C	H	N		C	H	N
IIIa	121—122	s 2,96	m 3,87	m 5,67	2,0	228 (4,4), 260 (4,1), 318 (3,8)	1647, 1700, 1713, 1723	44 (46,4), 85 (40,9), 131 (47,1), 133 (71,2), 145 (74,1), 146 (59,5), 147 (40,9), 158 (52,9), 160 (43,1), 188 (48,9), 201 (99,6), 202 (85,0), 203 (71,5), 204 (47,4), 243 (50,4), 244 (93,1), 246 (59,9), 287 (50,5), 344 (100,0), 345 (86,1), 346 (69,0)	22,4, 28,3, 29,5, 30,4 (four CH₃ grp.), 37,4 (N—CH₃), 47,3 (2-C), 45,3 (CH₂), 56,6 (3-C), 68,9 (CH), 110,7, 115,6, 120,1, 124,9, 126,6, 136,7 (6 arom. C), 169,2, 200,3, 200,8, 205,4 (C=O)	66,2	7,1	8,1	C₁₉H₂₄N₂O₄	66,3	7,0	8,1
IIIb	176—177	s 2,96	m 3,81	m 5,64	1,5	233 (4,4), 267 (4,0), 322 (3,8)	1660, 1712	—	—	60,2	6,2	7,4	C₁₉H₂₃ClN₂O₄	60,2	6,1	7,4
IIIc	196—197	s 2,97	m 3,80	m 5,66	1,8	236 (4,4), 267 (4,0), 327 (3,8)	1662, 1712	—	—	54,2	5,6	6,5	C₁₉H₂₃BrN₂O₄	53,9	5,5	6,6
IIId	157—158	s 2,97	m 4,19	m 5,40	1,8	238 (4,5), 316 (3,5)	1604, 1664, 1683	57 (67,2), 71 (40,8), 77 (63,6), 105 (100,0), 145 (53,9), 159 (82,4), 263 (96,1), 264 (71,4), 306 (43,0)	—	76,0	6,5	6,7	C₂₇H₂₆N₂O₃	76,0	6,2	6,6

mixing of cation Ia with acetylacetone in the presence of triethylamine in deuteromethanol at
−50 to +60°C immediately leads to the formation of furo[2,3-b]quinoxaline IIa. Disappearance
of the signals (σ_{NCH_3} = 3.05 ppm) of cycloadduct IIa and the formation of IIIa (σ_{NCH_3} = 2.96
ppm) are observed subsequently when the sample is maintained at 35 to 60°C. An endo cyclo-
adduct, which then undergoes conversion to IIId, is initially formed in a mixture of cation
Ia with benzoylacetone in the presence of triethylamine. We were unable to isolate cycload-
duct IIg preparatively, since as it is formed, it is rapidly converted to IIId.

It was important to ascertain whether the cleavage of the C_{9a}–O_1 and C_3–C_{3a} bonds in the
furo[2,3-b]quinoxalines takes place via a stepwise or concerted process. For this, we studied
the reaction of ethyl 2,9-dimethyl-3a,4,9,9a-tetrahydro-endo-furo[2,3-b]quinoxaline-3-carboxy-
late (IIf) with acetylacetone. The formation of IIIe would confirm a stepwise mechanism with
cleavage of exclusively one C_{9a}–O_1 bond of the furan ring. However, according to the data
from the PMR spectra of the reaction mixtures, the only product was IIIa. A similar result,
which constitutes evidence for cycloelimination of endo adducts II to starting cation Ia, was
obtained in their reactions with benzoylacetone, in which IIId is formed. Thus III is formed
by cycloelimination of II and subsequent twofold attack by the β-diketone. The latter process
is accompanied by detachment of an acetyl residue from the acetylacetone molecule, as in its
reaction with phthalic anhydride, which leads to 2-acetylindan-1,3-dione [7]

In the case under consideration migration of an acetyl group takes place intramolecularly un-
der the influence of the negatively charged N_4 atom. An examination of Stuart–Brieglebmodels
shows that this sort of migration of the acetyl group is completely probable.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-20
spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis
spectrophotometer. The NMR spectra* were recorded with Perkin–Elmer R-12B (60 MHz) and Bruker
HX-90 spectrometers with tetramethylsilane and hexamethyldisiloxane as the internal standards.
The mass spectra were obtained with a modified MKh-1301 mass spectrometer with a system for
direct introduction of the samples into the ion source at an accelerating voltage of 2 kV, an
ionizing-electron energy of 30 eV, an emission current of 1.5 mA, and a sample-vaporization
temperature of 150-190°C.

X-Ray Diffraction Study. The study was carried out with a Synthex P1 automatic diffrac-
tometer. The crystals of IIIb were rhombic with a 17.782(6), b 8.378(2), C 13.001(A) Å, space
group Pπa2$_1$, z = 4, and d_{calc} = 1.30 g/cm^3. The intensities of 950 reflections with $F^2 \geq 2\sigma$
and θ/2θ scanning over the range 2 ≤ 2θ ≤ 120° were measured with the automatic diffractometer.

The starting quinoxalines were obtained from the corresponding diamines by the methods
in [8, 9]. Cation Ia was obtained by dissolving the corresponding base in a threefold excess
of methyl iodide with subsequent separation of the salt crystals. The mixtures of 6- and 7-
halo-substituted quinoxalinium cations were obtained by the method in [10].

The characteristics of III are presented in Table 4.

1-Methyl-2-acetonyl-3-(penta-2,4-dion-3-yl)-4-acetyl-1,2,3,4-tetrahydroquinoxaline (IIIa).
A) From N-Methylquinoxalinium Iodide (Ia). A 3-ml (0.03 mole) sample of acetylacetone was
added to a suspension of 3 g (0.012 mole) of cation Ia in 6 ml of ethanol, and the mixture

was heated to 60°C. A 3-ml (0.03 mole) sample of diethylamine was added to the resulting suspension, during which starting salt Ia dissolved. The reaction mixture was then maintained at the indicated temperature for 5 min and allowed to stand at room temperature. After 4 h, the precipitated IIIa was removed by filtration and washed with ethanol and ether to give 2 g of colorless needles (from ethanol).

B) From 2,9-Dimethyl-3-acetyl-3a,4,9,9a-tetrahydro-endo-furo[2,3-b]-quinoxaline (IIa). A 3-g (0.013 mole) sample of IIa was heated in 6 ml of ethanol to 60°C, 3 ml (0.03 mole) of acetylacetone was added, and the mixture was maintained at the indicated temperature for 1 h and allowed to stand overnight at room temperature. The precipitated IIIa was removed by filtration and washed with ethanol and ether to give 1.8 g of colorless needles (from ethanol).

7-Chloro-1-methyl-2-acetonyl-3-(penta-2,4-dion-3-yl)-4-acetyl-1,2,3,4-tetrahydroquinoxaline (IIIb). This compound was similarly obtained from a mixture of salts Ib,c. Two recrystallizations from ethanol gave individual compound IIIb in the form of colorless needles. The yield was 1.1 g.

7-Bromo-1-methyl-2-acetonyl-3-(penta-2,4-dion-3-yl)-4-acetyl-1,2,3,4-tetrahydroquinoxaline (IIIc). This compound was similarly obtained from a mixture of salts Id,e. The yield was 1.3 g.

1-Methyl-2,3-diphenacyl-4-acetyl-1,2,3,4-tetrahydroquinoxaline (IIId). A) From N-Methylquinoxalinium Iodide (Ia). A 3-ml (0.03 mole) sample of diethylamine and 4 g (0.025 mole) of benzoylacetone were added at room temperature to a suspension of 3 g (0.012 mole) of cation Ia in 6 ml of ethanol. After a few minutes, the starting substances dissolved, and the reaction mixture was then allowed to stand at room temperature for 4 days. The precipitated IIId was removed by filtration and washed with ethanol and ether to give 2.7 g of colorless needles (from ethanol).

B) From IIa. An 8-g (0.05 mole) sample of benzoylacetone was added at 40°C to 4 g (0.017 mole) of IIa in 7 ml of ethanol, and the reaction mixture was maintained at the indicated temperature for 2 h and allowed to stand overnight. The precipitated IIId was removed by filtration and washed with ethanol and ether. The yield was 2 g.

LITERATURE CITED

1. O. N. Chupakhin, V. N. Charushin, L. M. Naumova, A. I. Rezvukhin, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 11, 1549 (1981).
2. T. Kauffmann, Angew. Chem., Int. Ed., 13, 627 (1974).
3. O. N. Chupakhin, V. N. Charushin, L. M. Naumova, and A. I. Rezvukhin, Dokl. Akad. Nauk SSSR, No. 2, 384 (1982).
4. V. N. Churashin, O. N. Chupakhin, and A. I. Rezvukhin, Heterocycles, 16, 195 (1981).
5. R. Aquilera, J.-C. Duplan, and C. Nofre, Bull. Soc. Chim. Fr., 4491 (1968).
6. L. E. Sutton (editor), Tables of Interatomic Distances and Configurations in Molecules and Ions, Supplement 1956-1959, London (1965).
7. W. A. Mosher and W. E. Meier, J. Org. Chem., 35, 2934 (1970).
8. C. Cavagnol and F. Y. Wiselogie, J. Am. Chem. Soc., 48, 795 (1947).
9. W. Cruba and H. Poradovska, Roczn. Chem., 48, 1237 (1974).
10. V. N. Charushin, M. G. Ponizovskii, O. N. Chupakhin, A. I. Rezvukhin, G. M. Petrova, and Yu. A. Efremov, Khim. Geterotsikl. Soedin., No. 11, 1543 (1981).