PREPARATION OF PYRIDINIUM YLIDS, 1,4-DIHYDROPYRIDINES, AND INDOLIZINES FROM γ-NITROPHENYL- AND γ-NITROBENZYL-PYRIDINES

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The transformations of N-phenacyl(p-nitrophenacyl, benzyl)-2,5-dimethyl-4-nitrophenyl (nitrobenzyl, benzyl)pyridinium bromides under the influence of potassium carbonate solution were studied. Stable pyridinium ylids were obtained in the case of γ-phenylpyridines that contain a nitro group in the benzene ring and in the case of γ-benzylpyridines with an N-nitro-substituted phenacyl group. The conclusion that electron-acceptor substituents have a stabilizing effect on the stability of the ylids was confirmed. Under these conditions γ-nitrobenzyl derivatives are converted to substituted 1,4-dihydropyridines. The positions at which deprotonation of the starting quaternary pyridinium salts occurs and the formation of 1,4- and 1,2-dihydropyridines were established by PMR spectroscopy. The corresponding pyridinium salts were converted to a new group of indolizines containing a p-nitrophenyl (p-nitrobenzyl) substituent in the 2 or 7 position by the Chichibabin method. It was established that substituted dihydropyridines are converted to indolizines; ideas that confirm the scheme of the previously proposed mechanism for the formation of indolizines through a step involving ylids are expressed.

Pyridinium ylids are labile systems. Many of them cannot be isolated, since they undergo various transformations during their synthesis. Stable ylids are formed from the corresponding quaternary pyridine salts when the ylid grouping contains electron-acceptor substituents, which promote delocalization of charge from the ylid carbon atom; this is one of the factors involved in the stabilization of ylids [1].

The stabilities of γ-aryl- and γ-arylmethylopyridinium ylids should also depend on the character of the substituent and its position in the γ-benzene ring, as well as in the aroylmethylid group. The high lability of 2,5-dimethyl-4-benzylpyridinium benzoylmethylid [2] and the stabilities of its analogs with aroyl substituents in the γ position [3] have been reported. The available information regarding pyridinium ylids of this type is limited to these examples. In this connection, it seemed of interest to ascertain the effect of the electron-acceptor nitro group in the corresponding substituted quaternary pyridinium salts on the formation of ylids from them and the stabilities of the latter and on the direction of deprotonation of these systems under the conditions of formation of the ylids.

Quaternary salts VI-XII were obtained from 2,5-dimethyl-4-(p-nitrophenyl) (I), [m-nitro-p-tolyl (II), p-nitrobenzyl (III), o,p-dinitrobenzyl (IV), benzyl (V)] pyridines [4] and bromoacetophenone, benzyl bromide, and p-nitrobromoacetophenone. (See Scheme on following page)

2,5-Dimethyl-4-[p-nitrophenyl-(XIII), m-nitro-p-tolyl (XIV)]pyridinium benzoylmethylids were obtained by treatment of quaternary salts VI and VII, which contain a γ-nitrophenyl grouping, with potassium carbonate solution. The elimination of a proton from the methylene group of the N-phenacyl grouping was established by comparison of the integral intensities of this group in the PMR spectra of ylids XIII and XIV (as well as XVI) in CF_3COOH (~2H) and CF_3COOD (~1H). In the case of quaternary salts that contain a benzyl grouping in the γ position of the pyridine ring there are two centers at which elimination of a proton may occur – the methylene group of the N-phenacyl grouping and the methylene group of the benzyl grouping. In the case of salts XI

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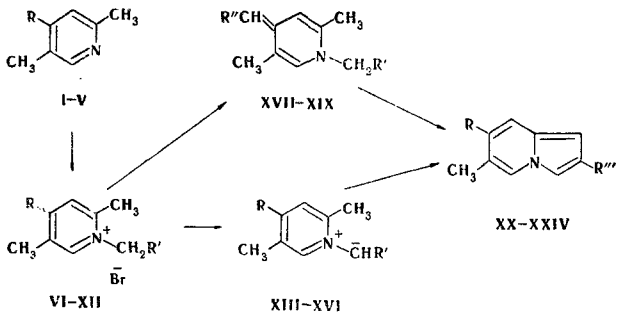


I, VI, XIII, XVII, XVIII, XX, XXII, XXIV R=R″=R‴=*p*-$NO_2C_6H_4$; II, VII, XIV, XXI R=*m*-NO_2-*p*-$CH_3C_6H_3$; III, VIII, IX, XII, XV, XXIII, XXIV R′=*p*-$NO_2C_6H_4CH_2$; IV, X R=*o*,*p*-$(NO_2)_2C_6H_3CH_2$; V, XI, XVI, XXII R′=$C_6H_5CH_2$; VI, VII, IX, X, XIII, XIV, XVIII, XIX R′=COC_6H_5; VIII, XVII, XX, XXI, XXIII R′=R‴=C_6H_5; XI, XII, XV, XVI R′=$COC_6H_4NO_2$-*p*; XIX R″=*o*,*p*-$(NO_2)_2C_6H_3$

and XII, which contain an N-(p-nitrophenacyl) grouping, a proton is also eliminated from the methylene group of this grouping to give 2,5-dimethyl-4-[p-nitrobenzyl (XV), benzyl (XVI)] pyridinium p-nitrobenzoylmethylids. The integral intensities of the benzyl methylene group (4.5 ppm, s, 2H) and the $N-CH_2$ group (6.3 ppm, s, 2H) are equalized in the PMR spectra of ylids XV and XVI in CF_3COOH, since a salt with the CF_3COO^- anion is formed. In the case of CF_3COOD the ratio of the intensity of the signals of these groups is ~2:1 ($Ar-CH_2-Ar'$ and N-CHD). Ylids XIII-XVI are colored compounds that remain unchanged during storage but undergo decomposition when they are melted. The relative stabilities of these ylids is due to the presence of a nitro group.

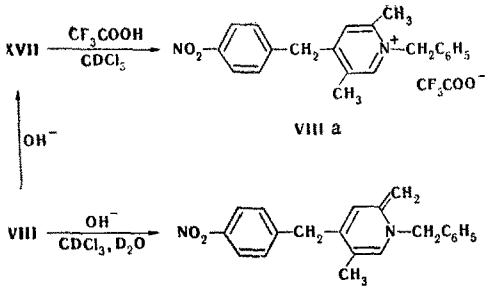
The IR spectra of ylids XV and XVI do not contain the band of a carbonyl group; the bands at 3510-3513 and 3380-3398 cm^{-1} are due to the contribution of the betaine form, which is also regarded as one of the factors involved in the stabilization of ylids [1].

When quaternary pyridinium salts containing a nitro group in the γ-benzyl grouping and benzyl (VIII) or phenacyl (IX and X) groupings attached to the nitrogen atom are treated with potassium carbonate, a proton is split out from the methylene group of the γ-benzyl grouping. This pathway was used to obtain 2,5-dimethyl-1-benzyl-4-(p-nitrobenzylidene)- (XVII) [1-phenacyl-4-(p-nitrobenzylidene)-(XVIII), 1-phenacyl-4-(o,p-dinitro-benzylidene)-(XIX)]-1,4-dihydropyridines in the form of dark-violet crystalline substances. As compared with starting quaternary salts VIII-X, as well as pyridinium benzoylmethylids (λ 250, 280, 320, 416, and 434 nm) [2, 3], an additional maximum in the long-wave region (560-570 nm) appears in the UV spectra of these compounds; this is due to the increase in the conjugation chain in these systems. The intense bands at 1696 and 1703 cm^{-1}, respectively, in the IR spectra of XVIII and XIX are related to the phenacyl carbonyl group. The ratio of the integral intensities of the protons of the methylene groups attached to the nitrogen atom and the C_4 atom of the pyridine ring of XVII-XIX (PMR spectrum in CF_3COOD) is ~2:1.

The significant diamagnetic shift of the α- and β-H signals from 9.45 and 7.63 ppm in the spectrum of VIII to 6.65 and 6.57 ppm in the spectrum of XVII constitutes evidence for the different character of the bonds in the nitrogen-containing ring of these compounds, as described in [5]. The changes in the position and integral intensity of the signal of the grouping between the nitrophenyl and nitrogen-containing rings on passing from salt VIII (4.30, s, 2H) to XVII (5.16, s, 1H) constitute evidence for conversion of the methylene group to a methylidyne group.

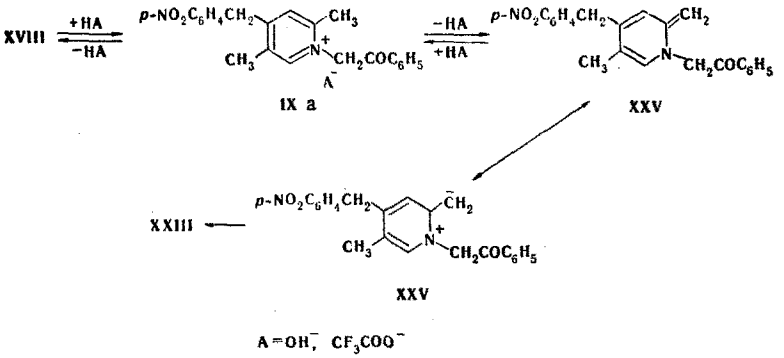
Under acidic dihydropyridination conditions the system is converted to a pyridine system. Signals of the starting compound and salt VIIIa are observed in the PMR spectrum as a solution of dihydropyridine XVII in $CDCl_3$ is gradually acidified with a 20% solution of CF_3COOH. The signals of the dihydropyridine system decrease and vanish as the acid concentration increases. As in the case of salt VIII, elimination of a proton from the α methyl group and the formation of 1,2-dihydropyridine structure XVIIa are evidently possible in the case of treatment of the quaternary salts with bases. Evidence for this is provided by the gradual decrease and subsequent disappearance of the signals of the α-methyl group when a solution of salt VIII in $CDCl_3$ is treated with a solution of potassium carbonate in D_2O. Similar changes in the signals (see Scheme on following page) of the methylene group attached to C_4 also occur simultaneously. On the basis of these data on deuterium exchange at the methylene group attached to C_4 and the α-methyl group it may be concluded that conjugate [with respect to VIII (the acid)] isomeric substituted 1,4- and 1,2-dihydropyridines (the base) exist.

Thus γ-arylpyridinium ylids that contain a nitro group in the aryl grouping are stable. The analogous ylids with a benzyl grouping in the γ position and with a nitro group in the phenyl ring of the benzoylmethylid



groups are stable. Under the conditions of the formation of ylids, quaternary N-benzyl(phenacyl)-γ-nitrobenzoylpyridinium salts are converted to substituted dihydropyridines rather than to ylids.

Quaternary salts VI, VII, XI, and XII, which form stable ylids, were converted under the conditions of the Chichibabin reaction [6] to 6-methyl-2-phenyl-7-(p-nitrophenyl)indolizine (XX), 6-methyl-2-phenyl-7-(m-nitro-p-tolyl)indolizine (XXI), 6-methyl-2-(p-nitrophenyl)-7-benzylindolizine (XXII), and 6-methyl-7-(p-nitrobenzyl)-2-(p-nitrophenyl)indolizine (XXIV) in relatively high yields. The corresponding indolizine is not formed from quaternary salt X or substituted dehydropyridine XIX under the conditions of the Chichibabin reaction. However, ~15% 6-methyl-2-phenyl-7-(p-nitrobenzyl)-indolizine (XXIII) and ~85% dihydropyridine XVIII (according to the data from the PMR spectrum) are formed under the same conditions from quaternary salt IX. It might have been assumed that indolizine XXIII is formed from the dihydropyridine in this case. A mixture of ~85% indolizine XXIII and ~15% starting XVIII was obtained by heating XVIII in moist ligroin. The similar formation of indolizine XXIII was established when dihydropyridine XVIII was heated in methanol and in water.



A = OH^-, CF_3COO^-

The formation of indolizine XXIII evidently occurs during cyclization of zwitterion XXV, the formation of which from 1,4-dihydropyridine XVIII is possible only in a proton-donor medium and was confirmed by the above-described deuterium exchange of the α-methyl group of the salt.

This mechanism for the formation of indolizines was previously proposed in [7].

Of the compounds described in the present communication, quaternary salts VII and IX have growth-regulating activity, while XVII has herbicidal activity.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CF_3COOH, CF_3COOD, and $CDCl_3$ were recorded with a BS-487 spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) and tetramethylsilane (TMS) as the internal standards. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol and chloroform were recorded with a UV-vis spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source and an ionizing-electron energy of 50 eV.

N-Phenacyl-2,5-dimethyl-4-(p-nitrophenyl)pyridinium Bromide (VI). A mixture of 5 g (0.012 mole) of pyridine base I, 6.6 g (0.033 mole) of bromoacetophenone, and 50 ml of acetone was refluxed for 3 h, after which the precipitate was separated and washed with absolute ether to give 8 g (0.033 mole) of colorless crystals of salt VI. PMR spectrum (CF_3COOH with HMDS as the standard): 8.25, s, 1H (α-H); 8.05 and 7.43, m, Σ4H; 7.75, d, 2H (2H-o-CO); 6.01, s, 2H ($N-CH_2$); 2.36, s, 3H ($\alpha-CH_3$); 2.06 ppm, s, 3H ($\beta-CH_3$). Quaternary salts VII-XII were similarly obtained from pyridine bases II-V and the corresponding bromo derivatives.

TABLE 1. N-Phenacyl(benzyl)-2,5-dimethyl-4-nitrophenyl(nitrobenzyl)pyridinium Bromides

Compound	mp, deg C	Found, %		Empirical formula	Calc., %		Yield, %
		Br	N		Br	N	
VI	221—223 (dec.)	18,8	6,3	$C_{21}H_{19}BrN_2O_3$	18,7	6,5	85
VII	193—195 (dec.)	17,9	6,1	$C_{22}H_{21}BrN_2O_3$	18,1	6,3	84
VIII	194—196	19,2	6,9	$C_{21}H_{21}BrN_2O_2$	19,4	6,8	97
IX*	208—210 (dec.)	18,1	6,6	$C_{22}H_{21}BrN_2O_3$	18,1	6,4	84
X	187—189 (dec.)	16,2	8,8	$C_{22}H_{20}BrN_3O_5$	16,5	8,6	97
XI	198—200 (dec.)	18,0	6,4	$C_{22}H_{21}BrN_2O_3$	18,1	6,3	76
XII	127—129 (dec.)	16,6	8,6	$C_{22}H_{20}BrN_3O_5$	16,5	8,6	83

* M^+ 342.

TABLE 2. 2,5-Dimethyl-4-nitrophenyl(nitrobenzyl, benzyl)-pyridinium Benzoylmethylids

Compound	mp, deg C (dec.)	N found, %	Empirical formula	N calc., %	Color	Yield, %
XIII*	182—184	8,3	$C_{21}H_{18}N_2O_3$	8,1	Brown	65
XIV	174—176	8,1	$C_{22}H_{20}N_2O_3$	7,8	Light-orange	80
XV	91—93	10,7	$C_{22}H_{19}N_3O_5$	10,4	Dark-orange	63
XVI	110—112	7,6	$C_{22}H_{20}N_2O_3$	7,8	Orange	74

* M^+ 328.

Their characteristics are presented in Table 1. The data from the PMR spectra confirm their structures.

2,5-Dimethyl-4-(p-nitrophenyl)pyridinium Benzoylmethylid (XIII). A total of 7 ml of a 10% solution of potassium carbonate was added with cooling (with tap water) to a solution of 0.5 g (1.17 mmole) of quaternary salt VI in 20 ml of acetonitrile, and the mixture was shaken and treated with 10 ml of cold water. It was then maintained at 8-10°C for 1 h, and the resulting precipitate was separated, washed with ice water, and dried in a vacuum desiccator over P_2O_5 to give 0.26 g (65%) of ylid XIII. PMR spectrum (CF_3COOH with HMDS as the standard): 8.19, s, 1H (α-H); 8.03 and 7.45, m, Σ4H; 7.7, d, 2H (2H-o-CO); 5.91, s, 2H (N$-CH_2$); 2.35, s, 3H (α-CH_3); 2.05 ppm, s, 3H (β-CH_3). The PMR spectrum of the compound in CF_3COOD was identical, except for the signal at 5.91 ppm, s, 1H (N$-$CHD). UV spectrum, λ_{max}(log ε): 210 (4.52), 265 (4.78), 320 (3.67), 390 (3.69), 440 nm sh (2.20).

Ylids XIV-XVI were similarly obtained (see Table 2). The ylid grouping in the PMR spectrum of XIV in $CDCl_3$ was found at 6.20 ppm, s, 1H ($N^+-\overline{C}H$); in the spectrum of XV in CF_3COOH (with TMS as the standard): 6.35 ppm, s, 2H (N$-CH_2$), in CF_3COOD; 6.35 ppm, s, 1H (N$-$CHD); in the spectrum of XVI in CF_3COOH (TMS): 6.23 ppm, s, 2H (N$-CH_2$), in CF_3COOD (TMS): 6.21 ppm, s, 1H (N$-$CHD).

2,5-Dimethyl-1-benzyl-4-(p-nitrobenzylidene)-1,4-dihydropyridine (XVII). A 7-ml sample of 10% potassium carbonate solution was added with shaking and cooling (0°C) to a solution of 0.5 g (1.2 mmole) of salt VIII in 20 ml of acetonitrile. The mixture turned green and then violet. Water (50 ml) was added in 10-ml portions, and the mixture was maintained at 8-10°C for 1 h. The resulting precipitate was dried over P_2O_5 to give 0.22 g (55%) of XVII as dark-violet crystals with mp 126-128°C. PMR spectrum ($CDCl_3$, HMDS as the standard): 6.65, s, 1H and 6.50, s, 1H (α-H and β-H); 5.16, s, 1H (Ar$-$CH=Ar'); 4.70, s, 2H (N$-CH_2$); 2.01, s, 3H (α-CH_3); 1.81 ppm, s, 3H (β-CH_3); spectrum in CF_3COOH: 8.04, s, 1H (α-H); 5.25, s, 2H (N$-CH_2$); 3.96, s, 2H (Ar$-CH_2-$Ar'); 2.30, s, 3H (α-CH_3); 2.07 ppm, s, 3H (β-CH_3); the spectrum in CF_3COOD was identical, except for the signal at 4.00 ppm, s, 1H (Ar$-$CHD$-$Ar'). IR spectrum: 1653 cm^{-1} (conjugated C=C). UV spectrum (in $CHCl_3$), λ_{max}(log ε): 260 (3.98), 332 (3.90), 560 nm (4.50). Found: C 75.7; H 6.1; N 8.5%; M^+ 332. $C_{21}H_{20}N_2O_2$. Calculated: C 75.9; H 6.0; N 8.44%; M 332.

Substituted dihydropyridnes XVIII and XIX were similarly obtained. Compound XVIII (54% yield) was obtained as dark-violet crystals with mp 132-134°C. PMR spectrum (CF_3COOH): 7.99, s, 1H (α-H); 5.80, s, 2H (N$-CH_2$); 4.01, s, 2H (Ar$-CH_2-$Ar'); 2.23, s, 3H (α-CH_3); 2.06 ppm, s, 3H (β-CH_3); the spectrum in CF_3COOD was identical except for the signal at 4.00 ppm, s, 1H (Ar$-$CHD$-$Ar'). IR spectrum: 1695 (CO) and

*Water is eliminated under the conditions of recording the mass spectrum, and this evidently explains the absence of a molecular ion.

TABLE 3. 6-Methyl-2-phenyl(nitrophenyl)-7-nitrophenyl(nitrobenzyl, benzyl)indolizines

Compound	mp, deg C (dec.)	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Found, %			Empirical formula	Calc., %			Color	Yield, %
				C	H	N		C	H	N		
XX	170—172		($CDCl_3$, TMS) 8,3, m, 2H (o,o'-NO_2); 6,60, s, 1H (3-H); 2,08, s, 3H (CH_3)	76,6	4,7	8,3	$C_{21}H_{16}N_2O_2$	76,8	4,8	8,5	Orange	75
XXI	174—176	1604 w, 1534 s, s 1343 (NO_2)	(CF_3COOH, TMS) 8,85, s, 1H (5-H); 8,21, s, 1H (o-NO_2); 7,86, s, 1H (8-H); 7,37, s, 1H (1-H); 5,94, s, 2H (3-2H); 2,80 and 2,52, s, each 3H ($2CH_3$).	77,0	5,4	8,5	$C_{22}H_{19}N_2O_2$	77,2	5,2	8,2	Light-orange	53
XXII	201—202	1596 s 1498, 1324 (NO_2)	($CDCl_3$, TMS) 8,17, m, and 7,67, m, 4H (Ph—NO_2-p); 6,54, s, 1H (3-H); 3,88, s, 2H (Ar—CH_2—Ar'); 2,06, s, 3H (CH_3)	77,3	5,5	8,5	$C_{22}H_{18}N_2O_2$	77,2	5,2	8,2	Orange (luster)	96
XXIII	160—162	1600 w, 1520 s, 1347 s (NO_2)	(CF_3COOH,(HMDS) 8,26, s, 1H (5-H); 7,83, m, 2H (o,o'-NO_2); 6,80, s, 1H (1-H); 5,41, s, 2H (3-2H); 3,96, s, 2H (Ar—CH_2—Ar'); 2,05, s, 3H (CH_3)	77,0	5,3	8,3	$C_{22}H_{18}N_2O_2$	77,2	5,2	8,2	Orange	54
XXIV	213—215	1594 s, 1514 s 1343 s (NO_2)	($CDCl_3$, TMS) 7,95, m and 7,90, m 4H (o,o-NO_2); 6,60, s, 1H (3-H); 3,88 s, 2H (Ar—CH_2—Ar'); 2,06, s, 3H (CH_3)	68,3	4,6	10,8	$C_{22}H_{17}N_3O_4$	68,2	4,4	10,9	Orange (luster)	53

1653 cm^{-1} (conjugated C=C). UV spectrum (in $CHCl_3$), λ_{max}(log ε): 252 (4.07), 450 (3.97), 560 nm (2.80). Found: N 7.9%; (M−18) 342*. $C_{22}H_{20}N_2O_3$. Calculated: N 7.8%; M 360. Compound XIX (93% yield) was obtained as dark-violet crystals with mp 143-144°C. PMR spectrum (CF_3COOH): 7.98, s, 1H (α-H); 5.75, s, 2H ($N-CH_2$); 4.27, s, 2H ($Ar-CH_2-Ar'$); 2.20, s, 3H (α-CH_3); 2.13 ppm, s, 3H (β-CH_3); the spectrum in CF_3COOD is similar, except for the signal at 4.28 ppm, s, 1H ($Ar-CHD-Ar'$). IR spectrum: 1703 (CO) and 1650 cm^{-1} (conjugated C=C). Found: N 10.1%; (M-18) 387*. $C_{22}H_{19}N_3O_5$. Calculated: N 10.4%; M 405.

6-Methyl-2-phenyl-7-(p-nitrophenyl)indolizine (XX). A) 7-g (16 mmole) sample of quaternary salt VI was refluxed for 1.5 h in 50 ml of a 40% solution of potassium carbonate, and the resulting precipitate was crystallized from ligroin to give 4.16 g of indolizine XX. Indolizines XXI-XXIV were similarly obtained (Table 3).

B) A 0.2-g (0.006 mole) sample of substituted dihydropyridine XVIII was refluxed in 40 ml of absolute methanol for 6 h, after which workup gave 0.05 g (37%) of indolizine XXIII.

C) A 0.2-g (0.006 mole) sample of XVIII was refluxed in 100 ml of moist ligroin for 6 h. According to the PMR spectrum, the residue (0.16 g) contained ~85% indolizine XXIII and ~15% starting XVIII.

D) A 0.3-g (0.009 mole) sample of dihydropyridine XVIII was refluxed in 100 ml of water for 3 h, after which the mixture was worked up to give 0.26 g (91%) of indolizine XXIII.

LITERATURE CITED

1. I. Surpateanu, J. P. Catteau, P. Karafiloglu, and A. Lablache-Combier, Tetrahedron, 32, 2647 (1976).
2. N. S. Prostakov, L. A. Gaivoronskaya, Kamara Maiga Sarata Mokhomon, V. P. Zvolinskii, A. A. Savina, Munzer Makhsida, and Victor Hugo Opaso Karrasko, Khim. Geterotsikl. Soedin., No. 4, 506 (1976).
3. N. S. Prostakov, V. I. Kuznetsov, A. A. Savina, M. A. Ryashentseva, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 5, 646 (1977).
4. N. S. Prostakov, A. P. Krapivko, A. T. Soldatenko, K. Furnaris, A. A. Savina, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 3, 365 (1976).
5. B. M. Goldschmidt, B. L. Van Duuren, and R. C. Goldstein, J. Heterocycl. Chem., 13, 517 (1976).
6. A. E. Chichibabin, Zh. Russk. Fiz. Khim. Obshchestva, 29, 477 (1927).
7. D. R. Bragg and D. G. Wibberley, J. Chem. Soc., No. 6, 3277 (1963).