SYNTHESIS AND REACTIONS OF 2-(4-PYRIDYL)INDOLE ANHYDRO BASES

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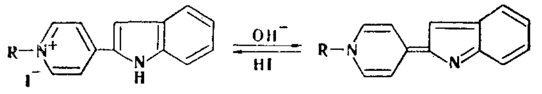
The corresponding anhydro bases are formed from quaternary salts of 2-(4-pyridyl)indole under the influence of a methanol solution of alkali. The 2-(4-pyridyl)indole cation and 1H-4-(2-indolenylidene)-1,4-dihydropyridine were subjected to quantum-chemical calculation, and the possibility of electrophilic substitution of the anhydro bases in the β position of indole was predicted on the basis of the results of the calculations. Thus, the reaction of the anhydro bases with acetyl nitrate and a solution of bromine in acetic acid leads to quaternary salts with a substituent in the β position of the indole ring, which are reconverted to anhydro bases under the influence of alkali with retention of the substituent in the β position. When the anhydro bases are refluxed in nitromethane and cyanoacetic and malonic esters in the presence of triethylamine, they form the corresponding adducts, which give the starting compounds under the influence of alkali, whereas upon reaction with methyl iodide in ethanol they give quaternary salts. All of these chemical transformations were confirmed by the IR, UV, PMR, and mass spectra.

Stable anhydro bases, the synthesis, reactivities, and physicochemical properties of which have been studied quite thoroughly [1-3], are formed in the reaction of quaternary salts of 3-(4-pyridyl)indole with alkali; it was also established that various structural factors, viz., annelation, aza substitution, the presence of a vinyl grouping between the rings, and the character of the substituents in both the pyridine and indole rings, have an effect on the formation of the corresponding anhydro bases [1, 2, 4, 5]. However, until recently little attention was paid to the effect of the order of fusion of the pyridine and indole rings on the reactivities of the anhydro bases of pyridylindoles. We have previously synthesized the anhydro base of 2-(4-pyridyl)indole [6], despite the opinion expressed in [7] that its existence is impossible, and have investigated some of its chemical transformations and physicochemical characteristics.

In the present research we undertook a systematic study of the formation and reactivities of the anhydro bases obtained from quaternary salts of 2-(4-pyridyl)indole. As we have previously shown 2-(4-pyridyl)indole methiodide (Ia) forms an anhydro base (IIa) smoothly and in quantitative yield when it is treated with a methanol solution of alkali [6]. Anhydro bases are also formed similarly from quaternary salts of 2-(4-pyridyl)indole (Ib-e):



I a-f II a-d

a $R=CH_3$; b $R=C_2H_5$; c $R=n\text{-}C_3H_7$; d $R=n\text{-}C_7H_{15}$; e $R=C_6H_5COCH_2$;
f $R=iso\text{-}C_3H_7$

An increase in the length of the chain of the N-alkyl group does not affect the formation of anhydro bases II — as in the case of salt Ia [6], quaternary salts Ib-d did not undergo dealkylation under the influence of alkali but gave the corresponding anhydro bases in quantitative yields. The results of quantum-chemical calculations of the 2-(4-pyridyl)indole cation*

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*The calculations were made within the framework of the Pariser–Parr–Pople (PPP) method by the method described in [1].

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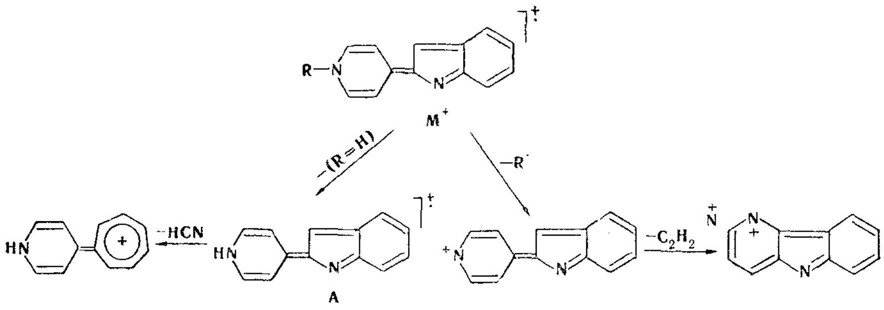
(Fig. 1) show that the most positive π-electron charge is concentrated on the pyridine nitrogen atom. It is somewhat higher than the charge on the indole nitrogen atom (0.34054 and 0.30064, respectively). However, despite this, deprotonation is observed even when the substituent attached to the nitrogen atom in the pyridinium cation contains a strongly acidifying group (the benzoyl group in Ie), and, of course, elimination of the benzoyl group also takes place along with deprotonation in this case to give IIa. The facile deprotonation of cations I is due not only to the polarity of the N–H bond but also to the strong solvation of the proton. In an attempt to carry out the reaction with quaternary salt if the corresponding anhydro base is not formed even in trace amounts — one observes complete dealkylation of the pyridine ring with liberation of the corresponding base, viz., 2-(4-pyridyl)indole. Considering the fact that 1-isopropyl-4-(2-indolyl)pyridinium iodide is formed with great difficulty in the reaction of the base and isopropyl iodide upon prolonged refluxing in n-butyl alcohol and always contains admixed unchanged base, in contrast to other salts of the I type, this reaction pathway can be explained by steric shielding of the N-isopropyl group.

Anhydro bases II are strong bases — their pK_a values range from 10 to 12. The length of the N-alkyl group has virtually no effect on the basicities of the anhydro bases. Two inflections (as also noted previously in [1, 2, 5]), one of which belongs to the base, the other of which belongs to its hydrated form, are observed on the titration curves of aqueous alcohol solutions of II.

We proved the structure of anhydro bases II by mass spectrometry in the case of IIa, b. It is known that the dissociative ionization of aromatic and heteroaromatic compounds is characterized by high stability of the molecules with respect to electron impact (W_M) and low fragmentation selectivity ($S_{1/2}$) [8]. Conjugated heteroatomatic compounds [8-10], the mass spectra of which do not contain ions formed by cleavage of the interannular ring, also have these properties. We have previously shown for isomeric anhydro bases of 3-(4-pyridyl)indole [3] that the initial acts in the fragmentation of the molecular ion ($[M^+]$) are associated with the elimination of a hydrogen atom and (R–H) and R particles. Then, as in previously investigated compounds of the diphenyl type [11], in the secondary steps of the fragmentation one observes the successive splitting out of C_2H_2 and HCN molecules and the formation of doubly-charged ions from $[M - (R{-}H)]^{++}$ and $[M - R]^{++}$. An M^+ peak corresponding to the calculated mass — the m/z value is 208* — is also recorded in the mass spectrum of IIa, while a peak with m/z 222 is recorded in the spectrum of IIb. Their intensities are considerably lower (by a factor of about two to three) than in the case of the isomeric 3-(4-pyridyl)indole anhydro base [3]. The stabilities with respect to electron impact are low for hetaryl compounds (W_M = 8.1) that have conjugation between the rings. A substantial difference between the investigated compounds and the previously studied isomeric anhydro bases [3] is the rather high intensities of the ions with m/z 167, 166, 140, and 139 due to successive elimination of HCN molecules initially from the $[M - (R{-}H)]^+$ and $[M - R]^+$ ions and then from the $[M - (R{-}H), -HCN]^+$ and $[M - R, -HCN]^+$ ions. As compared with the isomeric anhydro bases, the intensities of the indicated ions are higher by a factor of four to six. The character of the fusion of the pyridine and indole rings in II blocks secondary detachment of an HCN particle and gives rise to a different fragmentation mechanism. Elimination of an HCN molecule directly from the indolenine fragment to give a stable ion that includes a dehydrotropylium residue evidently takes place after the formation of the pseudomolecular $[M - (R{-}H)]^+$ ion with structure A:



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*Here and subsequently, the numbers that characterize the ions are the mass-to-charge ratios (m/z).

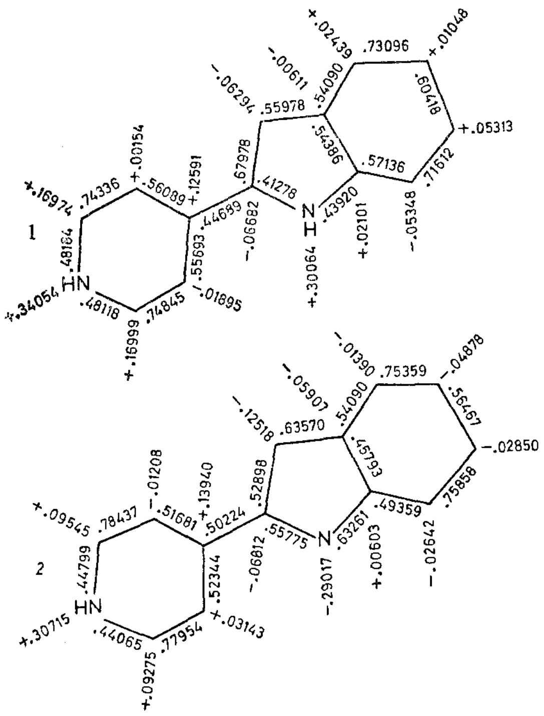
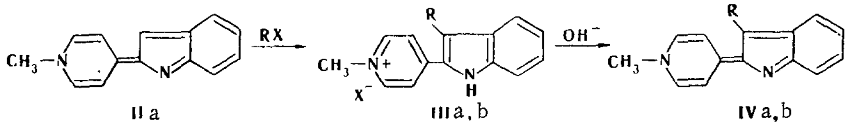


Fig. 1. Molecular diagrams: 1) 2-(4-pyridyl)indole cation; 2) 1H-4-(2-indolenylidene)-1,4-dihydropyridine.

The PMR spectrum of anhydro base IIb contains a series of signals centered at 1.1 and 4.3 ppm due to the protons of the methyl and methylene groups of the N-ethyl substituent. A complex multiplet of aromatic protons is observed at 6.5-8.0 ppm.

The anhydro bases of 2-(4-pyridyl)indole are bifunctional compounds. The results of quantum-chemical calculations show that their molecules contain several reaction — both nucleophilic and electrophilic — centers (Fig. 1), in connection with which these compounds should display activity with respect to various reagents. Judging from the data in [6], several electrophilic agents, viz., alkyl and acylium cations and the proton, actually add readily to the indolenine nitrogen atom of IIa, on which the highest negative charge is concentrated. In addition, in the reaction of the anhydro bases with water the hydroxide ion attacks the electrophilic α position of the pyridine ring to give covalent hydrates. In the anhydro base molecule (Fig. 1) a rather significant amount of σ-negative charge is also concentrated on the carbon atom in the β position of the indole ring (−0.12518). Under certain conditions the introduction of substituents also in the β position of indole is possible in the reaction of the anhydro bases with any electrophilic agents. We investigated the reaction of anhydro base IIa with acetyl nitrate and a solution of bromine in acetic acid under the conditions described in [12]. The reaction of base IIa with these electrophilic agents leads to quaternary salts III, which are substituted in the β position of indole. Upon reaction with alkali IIIa, b form the corresponding anhydro bases with substitution in the β position of indole (IV):



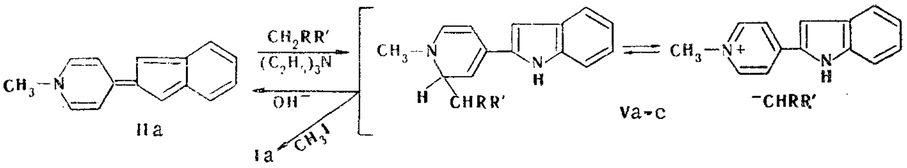
IIa IIIa,b IVa,b

IIIa, IV a R = NO_2; b R = Br; IIIa, X = NO_3^-; b X = Br^-

We proved the structure of one of them (IVa) by mass spectrometry. As in the case of the examined **IIa, b, in** the mass spectrum of IVa we recorded a molecular-ion peak corresponding to the calculated mass (253), in which elimination of the N-alkyl substituent in the form of a CH_2 particle to give an ion with a structure of the A type is realized in the first step of the fragmentation. The subsequent fragmentation of this ion proceeds via the known scheme and involves the successive elimination of HCN particles. However, fragmentation processes associated with the presence of a nitro group in the molecule take place more vigorously. Thus NO and NO_2 particles are split out from M^+ and the ion with structure A to give, respectively, ions with m/z 223, 207, 209, and 193. All of the described fragmentation processes are accompanied by dehydrogenation, which is characteristic for systems of the diphenyl type. The PMR spectrum of IVa contains a singlet signal at 4.2 ppm, which is formed by the protons of the N-methyl group, and a complex multiplet of aromatic protons at 6.7-8.3 ppm.

Alkyl substituents cannot be introduced directly in the β position of the indole ring even in the case of prolonged refluxing of II with excess alkylating agent.

The presence of a rather high σ-positive π-electron charge in the α position of the pyridine ring in anhydro bases II (see Fig. 1) provides a basis for the assumption that other nucleophilic reagents such as the anions of some CH acids can, like the hydroxide ion, react with these compounds. In fact, we found that adduct Va is formed when anhydro base IIa is refluxed in nitromethane in the presence of triethylamine. Cyanoacetic and malonic esters react similarly with base IIa:



a R=H; $R^1=NO_2$; b R=CN; $R^1=COOC_2H_5$; c $R=R^1=COOC_2H_5$

Compounds V are yellow crystalline substances that are quite soluble in polar solvents but only slightly soluble in nonpolar solvents. Their UV spectra recorded in polar solvents are similar to the UV spectrum of 2-(4-pyridyl)indole methiodide. This fact constitutes evidence in favor of dissociation of dihydro structure V in polar media, as previously noted in similar systems [13]. Compounds V react with alkali to give anhydro base IIa and with hydriodic acid to give 2-(4-pyridyl)indole methiodide (Ia). Salt Ia is also formed in the reaction of V with methyl iodide in ethanol or acetonitrile. Alkylation of the anion of the CH acid in V evidently occurs under the influence of methyl iodide.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform and suspensions in mineral oil were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in methanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with a Varian MAT-311A spectrometer at an accelerating voltage of 3 kV, a cathode emission current of 300 mA, an ionizing voltage of 75 eV, and an ion-source temperature of 250-300°C. The potentiometric determination of the pK_a values of the bases was carried out with a pH-340 apparatus by titration of aqueous alcohol solutions of the compounds (c 10^{-2} and 10^{-3} mole/liter, 10% methanol) with a 0.1 N solution of HCl. The pK_a value was assumed to be equal to the pH value at the half-neutralization point. Quaternary salts Ia-f were obtained by the method described in [14]. The principal characteristics of salts I that are not described in [14] are given in Table 1. We have previously presented the properties of anhydro base IIa [6].

1-Ethyl-4-(2-indolenylidene)-1,4-dihydropyridine (IIb). A suspension of 3.5 g (0.01 mole) of 1-ethyl-4-(2-indolyl)pyridinium iodide in 15 ml of a saturated methanol solution of KOH was heated until the iodide dissolved completely, after which the solution was cooled, and the precipitate was removed by filtration and recrystallized from a 5% solution of KOH in methanol to give 2 g (84%) of a product with mp 225-226°C and pK_a 11.4. IR spectrum: 1655 (C=N) and 1607 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 215 (4.05), 249 (3.60), 391 (3.05), and 403 nm (3.50). PMR spectrum: 1.1 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), and 6.5-8.0 ppm (9H, aromatic protons). Mass spectrum, m/z values (%): 51 (8.1); 5.5 (5.2); 57 (6.8); 63 (10.5); 69 (6.1); 69.5 (3.8); 70.5 (6.6); 77 (6.3); 83.5 (9.3); 88 (3.0); 89 (15.5); 90 (13.8); 93 (5.4); 96.5 (3.6); 97 (7.4); 111 (3.1); 127 (5.2); 139 (12.1); 140 (10.2); 166 (24.6); 167 (23.2); 192

(10.5); 193 (29.9); 194 (100.0); 195 (20.0); 206 (10.1); 207 (21.1); 221 (14.7); 222 (44.3); 223 (14.9); W_M = 6.2. Found: C 79.8; H 6.4; N 12.9%. $C_{15}H_{14}N_2$. Calculated: C 80.1; H 6.3; N 12.6%.

1-Methyl-4-(3-nitro-2-indolyl)pyridinium Nitrate (IIIa). A solution of 1 ml of HNO_3 in 10 ml of acetic anhydride was added dropwise at 0-5°C to a solution of 1 g (0.005 mole) of 1-methyl-4-(2-indolenylidene)-1,4-dihydropyridine (Ia) in 10 ml of acetic anhydride, after which the mixture was allowed to stand for 20 h. It was then treated with ether, and the resulting precipitate was removed by filtration and recrystallized from acetonitrile to give 0.6 g (98%) of a product with mp 228-229°C. UV spectrum, λ_{max} (log ε): 207 (4.57), 253 (4.03), 342 (3.94), and 391 nm (3.95). Found: C 52.9; H 3.6; N 17.5%. $C_{14}H_{12}N_4O_5$. Calculated: C 53.2; H 3.8; N 17.7%.

1-Methyl-4-(3-nitro-2-indolenylidene)-1,4-dihydropyridine (IVa). A suspension of 0.5 g (1.5 mmole) of 1-methyl-4-(3-nitro-2-indolyl)pyridinium nitrate in 5 ml of a saturated methanol solution of KOH was heated until the salt dissolved completely, after which the solution was cooled, and the precipitate was removed by filtration and recrystallized from methanol to give 0.3 g (79%) of a product with mp 260-261°C and pK_a 9.0. IR spectrum: 1648 (C=N), 1610 (C=C), and 1370 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 223 (4.08), 254 (3.85), 387 (3.77), and 408 nm (3.81). PMR spectrum: 4.2 (s, 3H, $N-CH_3$) and 6.7-8.3 ppm (8H, aromatic protons). Mass spectrum, m/z values (%): 51 (30.6); 52 (8.2); 6.2 (11.2); 6.3 (22.1); 69.5 (6.7); 75 (15.8); 76 (21.8); 77 (22.9); 78 (25.8); 88 (11.1); 89 (19.0); 90 (14.0); 93 (14.0); 102 (18.9); 103 (13.5); 104 (10.0); 105 (14.4); 106 (15.3); 127 (16.6); 128 (12.5); 129 (15.6); 138 (8.8); 139 (29.6); 140 (26.8); 142 (22.8); 152 (14.3); 153 (11.2); 154 (17.6); 155 (15.0);

TABLE 1. 2-(4-Pyridyl)indole Derivatives

Compound	mp,[a] °C	pK_a	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Found, %				Empirical formula	Calc., %				Yield, %
					C	H	Hal	N		C	H	Hal	N	
Ib	215—217	—	—	207 (4,65) 255 (4,07) 392 (4,46)	51,6	4,4	36,5	8,0	$C_{15}H_{15}IN_2$	51,4	4,3	36,3	8,0	69
Ic	242—243	—	—	205 (4,61) 254 (4,17) 397 (4,36)	53,0	4,4	35,1	7,9	$C_{16}H_{17}IN_2$	52,8	4,7	34,8	7,8	82
Id	162—164	—	—	207 (4,73) 255 (4,24) 395 (3,61)	56,9	6,2	57,1	6,6	$C_{20}H_{25}IN_2$	57,1	6,0	30,2	6,7	72
Ie	293—294	—	—	204 (4,58) 229 (4,34) 255 (4,11) 395 (4,61)	64,0	3,9	20,6	7,2	$C_{21}H_{16}BrN_2O$	64,3	4,1	20,4	7,1	63
If	268—269	—	—	206 (4,56) 217 (4,58) 246 (4,18) 333 (4,39) 396 (4,60)	52,6	4,6	34,9	7,9	$C_{16}H_{17}IN_2$	58,2	4,7	34,8	7,7	46
IIc	215—216	9,9	1600 (C=C) 1650 (C=N)	223 (4,05) 253 (3,93) 395 (4,22)	81,4	6,5	—	11,7	$C_{16}H_{16}N_2$	81,3	6,8	—	11,9	90
IId	246—247	10,0	1620 (C=C) 1645 (C=N)	223 (4,19) 254 (3,84) 396 (3,96)	82,3	3,1	—	9,9	$C_{20}H_{24}N_2$	82,2	3,2	—	9,6	89
IIIb	298—300	—	—	206 (4,54) 253 (4,01) 380 (4,01)	45,4	3,0	43,2	7,8	$C_{14}H_{12}BrN_2$	45,6	3,3	43,5	7,6	89
IVb	294—295	9,0	1600 (C=C) 1648 (C=N)	223 (4,29) 253 (3,98) 408 (4,22)	58,3	3,9	28,1	10,0	$C_{14}H_{11}BrN_2$	58,5	3,8	27,9	9,8	88
Vb	212—213	—	1650 (C=N) 1760 (C=O) 2260 (C≡N)	224 (4,18) 254 (3,90) 392 (4,21)	70,8	5,7	—	13,2	$C_{19}H_{19}N_3O_2$	71,0	5,9	—	13,1	48
Vc	265—266	—	1645 (C=N) 1740 (C=O) 3480 (NH)	212 (3,78) 255 (3,90) 390 (4,15)	68,2	6,3	—	7,4	$C_{21}H_{24}N_2O_4$	68,5	6,5	—	7,6	75

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[a] From methanol.

156 (15.7); 164 (15.5); 165 (12.8); 166 (28.6); 167 (23.0); 192 (23.8); 193 (27.7); 194 (79.3); 195 (18.1); 205 (20.9); 206 (33.8); 207 (23.3); 208 (32.4); 209 (34.2); 210 (7.5); 212 (6.5); 221 (11.6); 222 (18.7); 223 (49.6); 224 (12.7); 237 (5.1); 239 (100.0); 240 (15.4); 253 (97.2); 254 (16.5); $W_M = 5.6$. Found: C 66.7; H 4.3; N 16.6%. $C_{14}H_{11}N_3O_2$. Calculated: C 66.4; H 4.0; N 16.6%.

1-Methyl-2-nitromethyl-4-(2-indolyl)-1,2-dihydropyridine (Va). A mixture of 2.1 g (0.01 mole) of 1-methyl-4-(2-indolenylidene)-1,4-dihydropyridine, 1.2 g (0.02 mole) of nitromethane, and 1 ml of triethylamine in 15 ml of dry acetonitrile was refluxed for 1 h, after which it was cooled and treated with ether. The precipitate was removed by filtration and recrystallized from nitromethane to give 2.5 g (90%) of a product with mp 244-245°C. IR spectrum: 1372 (NO_2) and 3490 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 210 (4.12), 248 (4.00), 338 (3.88), and 391 nm (3.90). Found: C 67.0; H 5.9; N 15.9%. $C_{15}H_{15}N_3O_2$. Calculated: C 66.9; H 5.6; N 15.6%.

Other 2-(4-pyridyl)indole derivatives, the principal characteristics of which are presented in Table 1, were also obtained by similar methods.

LITERATURE CITED

1. A. K. Sheinkman, B. P. Zemskii, T. V. Stupnikova, Yu. B. Vysotskii, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 11, 1477 (1978).
2. T. V. Stupnikova, B. P. Zemskii, Yu. B. Vysotskii, R. S. Sagitullin, and Kh. Ya. Lopatinskaya, Khim. Geterotsikl. Soedin., No. 7, 959 (1980).
3. N. A. Klyuev, T. V. Stupnikova, S. N. Barangov, and P. B. Kurapov, Dokl. Akad. Nauk Ukr. SSR, Ser. B, No. 9, 46 (1980).
4. T. V. Stupnikova, Kh. Ya. Lopatinskaya, B. P. Zemskii, Yu. B. Vysotskii, and R. S. Sagitullin, Khim. Geterotsikl. Soedin., No. 10, 1365 (1980).
5. T. V. Stupnikova, V. N. Kalafat, N. A. Klyuev, V. P. Marshtupa, and R. S. Sagitullin, Khim. Geterotsikl. Soedin., No. 10, 1360 (1980).
6. T. V. Stupnikova, L. A. Rybenko, A. N. Kost, R. S. Sagitullin, A. I. Kolodin, and V. P. Marshtupa, Khim. Geterotsikl. Soedin., No. 6, 761 (1980).
7. A. P. Gray and W. L. Archer, J. Am. Chem. Soc., 79, 3554 (1957).
8. P. B. Terent'ev, Mass Spectroscopy in Organic Chemistry [in Russian], Vysshaya Shkola, Moscow (1979).
9. N. A. Klyuev, A. K. Sheinkman, R. A. Khmel'nitskii, G. A. Mal'tseva, and N. R. Kal'nitskii, Zh. Org. Khim., No. 13, 1079 (1977).
10. N. A. Klyuev, R. A. Khmel'nitskii, G. A. Mal'tseva, V. A. Ivanov, and B. M. Zolotarev, Khim. Geterotsikl. Soedin., No. 7, 979 (1978).
11. A. A. Polyakov and R. A. Khmel'nitskii, Mass Spectrometry in Organic Chemistry [in Russian], Khimiya, Leningrad (1972).
12. M. M. El'chaninov, A. M. Simonov, and L. Ya. Oleinikova, Khim. Geterotsikl. Soedin., No. 1, 71 (1980).
13. G. V. Boyd and A. D. Ezekiel, J. Chem. Soc., No. 7, 1866 (1967).
14. W. I. Fanschawa, V. Baner, S. R. Safir, D. A. Blichens, and S. I. Riggi, J. Med. Chem., 13, 933 (1970).