CHEMICAL REACTIONS OF 4,5,6,7-TETRAHYDRO-4,5,7-TRIMETHYLPYRROLO[3,2-*c*]PYRIDINE AND ITS 2-FORMYL DERIVATIVE

A. V. Varlamov, T. N. Borisova, A. É. Aliev, I. A. Stazharova, A. A. Sinitsyna, and E. A. Sakhnova

N-Alkyl substituted tetrahydropyrrolo[3,2-c]pyridines have been obtained by alkylation of 4,5,6,7-tetrahydro-4,-5, 7-trimethylpyrrolo[3,2-c]pyridine and its 2-formyl derivative chloroalkyldimethylamines, acrylonitrile, methyl acetylenedicarboxylate and dichloroethane. 2-Formyl substituted tetrahydropyrrolo[3,2-c]pyridine has been reduced with sodium borohydride and condensed with monoethanolamine and hydroxylamine. The stereochemistry of the products has been studied by ^1H NMR spectroscopy.

Because they are difficult to prepare tetrahydropyrrolo[3,2 -*c*]pyridines have remained practically unstudied until recently. These compounds are of interest as potential biologically active compounds and as starting materials for the synthesis of pyrrole containing polycyclic systems, similar to natural materials. Among the few tetrahydropyrrolo[3,2-*c*]pyridines described in the literature there are substances with antispasmodic and hypotensive properties which show activity in the treatment of thrombosis [1].

A new method we developed for the preparation of tetrahydropyrrolo[3,2-*c*]pyridines based on the heterocyclization of piperidin-4-one oximes with acetylene under the conditions of the Trofimov reaction [2, 3] has made these compounds readily available and has permitted a systematic study of their chemical reactions and stereochemistry to be started [4, 5].

The present paper is concerned with the N-alkylation of the tetrahydropyrrolo[3,2-*c*]pyridine I with methyl groups at $C_{(4)}$ and $C_{(7)}$ in *trans*-diequatorial configuration and of the 2-formyl derivative II, and also reactions of the latter at the formyl group. These syntheses permit the introduction pharmacophoric groups at the pyrrolyl nitrogen atom and at position 2 of tetrahydropyrrolo[3,2-*c*]pyridine.

2-Formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (II) was made by the Vilsmeier–Haack reaction as described previously [2]. The yield of compound II was increased to 90% by use of absolute DMF and freshly distilled phosphorus oxychloride.

β-Chloroethyl- and γ-chloropropyldimethylammonium hydrochlorides, dichloroethane, acrylonitrile, and methyl acetylenedicarboxylate were used as alkylating agents for the N-alkylation of compounds I and II.

I, II — III–IX

I, III, IV, VIII R = H; II, V—VII, IX R = CHO; III, V $R^1 = (CH_2)_2N(CH_3)_2$; IV, VI $R^1 = =(CH_2)_3N(CH_3)_2$; VII $R^1 = CH_2CH_2Cl$; VIII $R^1 = CH_2CH_2CN$; IX $R^1 = C(CO_2CH_3) = CH(CO_2CH_3)$

Alkylation of compounds I and II with chloroalkyldimethylamines and dichloroethane were carried out by interphase catalysis in benzene in presence of tetrabutylammonium iodide and 50% aqueous sodium hydroxide, while alkylations with acrylonitrile and methyl acetylenedicarboxylate were carried out under Michael conditions in presence of Triton B and sodium hydride respectively. The N-alkyl tetrahydropyrrolo[3,2-*c*]pyridines III-IX are sticky yellow oils which rapidly darken in air.

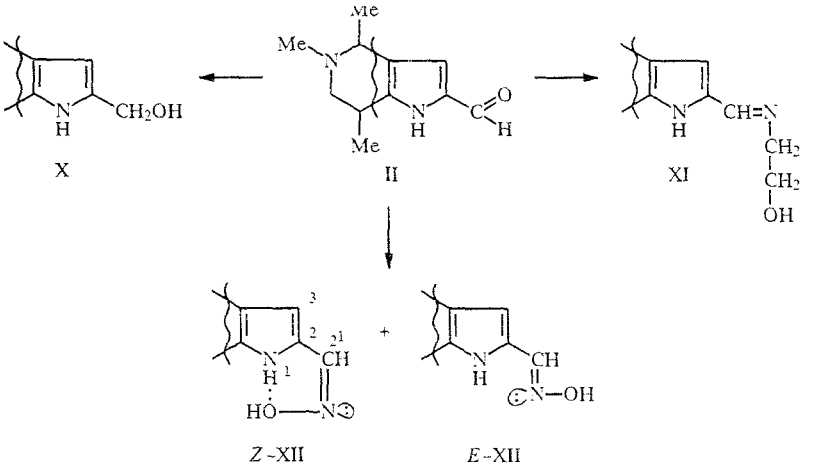
Russian Foreign Student University, Moscow 117198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 681-687, May, 1993. Original article submitted February 3, 1993.

 0009-3122/93/2905-0582$12.50

The 2-formyl compound II is more active in alkylation reactions than I since the pyrrole hydrogen is more acidic because of the electron-accepting effect of the formyl group. Alkylation under interphase catalysis conditions was accompanied by oxidations and polymerization so that yields did not exceed 50-60% as a rule.

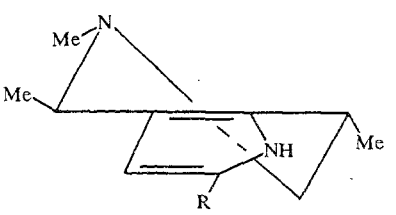
Synthetic conversions of the formyl group in compound II permit the preparation of tetrahydropyrrolo[3,2-*c*]pyridines with hydroxy- and iminomethyl groups in position 2. These compounds are interesting for later conversion into more complex substances. With this in mind, the reduction of compound II with sodium borohydride and its condensation with monoethanolamine and hydroxylamine have been carried out. The 2-hydroxymethyl derivative X was obtained in 84% yield.

The Schiff base XI was formed as light yellow crystals in 92% yield on boiling compound II with monoethanolamine in absolute toluene. Compound XI appears to be very sensitive to moisture. Oxime XII was obtained in 75% yield by the condensation of compound II with hydroxylamine hydrochloride in the presence of sodium acetate. In contrast to the azomethine XI, the oxime XII is formed as a 1:7 mixture of the *Z*- and *E*-isomers according to the ^{1}H NMR spectra (Table 1). The configurations of the geometric isomers of oxime XII are assigned on the basis of the size of the chemical shift of the azomethine proton, 2′-H, which depends on the position of the proton relative to the unshared pair of electrons of the azomethine nitrogen. When these are in the *cis*-configuration the azomethine proton undergoes a weak field shift [6]. Consequently the isomer with the weaker field 2′-H signal was assigned the *Z*-configuration, and the isomer with the stronger field signal for this proton was assigned the *E*-configuration.



The results on the isomer composition of oxime XII permit the prediction that the Schiff base XI is formed as the *E*-isomer.

The structures of the substituted tetrahydropyrrolo[3,2-*c*]pyridines III-XII were confirmed by ^{1}H NMR spectroscopy (Tables 1-3) and mass spectroscopy (Table 4). It was shown previously that tetrahydropyridyl unit in tetrahydropyrrolo[3,2-*c*]pyridines has the half—chair conformation [5]. In that study the conformational equilibria of isomers of compound I with *cis*- and *trans*-configurations of the methyl groups at $C_{(4)}$ and $C_{(7)}$ and also of N-vinyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine and its 2- and 3-nitro derivatives, which have the 4-CH_3 and 7-CH_3 groups in the *cis*-configuration, have been studied. In agreement with the results of that work the large values of the *trans*-vicinal coupling constant $^3J_{6a7a}$ in the ^{1}H NMR spectra of compounds X-XII indicate that they are conformationally pure. Hence compounds X-XII exist essentially as single conformers with the *trans*-diequatorial orientation of the methyl groups in positions $C_{(4)}$ and $C_{(7)}$.



X-XII

R = CH_2OH, $CH{=}NCH_2CH_2OH$; $CH{=}NOH$

TABLE 1. Proton Chemical Shifts in the ^1H NMR Spectra of the Tetrahydropyrrolo[3,2-*c*]pyridines III-XII

Compound	δ, ppm									Substituent at position 1	Substituent at position 2
	2-H	3-H	4-H	6*a*-H	6*e*-H	7-H	4-CH_3	5-CH_3	7-CH_3		
III	6,51	5,89	3,29	2,24	2,99	3,06	1,23	2,39	1,26	2,26 NMe_2 2,61...3,95 $(CH_2)_2$	—
IV	6,50	5,89	3,29	2,22	2,99	3,05	1,23	2,40	1,28	2,20 NMe_2 1,88...3,91 $(CH_2)_3$	—
V	—	6,67	3,42	2,28	3,04	3,06	1,25	2,40	1,31	2,31 NMe_2 2,52...4,48 $(CH_2)_2$	9,37 CHO
VI	—	6,67	3,42	2,29	3,04	3,07	1,26	2,40	1,30	2,24 NMe_2 1,81...4,32 $(CH_2)_3$	9,37 CHO
VII*	—	6,86	5,13	3,95	4,69	3,68	1,72	3,01 3,69	1,50	4,29, 5,01 NCH_2 3,84 CH_2Cl	9,51 CHO
VIII	6,54	5,94	3,31	2,25	3,00	3,03	1,22	2,39	1,25	4,17, 4,09 NCH_2 2,7 CH_2CN	—
IX	—	6,80	3,47	2,33	3,01	2,87	1,04	2,41	1,34	3,64, 3,84 OCH_3 7,05 =CH	9,36 CHO
X	—	5,85	3,16	2,22	2,96	3,09	1,15	2,42	1,33	**	1,76 OH 4,57 CH_2
XI	—	6,10	3,13	2,22	2,99	3,11	1,20	2,43	1,34	**	3,59 NCH_2, 3,90 OCH_2 7,76 CH=N
XII *Z*	—	6,12	3,25	2,27	3,04	3,18	1,17	2,46	1,37	**	7,90 CH=N, 8,98 OH
XII *E*	—	6,20	3,25	2,27	3,05	3,18	1,17	2,47	1,39		7,18 CH=N, 9,77 OH

*Spectrum of the iodomethylate.

**Not measured successfully.

TABLE 2. Spin–Spin Coupling Constants in the ^1H NMR Spectra of the Tetrahydropyrrolo[3,2-*c*]pyridines III-XII

Compound	Coupling constant, Hz							
	4,4-CH_3	7,7-CH_3	6*a*,6*e*	6*a*,7*a*	6*e*,7*a*	4,7	2,3	1,3
III	6,6	6,7	-11,6	8,2	5,5	1,2	3,0	—
IV	6,6	6,4	-11,4	8,4	5,5	1,7	3,0	—
V	6,6	6,6	-11,5	7,0	5,5	1,1	—	—
VI	6,6	6,7	-11,7	6,5	5,5	1,2	—	—
VII	6,6	6,6	-12,8	11,6	7,02		—	—
VIII	6,6	6,4	-13,28	9,8	5,5	1,5	3,0	—
IX	6,3	6,7	-11,8	9,7	5,7	1,5	—	**
X	6,4	6,7	-11,4	10,2	5,3	2,1	—	2,4
XI*	6,3	7,0	-11,6	10,4	5,3	1,4	—	**
XII	6,4	6,7	-11,6	10,4	5,6		—	2,0

*$^4J_{(H2'NCH_2)}$ = 1 Hz.

**Not measured successfully.

TABLE 3. Data on the Conformational Composition of Compounds III-VI, VIII, and IX ($CDCl_3$)

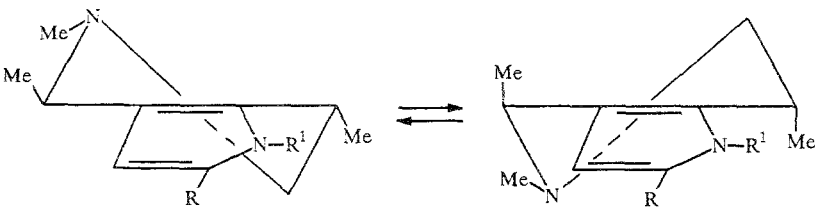
Compound	Conformer populations, %		Compound	Conformer populations, %	
	4e, 7e	4a, 7a		4e, 7e	4a, 7a
III	45	55	VI	40	60
IV	45	55	VIII	44	56
V	40	60	IX	47	53

TABLE 4. Mass Spectral Data for the Tetrahydropyrrolo[3,2-*c*]pyridines III-XII

Compound	m/z (I_{rel}, %)
III	58 (100), 72 (74), 134 (12), 147 (10), 148 (12), 163 (11), 177 (4), 192 (4), 220 (74), 235 (22) M^+
IV	58 (100), 86 (59), 120 (21), 135 (33), 148 (8), 149 (9), 163 (13), 177 (6), 206 (5), 234 (65), 249 (23) M^+
V	58 (100), 72 (26), 149 (20), 177 (11), 191 (7), 192 (2), 220 (2), 248 (15), 263 (24) M^+
VI	58 (100), 86 (54), 148 (16), 149 (7), 191 (58), 206 (7), 234 (6), 262 (52), 277 (25) M^+
VII	149 (5), 176 (8), 211/213 (10), 239/241 (100), 254*/256 (5) M^+
VIII	149 (100), 164 (4), 174 (12), 175 (7), 202 (69), 216 (3), 217 (4) M^+
IX	118 (51), 134 (51), 136 (49), 151 (99), 161 (100), 179 (96), 194 (13) M^+
XI	161 (10), 172 (4), 185 (4), 190 (4), 192 (34), 220 (100), 235 (33) M^+
XII	131 (13), 146 (7), 147 (10), 149 (58), 158 (20), 164 (99), 175 (35), 192 (100), 207 (38) M^+

*Relative intensities are calculated for the peaks corresponding to the ^{35}Cl isotope.

As the values of the *cis*- and *trans*-coupling constants $^3J_{6,7}$ show (Table 2) conformational equilibria exist for compounds III-VI, VIII and IX.



trans -(4e, 7e) trans -(4a, 7a)

Using previous results [7] the conformer population in compounds in compounds III-VI, VIII, and IX has been estimated by the method of averaged parameters (Table 3). The reason for the conformational heterogeneity of these compounds is the steric interaction between the methyl group at $C_{(7)}$ and the substituent on the pyrrole nitrogen.

Molecular ion peaks corresponding to the empirical formulas were observed in the mass spectra of compounds III-VIII, and X-XII. Fragmentation of the M^+ ions of these compounds is characterized by both the normal decomposition pathways for the scission of the tetrahydropyrrolopyridine system [8] and specific pathways connected with decomposition of substituents at positions 1 and 2. The general decomposition pathways are associated with hydrogen or methyl from position 4 and retrodiene decomposition which explain the fragment ions $[M - H]^+$, $[M - CH_3]^+$ and $[M - CH_2{=}N{-}CH_3]^+$. The intensity of the last peak is 2-12% in the mass spectra of N-alkyl-substituted compounds as a result of other more energetically favorable decomposition pathways. The appearance of intense fragment ions $CH_2{=}N^+$ 58, $CH_2{=}CH{-}NH(CH_3)_2^+$ 72 and $CH_2{=}CH{-}CH_2N(CH_3)_2^+$ 86 is connected with scission of the dimethylaminoalkyl radical in the dissociation of compounds III-VI (here and below *m/z* values are given for the ion peaks). Elimination of CO during dissociation of compounds V and VI as a second stage of decomposition from the $[M - CH_2{=}N{-}CH_3]^+$ ion. Elimination of $CH_2{=}CHCl$ from the same ion occurs during fragmentation of the β-chloroethyl-substituted compound VII. Decomposition of the β-cyanoethyl radical explains the appearance of fragment ions $[M - CH_2{=}CH{-}CN]^+$ 164 and $[M - CH_3 - HCN]^+$ 175 in the mass spectrum of compound

VIII. Elimination of particles associated with decomposition of substituents during dissociative ionization of the 2-substituted tetrahydropyrrolopyridines X-XII is basically observed in successive decomposition stages of $[M - CH_3]^+$, $[M - CH_2{=}N{-}CH_3]^+$ and $[M - CH_2{=}N{-}CH{-}CH_3]^+$ ions. The Schiff base is an exception in which the CH_2CH_2OH particle is eliminated by α-elimination from the M^+ ion. In the case of compounds X and XII water or hydroxyl units are eliminated from the ions mentioned above, or CH_2CH_2OH (α-scission) and CH_2OH (β-scission) in the case of compound XI.

EXPERIMENTAL

^1H NMR spectra were recorded with a Bruker WM-400 spectrometer. Mass spectra were recorded with MX-1303 and Kratos MS 2SRF instruments with direct insertion of samples into the ion source and an ionizing voltage of 70 eV. IR spectra of KBr disks were recorded with a Zeiss UR-20 spectrometer. Column chromatography used Brockman aluminum oxide of activity 2 and L40/100 grade silica gel (Czechoslovakia). Aluminum oxide (Alufol) and silica gel (Silufol UV-254) strips were used for thin layer chromatography.

Elemental analysis results agreed with calculated values.

Alkylation of 4,5,6,7-tetrahydro-4,5,7-trimethyl- and 2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridines with Alkyl Halides. Sodium hydroxide (5 ml, 50% aqueous) was added to a solution of compound I or II (3 mmole), tetrabutylammonium iodide (3 mmole) and the alkylating agent (3.1 mmole) in benzene (50 ml) at 0°C. The mixture was boiled for 24 h (TLC monitoring). Water (50 ml) was added, the benzene layer was separated, and the water was extracted with benzene (3 × 15 ml). The combined extracts were dried with magnesium sulfate. The brownish oily residue which remained after solvent removal was purified by boiling with activated charcoal in a mixture of heptane and ethyl acetate. The alkylation products III-VII were obtained as yellow oils. Dichloroethane was used as the solvent in the synthesis of the N-(β-chloroethyl) substituted compound VII.

1-(β-Dimethylaminoethyl)-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (III, $C_{14}H_{25}N_3$). Yield 62%, R_f 0.11 (Silufol, ammonia–propanol-2 1:30).

1-(γ-Dimethylaminopropyl)-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (IV, $C_{15}H_{27}N_3$). Yield 88%, R_f 0.4 (Silufol, ammonia–propanol-2 1:20). M^+ 249.

1-(β-Dimethylaminoethyl)-2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (V, $C_{15}H_{25}N_3O$). Yield 42%, R_f 0.27 (Silufol, ammonia–propanol-2 1:20). IR spectrum: 1660 cm^{-1} (C=O).

1-(γ-Dimethylaminopropyl)-2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (VI, $C_{16}H_{27}N_3O$). Yield 50%, R_f 0.11 (Silufol, ammonia–propanol-2 1:10). IR spectrum: 1655 cm^{-1} (C=O). M^+ 277.

1-(β-Chloroethyl)-2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (VII, $C_{13}H_{19}ClN_2O$). Yield 20%, R_f 0.82 (Alufol, ethyl acetate). IR spectrum: 1658 cm^{-1} (C=O). Found: M^+ 254/256. Calc. (for ^{35}Cl isotope): M 254. Iodomethylate: yellow crystals, m.p. 155°C (dec.) from an acetone and ether mixture.

1-(β-Cyanoethyl)-4,5,6,7-tetrahydro-2-formyl-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (VIII, $C_{13}H_{18}N_3$). Triton B (0.05 ml) and acrylonitrile (6.36 g, 0.12 mmole) were added consecutively to a solution of compound I (0.5 g, 3 mmol) in dioxane (10 ml). The mixture was boiled for 5 h, poured into water (30 ml), and extracted with ether (4 × 25 ml). The ether extract was dried over magnesium sulfate and the ether removed. The residue (0.7 g) was chromatographed on an alumina column (h = 40 cm, d = 1.5 cm) with ethyl acetate as eluent to give compound VIII as a yellow oil (yield 0.22 g, 33%), R_f 0.75 (Alufol). Found: M^+ 217. Calculated: M 217. Iodomethylate: yellow crystals, m.p. 211-212°C (dec.) from an acetone and ether mixture.

1-(1′,2′-Dimethoxycarbonylvinyl)-2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (IX, $C_{17}H_{22}N_2O_5$). Sodium hydride (0.02 g, 0.8 mmole) was added to a solution of compound II (0.13 g, 0.7 mmole) and dimethyl acetylenedicarboxylate (0.2 g, 1.4 mmole) in absolute methylene chloride (15 ml). The mixture was boiled for 8 h, water added (10 ml), and the mixture extracted with methylene chloride. The extract was dried over magnesium sulfate, the solvent removed and the residue (0.22 g) was chromatographed on an alumina column (h = 30 cm, d = 1.5 cm). Compound IX was eluted with hexane as a yellow oil (yield 0.12 g, 50%), R_f 0.64 (Alufol, ethyl acetate). IR spectrum: 1660 (CHO), 1740 cm^{-1} ($COOCH_3$). $[M - CH_3]^+$ 319.

2-Hydroxymethyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (X, $C_{11}H_{18}N_2O$). Sodium borohydride (0.15 g, 4 mmole) was added to a solution of compound II (0.2 g, 1 mmole) in ethanol (10 ml) at 20°C. After 3 h the ethanol was removed in vacuum, water (15 ml) was added, the mixture was extracted with chloroform (3 × 40 ml), the chloroform

extract was dried over magnesium sulfate. The residue after removal of chloroform was crystallized from ethyl acetate to give white crystals of compound X (yield 0.17 g, 84%), m.p. 150-151°C, R_f 0.47 (Silufol, ammonia–propanol-2, 1:5). IR spectrum: 3220 and 3190 cm^{-1} (hydrogen bonded NH and OH). M^+ 194.

2-[N-(β-Hydroxyethyl)aminoethyl]-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine (XI, $C_{13}H_{21}N_3O$). A solution of compound II (1.5 g, 7.8 mmole) and monoethanolamine (0.5 g, 8 mmole) in absolute toluene (20 ml) was refluxed for 4 h with a Dean and Stark head. The solution was cooled and yellow crystals of compound XI were filtered off (1.67 g, 92%), m.p. 145-146°C (from a heptane and ethyl acetate mixture). R_f 0.56 (Silufol, ammonia–propanol-2, 1:20). IR spectrum: 3245 (hydrogen bonded NH and OH), 1650 cm^{-1} (C=N). M^+ 235.

2-Hydroxyiminomethyl-4,5,6,7-tetrahydro-4,5,7,-trimethylpyrrolo[3,2-*c*]pyridine (XII, $C_{11}H_{17}N_3O$). Compound II (1 g, 5 mmole), hydroxylamine hydrochloride (0.73 g, 10 mmole) and sodium acetate (2.04 g, 15 mmole) were boiled in ethanol (20 ml) for 5 h. The ethanol was removed, water (20 ml) was added, and the mixture was extracted with chloroform (3 × 50 ml). The chloroform extracts were dried with magnesium sulfate and the solvent removed to give white crystals of the oxime XII (yield 0.72 g, 75%), m.p. 179-180°C (from a mixture of heptane and ethyl acetate), R_f 0.7 (Silufol, ammonia–propanol-2, 1:20). IR spectrum: 3440, 3320, 3180 and 2750 (hydrogen bonded NH and OH), 1655 (C=N), and 910 cm^{-1} (N-O). M^+ 207.

REFERENCES

1. U.S.Pat. 3 992 544 (J. L. Archibald and K. Heatherington), C.A., **86**, 140015 (1977).
2. T. N. Borisova, A. V. Varlamov, N. D. Sergeeva, A. T. Soldatenkov, V. P. Zvolinskii, A. A. Astakhov, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.*, No. 7, 973 (1987).
3. T. N. Borisova, A. V. Varlamov and N. S. Prostakov, Abstr. First All-Union Conference on the Chemistry, *Biochemistry and Pharmacology of Indole Derivatives* [in Russian], Tbilisi (1986), p. 39.
4. T. N. Borisova, I. A. Stazharova, A. É. Aliev, N. S. Prostakov, and A. V. Varlamov, *Khim. Geterotsikl. Soedin.*, No. 10, 1375 (1991).
5. A. É. Aliev, A. A. Sinitsyna, T. N. Borisova, I. A. Stazharova, N. S. Prostakov, and A. V. Varlamov, *Khim. Geterotsikl. Soedin.*, No. 1, 75 (1993).
6. A. É. Aliev, *Candidate of Chemical Science Thesis*, Moscow (1988), p. 144.
7. U. Burkert and N. Allinger, *Molecular Mechanics* [Russian translation], Mir, Moscow (1986), p. 364.
8. E. E. Stashenko, P. I. Zakharov, T. N. Borisova, B. S. Subbotin, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.*, No. 2, 212 (1988).