PURINES, PYRIMIDINES AND CONDENSED SYSTEMS BASED ON THEM. 10.* REACTIVITY OF 1,3-DIMETHYL-6-CHLOROLUMAZINE WITH RESPECT TO AMINES: COMPETITION OF AMINODECHLORINATION AND AMINODEHYDROGENATION REACTIONS

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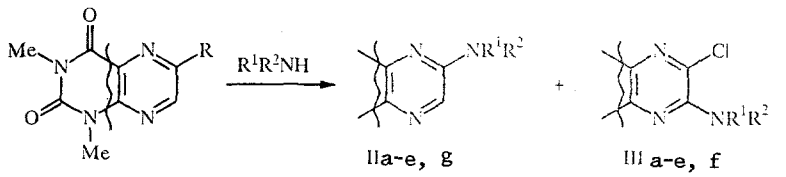
1,3-Dimethyl-6-chlorolumazine reacts with secondary alkylamines and hydrazine to form 1,3-dimethyl-6-amino(hydrazino) derivatives in good yields. At the same time, 6-chloro-7-amino-1,3-dimethyllumazines are formed by the action of primary amines and liquid ammonia, in addition to the nucleophilic substitution products of chlorine.

It has recently been shown that through the action of alkylamines on 1,3-dimethyllumazine (Ia) in the presence of an oxidizing agent, a nucleophilic substitution of hydrogen takes place at the 7-position, leading to the formation of 7-alkylaminolumazines in moderate yield [2]. It was of interest to carry out an intramolecular variant of this reaction. For this purpose, we tried in the present work to synthesize 6-(2-aminoethylamino)-1,3-dimethyl lumazine (IIa) in order, as a result of a subsequent cyclization to convert to compound VII. As the starting compound, 1,3-dimethyl-6-chlorolumazine (Ib) was used [3].



Ia R = H, Ib R = Cl; IIa IIIa NR^1R^2 = $HNCH_2CH_2NH_2$; Ib, IIIb NR^1R^2 = $HNCH_2CH_2OH$; IIc IIIc NR^1R^2 = HNC_2H_5; IId NR^1R^2 = piperidino IIe NR^1R^2 = morpholino IIIf NR^1R^2 = NH_2; IIg NR^1R^2 = $NHNH_2$

It was found that in the course of a brief interaction of compound Ib with an excess of freshly distilled ethylenediamine at room temperature, two compounds are formed. One of them (yield 30%) does not contain chlorine, and in its PMR spectrum there is a singlet of the aromatic proton in the region of ~8 ppm. This compound has a yellow color characteristic of 6-aminolumazines, and thus, it is the expected substitution product IIa. The second, a colorless compound, contains chlorine, and there are not signals of aromatic protons in its PMR spectrum. Judging from these and all the other data, including the

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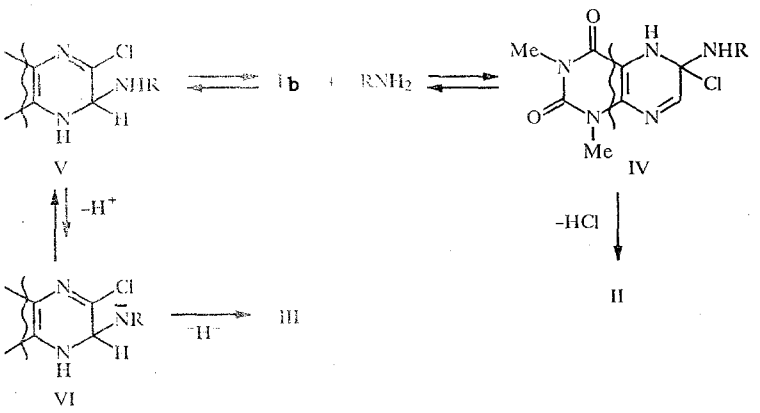
mass spectrum, this compound is a product of a nucleophilic substitution of hydrogen at the 7-position by an ethylenediamine residue – IIIa. Its yield was 38%. In a similar way, cholorolumazine Ib reacts with ethanolamine (ratio IIb: IIIb – 35 and 23%) and ethylamine (IIc:IIIc – 41 and 36%). Because of the volatility of ethylamine, the latter reaction was carried out at room temperature in a sealed ampule. When it was carried out in a flask at −15 to −10°C, the ratio of the reaction products changed sharply in favor of the aminodechlorination product (IIc:IIIc – 51 and 14%).

Somewhat odd in this series is the behavior of liquid ammonia. When compound Ib is treated with it at −70 to −65°C without the use of a special oxidizing agent, only 7-amino-6-chloro-1,3-dimethyllumazine (IIIf) is obtained (yield 20%). The product of aminodechlorination was not observed in the reaction mixture, and about 44% of the starting compound was regenerated.

In contrast to ammonia and primary alkylamines, secondary alkylamines react with compound Ib to give only the substitution of chlorine. Thus, a brief stirring of Ib with an excess of piperidine and morpholine leads to the formation of 6-amino derivatives IId and IIe in a yield of 83 and 47%, respectively. The formation of 6-dimethylamino- and 6-hydrazino derivatives by the action of dimethylamine in alcohol and hydrazine hydrate on Ib has been reported previously in [3].

The data of the quantum mechanical calculation (the MOX method) show that in the Ib molecule, as also in Ia [2], the positive π-charge on the $C_{(7)}$ atom (+0.118) is substantially higher than on $C_{(6)}$ (+0.068). It is therefore logical to assume that under kinetically controlled conditions, the σ-complex V will form more easily than the geminal σ-complex IV. It is probable that this is one of the main reasons for the fact that at low temperature (liquid ammonia), the product of the aminodechlorination is practically not formed, although the formation reaction of amine IIIf also proceeds slowly. With increase in the temperature of the mixture, the equilibrium concentration of the σ-complex IV should increase, and since it undoubtedly aromatizes more readily than V (the chloride ion as a leaving group is superior to the hydride ion), the proportion of compound II in the reaction mixture becomes significant. The temperature changes, of course, cannot be the only factor controlling the ratio of products II and III. A noteworthy example is the very difficulty explainable fact that in the reaction of compound Ib with ethylamine, the yield of amine IIIc decreases by a factor of three with decrease from room temperature to −15 to −10°C, while the yield of compound IIc even increases somewhat.



It is also noteworthy that in the case of secondary amines, the aminodehydrogenation product III is never obtained. We offer an explanation that for splitting off the hydride ion from the σ-complex V, an additional ionization of the N−H bond in the nucleophile participating in the addition is necessary, i.e., the formation of an anionic σ-complex VI. It is clear that this is only possible in the case of primary amines. Proofs for the participation of similar anionic σ-complexes in the Chichibabin reaction are given in the literature [4, 5].

The competition of the aminodehalogenation reactions and the Chichibabin reaction or even a complete predominance of the latter has been described for 2-chloropteridine [6], 3-bromo-4-dimethylaminopyridine [7], 1-methyl-2-nitro-4-bromoimidazole [8] and bromonaphthyridines [9]. An unusual fact for chlorolumazine Ib is that the Chichibabin reaction proceeds not with the anionic but neutral nucleophiles and does not require an external oxidizing agent. It is clear that the role of the hydrode ion acceptor is played in this case by the atmospheric oxygen.

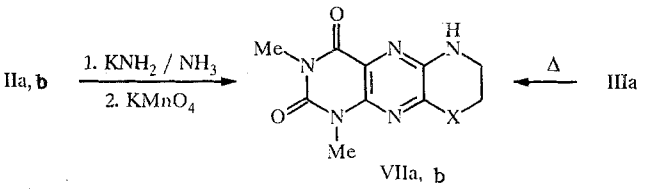
Unfortunately, we did not succeed in carrying out an intramolecular amination of compounds IIa,b. In their reaction with potassium amide in liquid ammonia (to increase the nucleophilicity of the terminal NH_2 and OH groups, they must be

TABLE 1. Physicochemical Characteristics of the Obtained Compounds

Compound	IR spectrum (mineral oil), cm^{-1}	PMR spectrum, δ, ppm	Mass spectrum, m/z (1 > 10%), amu*
Ib		in DMSO-D_6: 3,33 (3H,s, $N_{(3)}$–CH_3), 3,54 (3H,s, $N_{(1)}$–CH_3), 8,91 (1H, s, 7-H)	$[M+2]^+$ 228 (33), $[M+1]^+$ 227 (10), $[M]^+$ 226 (100), 197 (14), 171 (10), 170 (10), $[M-CH_3NCO]^+$ 169 (23), 143 (28), $[M-CH_3NCO-CO]^+$ 141 (75), 116 (20), $[M-CH_3NCO-CO-HCN]^+$ 114 (54), 113 (23)
IIa	1655, 1700 (C=O); 3250, 3360 (NH_2)	B $CDCl_3$: 3,00 (2H,t, J = 5,9 Hz, $C\underline{H}_2NH_2$), 3,51 (3H,s, $N_{(3)}$–CH_3), 3,57 (2H, t, J = 5,9 Hz, $C\underline{H}_2NH$), 3,66 (3H,s, $N_{(1)}$–CH_3), 5,3...5,5 (m, NH, NH_2), 8,05 (1H,s, 7-H) in DMSO-D_6: 2,9 (2H, m, $C\underline{H}_2NH_2$), 3,29 (3H,s, $N_{(3)}$–CH_3), 3,3 (2H,m, $NHC\underline{H}_2$), 3,49 (2H,s, $N_{(1)}$–CH_3), 7,26 (m, NH & NH_2), 8,17 (1H,s, 7-H)	$[M]^+$ 250 (16), $[M-CHO]^+$ 221 (100), 220 (48), $[M-CH_2CH_2NH]^+$ 207 (10), $[M-CH_3NCO]^+$ 193 (54), 192 (15), 107 (12)
IIb	1660, 1693 (C=O); 3256 (NH), 3425 (OH)	in DMSO-D_6: 3,3 (3H,s, $N_{(3)}$–CH_3), 3,49 (3H, s, $N_{(1)}$–CH_3), 3,4 (2H,m, CH_2N), 3,3 (2H, m, CH_2O), 4,74 (1H,t, J = 5,2 Hz, OH), 7,24 (1H, br.t., J = 5,2 Hz NH), 8,20 (1H,s, 7-H)	M^+ 251 (25), $[M-CH_2O]^+$ 221 (60), $[M-CH_2OH]^+$ 220 (100), $[M-CH_2CH_2OH]^+$ 207 (13), $[M+2-NHCH_2CH_2OH]^+$ 193 (15), 197 (9)
IIc	1686, 1712 (C=O); 3349 (NH)	B $CDCl_3$: 1,3 (3H,t, J = 7,2 Hz, $CH_2C\underline{H}_3$), 3,3...3,6 (2H,m, $C\underline{H}_2CH_3$), 3,51 (3H,s $N_{(3)}$–CH_3), 3,66 (3H,s, $N_{(1)}$–CH_3), 4,9 (br.s NH), 8,01 (1H,s, 7-H) in DMSO-D_6: 1,18 (3H,t, J = 7,2 Hz, $CH_2C\underline{H}_3$), 3,2...3,4 (2H, m, CH_2N), 3,30 (3H, s, $N_{(3)}$–CH_3), 3,50 (3H,s, $N_{(1)}$–CH_3), 7,21 (1H, t, J = 5,1 Hz NH), 8,13 (1H,s., 7-H)	—
IIIa	1650, 1700 (C=O); 3050...3250 vm. c. ($NHNH_2$)	in DMSO-D_6: 2,80 (2H, t, J = 6,3 Hz, $C\underline{H}_2NH_2$), 3,25 (3H,s, $N_{(3)}$–CH_3), 3,46 (3H, s, $N_{(1)}$–CH_3), 3,48 (2H, t, J = 6,3 Hz $C\underline{H}_2NH$) in $CDCl_3$: 3,06 (2H, t, J = 5,7 Hz, $C\underline{H}_2NH_2$), 3,47 (3H,s, $N_{(3)}$–CH_3), 3,61 (3H, s, $N_{(1)}$–CH_3), 3,61 (2H, t, J = 5,7 Hz, $C\underline{H}_2NH$), 6,6...6,8 (m, NH, NH_2)	$[M+2]^+$ 286 (10), M^+ 284 (33), $[M-CHO]^+$ 257 (34), 256 (20), 255 (100), 254 (22), $[M-HCl]^+$ 248 (46), 242 (19), 241 (10), 226 (21), 220 (19), 191 (32), 107 (10)
IIIb	1653, 1706 (C=O); 3270, 3373 (NH)	in DMSO-D_6: 3,26 (3H, s, $N_{(3)}$–CH_3), 3,46 (3H,s, $N_{(1)}$–CH_3), 3,5 (2H,m, NCH_2), 3,6 (2H,m, OCH_2), 4,8 (1H,t, J = 5,6 Hz, OH), 8,03 (1H, br.t., J = 4,6 Hz, NH)	$[M+2]^+$ 287 (16), M^+ 285 (52), $[M-CHO]^+$ 256 (42), 255 (15), 254 (100), 236 (11), 226 (14), 220 (15), 197 (12), 169 (11), 161 (13), 129 (15), 107 (14)
IIIc	1660, 1712 (C=O); 3302 (NH)	in $CDCl_3$: 1,36 (3H, t, J = 7,2 Hz $CH_2C\underline{H}_3$), 3,5...3,7 (2H,m, $C\underline{H}_2CH_3$), 3,47 (3H,s, $N_{(3)}$–CH_3), 3,62 (3H,s, $N_{(1)}$–CH_3), 6,01 (1H,br.s, NH) in DMSO-D_6: 1,21 (3H, t J = 7,2 Hz, $CH_2C\underline{H}_3$), 3,4...3,6 (2H,m, $C\underline{H}_2CH_3$), 3,26 (3H, s, $N_{(3)}$–CH_3), 3,46 (3H, s, $N_{(1)}$–CH_3), 8,21 (1H, t, J = 5,2 Hz, NH)	—
IIIf	1652, 1719 (C=O); 3190, 3349 (NH_2)	in $CDCl_3$: 3,46 (3H,s, $N_{(3)}$–CH_3), 3,58 (3H, s, $N_{(1)}$–CH_3), 5,69 (br., NH_2) in DMSO-D_6: 3,25 (3H, s, $N_{(3)}$–CH_3), 3,44 (3H, s, $N_{(1)}$–CH_3), 7,97 (br., NH_2)	—

*Peaks with m/z < 100 amu are omitted.

ionized) and the subsequent oxidation with potassium permanganate (comp. [2, 9]), high-melting red-orange compounds were isolated, apparently having a salt-like structure, different from that of VII. This is indicated by the solubility of the compounds in alcohol and in water, their high melting points (>320°C) and the presence of a residue on ignition. The solutions of the compounds obtained luminescence intensely. In the PMR spectra of these compounds in D_2O, the signals in the 2.95...3.31 ppm region are strongly broadened, which can be due to the presence of paramagnetic impurities in them. Because of the low volatility of the reaction products, a satisfactory mass spectrum could not be obtained. In the UV spectra there are two absorption maxima in the visible region (367, 416 nm).



An attempt to close the ring in compound IIIa by prolonged boiling (1-3 days) in various solvents (alcohol, DMFA, dioxane, water) also was unsuccessful. The negative result of these experiments can be explained by the fact that the amino group which enters the reaction passivates its repeated nucleophilic substitution.

EXPERIMENTAL

The IR spectra were run on a Specord-75-IR spectrophotometer in mineral oil. The PMR spectra were recorded on a Bruker WH-90 spectrometer (working frequency 90 MHz, internal standard – TMS). The mass spectra were recorded on a MAT-311A spectrometer, with direct introduction of the sample to the ionic source, under standard conditions of exposure. The course of the reactions and the purity of the compounds were monitored by TLC on Al_2O_3, 3-4 grade of activity according to Brockmann, with development by iodine vapors and UV light.

The physicochemical characteristics of the synthesized compounds are given in Table 1. The elemental analysis data of the synthesized compounds for C, H, N, Cl correspond to the calculated values.

1,3-Dimethyl-6-chlorolumazine (Ib, $C_6H_7ClN_4O_2$). We did not succeed in reproducing the method described in [3]. The procedure that we have developed was more effective.

A 2 ml portion of water was added dropwise with effective stirring to a suspension of 2.08 g (0.01 mole) of 1,3-dimethyl-6-oxo-5,6-dihydrolumazine [3] in 60 ml of a freshly prepared $POCl_3$ (caution! exothermic!). After complete dissolution of the starting compound, the mixture was stirred with boiling for 8 h. The excess of $POCl_3$ was then distilled off on a water bath under reduced pressure. The viscous residue was treated with 50 g of ice (cautiously!), and after cooling the solution was extracted with chloroform (5 × 40 ml). The chloroformic extract was evaporated to dryness. Yield, 1.75 g (77%). Colorless crystals, mp 154°C (from ethanol), which corresponds to the data in [3].

1,3-Dimethyl-6-(2-aminoethylamino)lumazine (IIa, $C_{10}H_{14}N_6O_2$) and 1,3-dimethyl-6-chloro-7-(2-aminoethylamino)lumazine (IIIa. $C_{10}H_{13}ClN_6O_2$). A 0.45 g portion (2 mmoles) of compound Ib and 2 ml of a freshly distilled ethylenediamine were mixed together in a porcelain dish. The mixture was ground to complete dissolution of the starting compound. After 10 ml a precipitate of compound IIIa separated out from the brown solution. It was filtered, washed with alcohol and ether. Yield, 0.22 g (38%). Colorless needles, mp 186-188°C (from ethanol).

After separation of compound IIIa the filtrate was allowed to stand overnight in air in a porcelain dish. The precipitate that separated out was filtered off, washed with a small amount of glacial alcohol and ether, and recrystallized from a minimal amount of ethanol. Yield, 0.15 g (30%). Yellow-mustard needles, mp 212-214°C, compound IIa.

The two compounds are sparingly soluble in chloroform. In contrast to compound IIIa, compound IIa is readily soluble in water and ethanol.

1,3-Dimethyl-6-(2-hydroxyethylamino)lumazine (IIb, $C_{10}H_{13}N_5O_3$) and 1,3-dimethyl-6-chloro-7-(2-hydroxyethylamino)lumazine (IIIb, $C_{10}H_{12}ClN_5O_3$). A 0.2 g portion (0.9 mmole) of compound Ib was mixed in a porcelain

dish with 3 ml of freshly distilled ethanolamine. The mixture was slightly heated to effect complete dissolution of the compound, and was allowed to stand in air. After 5-6 h a voluminous bright-yellow precipitate (0.22 g) separated out. It was filtered off and washed with cold alcohol and ether. After the evaporation of the filtrate another 40 mg separated out. The material was recrystallized from ethanol (~30-35 ml). Yield, 80 mg (35%) of compound IIb: Yellow-mustard needles, mp 243-245°C.

The mother liquor remaining after the recrystallization of compound IIb was evaporated to a volume of 5-7 ml and cooled. A precipitate again separated out, which was filtered and recrystallized from a minimal amount of alcohol. Yield of compound IIIb 60 mg (23%). Yellowish needles, mp 227-230°C.

1,3-Dimethyl-6-ethylaminolumazine (IIc, $C_{10}H_{13}N_5O_2$) and 1,3-dimethyl-6-chloro-7-ethylaminolumazine (IIIc, $C_{10}H_{12}ClN_5O_2$). **A.** In a three-necked flask fitted with a thermometer and a stirrer, 0.25 g (1.1 mmole) of compound Ib was added to 30 ml of ethylamine cooled to −15°C. An orange-colored solution formed instantly. The solution was stirred at −15 to −10°C for 8 h. The amine was then allowed to evaporate freely. The pink-colored residue was dissolved in 20 ml of chloroform. The insoluble part was filtered off and recrystallized from alcohol. Compound IIc, yield, 10 mg (4%), yellow-green needles, mp 266-268°C.

The chloroformic extract was passed through a column containing Al_2O_3, eluting first with ether a red band (R_f 0.25, a violet spot in UV light), and then eluting a yellow band with chloroform (R_f 0.20, a green spot in UV light). The two fractions were recrystallized from ethanol. The red band gave a white crystalline substance, mp 242-243°C – compound IIIc, yield 40 mg (14%). The yellow band gave a yellow substance, mp 266-268°C – compound IIc, overall yield 0.13 g (51%).

B. A solution of 0.12 g (0.53 mmole) of compound Ib in 6 ml of ethylamine was held in a sealed ampule at room temperature for 18 h. A greenish precipitate formed gradually. The contents of the ampule were evaporated to dryness. The residue was treated with 8 ml of chloroform. The insoluble part was filtered off and washed with ether. Compound IIc, yield 25 mg (20%), yellow-green needles, mp 266-268°C (from ethanol). The chloroformic extract was passed through a column containing Al_2O_3, eluting first compound IIIc, as described above, and then compound IIc. The yield of IIc was 30 mg (21%), overall yield 41%. The yield of compound IIIc was 45 mg (36%).

1,3-Dimethyl-6-piperidinolumazine (IId, $C_{13}H_{17}N_5O_2$). A 0.1 g portion (0.4 mmole) of compound Ib was mixed in a porcelain dish with 10 ml of a freshly distilled piperidine and the mixture was ground to a complete dissolution of the starting compound. The solution immediately acquired a bright-yellow color. After 10 min, the reaction mixture was evaporated in air to dryness. The residue was dissolved in chloroform and passed through a column containing Al_2O_3 (eluent – chloroform). A bright-yellow fraction with R_f was collected (a green spot in UV light). Yield 0.1 g (83%). Bright-yellow needles, mp 166-168°C (from ethanol), which do not give a depression of the melting point in mixture with an authentic sample [10].

1,3-Dimethyl-6-morpholinolumazine (IIe, $C_{12}H_{15}N_5O_3$). A 0.23 g portion (1 mmole)) of compound Ib was mixed in a porcelain dish with 10 ml of freshly distilled morpholine and the mixture was ground to a complete dissolution of the starting compound (slight heating can be applied). The solution gradually acquired a bright-yellow. After 24 h the reaction mixture was evaporated in air. The residue was dissolved in a minimal amount of chloroform and passed through a column containing Al_2O_3 (1.5 × 30 cm). First the starting compound was eluted with ether (120 mg was regenerated). Then a bright-yellow reaction product was eluted – compound IIe – with chloroform. Yield, 0.13 g (47%). Bright-yellow needles, mp 188-191°C (from ethanol), which does not give a depression of the melting point in mixture with an authentic sample [10].

1,3-Dimethyl-6-chloro-7-aminolumazine (IIIf, $C_8H_8ClN_5O_2$). A suspension of 0.45 g (2 mmoles) of compound Ib in 80 ml of liquid ammonia was stirred for 6 h at −75 to −70°C. The ammonia was then allowed to evaporate freely. The dry residue was treated with 50 ml of chloroform. The insoluble part was recrystallized from water. Compound IIIf, yield 30 mg. The chloroformic extract was passed through a column with Al_2O_3 (eluent chloroform). First the starting compound was eluted (200 mg was regenerated). Then the reaction product was eluted – compound IIIf, yield 70 mg. The overall yield was 100 mg (20%), colorless crystals, mp 308-309°C (from water).

1,3-Dimethyl-6-hydrazinolumazine (IIg, $C_8H_{10}N_6O_2$). A 0.23 g portion (1 mmole)) of compound Ib was mixed in a porcelain dish with 7 ml of hydrazine hydrate. The mixture was stirred for 15 min. The solution thus became dark-yellow, and the precipitate of the starting compound clearly changed. The bright yellow precipitate that separated out was filtered off, and washed with alcohol and ether. Yield, 0.14 g (62%). Bright-yellow needles, mp 269-271°C (dec., from DMSO), which corresponds to the data in [3]. The compound decomposes on heating in water. IR spectrum (mineral oil), cm^{-1}: 1680, 1733 (C = 0), 3204, 3324 (NH, NH_2), 2700-3400 (ass. NH).

REFERENCES

1. L. P. Smirnova, A. F. Pozharskii, I. A. Ivanova, and A. I. Chernyshev, Khim. Geterotsikl. Soedin., No. 2, 219 (1992).
2. A. V. Gulevskaya, A. F. Pozharskii, and L. V. Lomanchenkova, Khim. Geterotsikl. Soedin., No. 11, 1575 (1990).
3. H. Steppan, J. Hammer, R. Bauar, R. Gottlieb, and W. Pleiderer, Ann., No. 12, 2135 (1982).
4. A. F. Pozharskii, A. M. Simonov, and V. N. Doron'kin, Usp. Khim., **47**, 1933 (1978).
5. C. K. McGill and A. Rappa, Adv. Heter. Chem., **44,** 1, (1988).
6. H. Hara, and H. C. Van der Plas, J. Heter. Chem., **19**, 1527 (1982).
7. M. P. Groziak and L. M. Melcher, Heterocycles, **26**, 2905 (1987).
8. B. D. Palmer and W. A. Denny, J. Chem. Soc., Perkin 1, No. 1, 95 (1989).
9. H. C. Van der Plas, Khim. Geterotsikl. Soedin., No. 8, 1011 (1987).
10. A. V. Gulevskaya, A. F. Pozharskii, S. V. Shorshnev, and V. V. Kuz'menko, Mendeleev Commun., No. 2, 46 (1991).