AZAINDOLE DERIVATIVES.

59.* SYNTHESIS AND CHEMICAL PROPERTIES

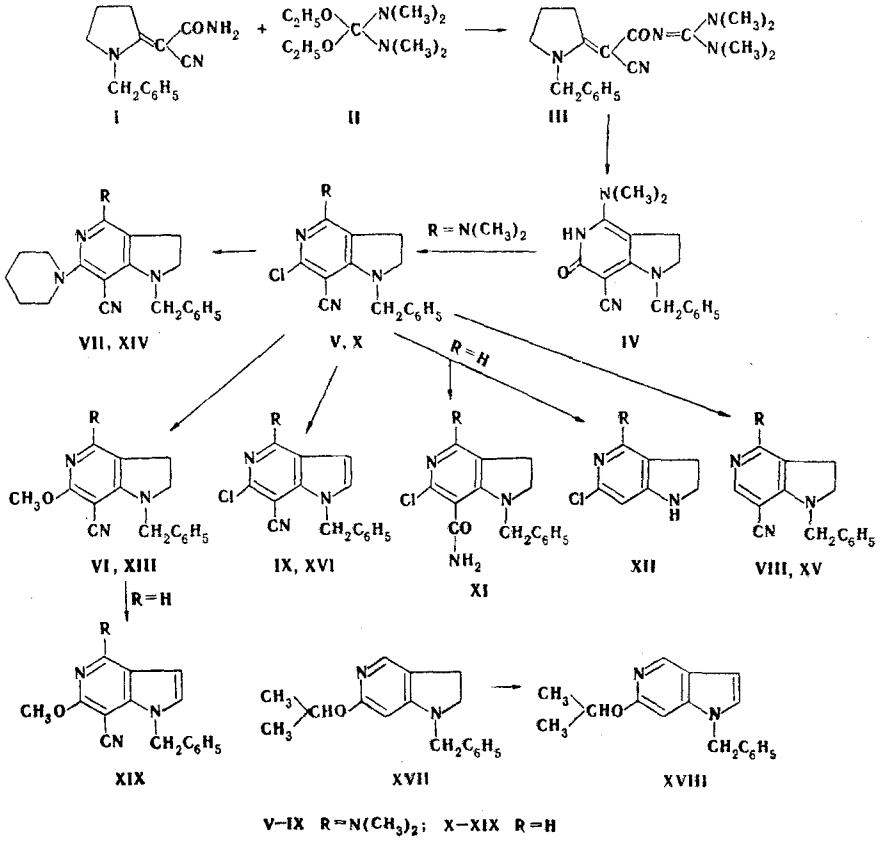
OF 1-BENZYL-4-DIMETHYLAMINO-6-CHLORO-7-CYANO-5-AZAINDOLINE

V. A. Azimov, N. N. Bychikhina, and L. N. Yakhontov

UDC 547.75.83.07

The condensation of 1-benzyl-2-cyanocarbamoylmethylene-pyrrolidine with tetramethylurea diethylacetal and subsequent cyclization gave 1-benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindoline, for which nucleophilic substitution and dehydrogenation reactions are described. The reactivity of this product is compared with that of 1-benzyl-6-chloro-7-cyano-5-azaindoline.

5-Azaindole derivatives have recently attracted considerable attention as 3,9-dideaza analogs of purine bases and 3-deaza analogs of pyrrolopyrimidine bases that participitate in nuclein metabolism [2, 3]. We have previously described new methods for the synthesis of 5-azaindole (for example, see [4]) and various derivatives substituted in the pyrrole and pyridine (for example, see [5, 6]) fragments of the molecule. The preparation of a number of 5-azaindoles that are monosubstituted and disubstituted in the pyridine ring was also reported in the seventies by other authors (for example, see [2, 7, 8]). 5-Azaindole derivatives that simultaneously contain three substituents in the pyridine part of the molecule have remained unknown.



*See [1] for Communication 58.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 215-220, February, 1981. Original article submitted May 20, 1980.

0009-3122/81/1702-0155$07.50

As the basis for the synthesis of compounds of this type we used the condensation of 1-benzyl-2-(cyanocarbamoylmethylene)pyrrolidine (I) with tetramethylurea diethylacetal (II) and subsequent cyclization of the resulting 1-benzyl-2-[cyanobis(N-dimethylamino)methylenecarbamoylmethylene]pyrrolidine (III).

In contrast to the known condensations of amides with dimethylformamide diethylacetal, which lead to acylformamidines [6, 8], the analogous reaction of amides with acetals of substituted ureas have not been previously studied, and, in view of the thermal instability of acetals of this type, the possibility of such processes was not apparent. The instability of diethylacetal II at elevated temperatures and the formation during its condensation with amide I of ethanol, which decomposes acetal II with splitting out of dimethylamine and the formation of $(CH_3)_2NC(OC_2H_5)_3$, required the use in this reaction of a threefold excess of acetal II. In this case the yield of III was 85%. Brief heating of III in an argon atmosphere led to the formation of a pyridone ring with splitting out of dimethylamine and the formation of 1-benzyl-4-dimethylamino-6-hydroxy-7-cyano-5-azaindoline (IV). According to IR and UV spectroscopic data, the latter exists primarily in the oxo form. Treatment of IV with phosphorus oxychloride made it possible to obtain 1-benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindoline (V) in 74% yield.

The synthesis of the 4-dibenzylamino analog of V by a similar scheme did not give positive results. Treatment of tetrabenzylurea with dimethyl sulfate with heating or with boron trifluoride etherate in methylene chloride led to the formation of the corresponding complexes, according to the results of thin-layer chromatography (TLC) on Silufol (in ethyl acetate). However, the production of a methylenecarbamoylmethylene derivative similar to III was not observed upon subsequent treatment of these complexes with sodium methoxide or ethoxide in the corresponding alcohol and subsequent addition of amido nitrile I. The reason for this evidently was steric hindrance of tetrabenzylurea acetals. The results of treatment of the resulting complexes with sodium methoxide or ethoxide with cooling and subsequent passage of dry ammonia gas through the reaction mass also constitute evidence in favor of this assumption. The absence of even traces of tetrabenzylguanidine the product of the reaction of tetrabenzylurea acetal with ammonia during the mass-spectrometric analysis of the reaction mixture (with gradual raising of the temperature to 350°C) constitutes evidence that tetrabenzylurea acetal is not formed in the reaction. Steric hindrance to the formation of the indicated acetal is also easily observed in the construction of a Stuart–Briegleb molecular model.

A comparison of the chemical properties of azaindoline V and the previously synthesized [10] 1-benzyl-6-chloro-7-cyano-5-azaindoline (X), which differs from V with respect to the absence of a 4-dimethylamino substituent, showed some differences in the reactivities of these substances.

Thus, for example, 4-unsubstituted X is converted to amide XI in 95% yield upon prolonged (100 h) refluxing with 7% aqueous sodium hydroxide solution. Compound V remains unchanged under the same conditions. When 4-unsubstituted X is heated at 190-210°C for 30 min with 100% phosphoric acid, it loses a benzyl group and a nitrile residue and is converted to 6-chloro-5-azaindoline (XII). Under the same conditions V undergoes complete resinification in only 15 min. In addition, the nitrile groups in V and X are not saponified by refluxing with concentrated hydrochloric acid (5 h) and do not undergo alcoholysis upon refluxing (13 h) with an ethanol solution of hydrogen chloride. The chlorine atom in both V and X undergoes substitution under the influence of strong nucleophilic agents: 1-benzyl-4-dimethylamino-6-methoxy-7-cyano-5-azaindoline (VI) and 1-benzyl-6-methoxy-7-cyano-5-azaindoline (XIII), respectively, are formed with sodium methoxide, while 6-(N-piperidino) derivatives VII and XIV are formed with piperidine.

It should be noted that, as previously observed in the case of 6-chloro-7-azaindolines [9], the nucleophilic substitution of chlorine in the investigated 6-chloro-5-azaindolines V and X proceeds under rather severe conditions: in a bomb at 180-185°C (10 h) with amines, and in DMF at 80°C (6 h) with sodium methoxide. Dehalogenation of V and X in the presence of a palladium catalyst made it possible to convert them to 6-unsubstituted 5-azaindolines VIII and XV, while dehydrogenation with activated manganese dioxide led to the corresponding 4,6,7-tri- and 6,7-disubstituted 5-azaindoles IX and XVI. Similarly, 1-benzyl-6-isopropoxy-5-azaindole (XVIII) was obtained from 1-benzyl-6-isopropoxy-5-azaindoline (XVII) [10], while 1-benzyl-6-methoxy-7-cyano-5-azaindole (XIX) was obtained from 1-benzyl-6-methoxy-7-cyano-5-azaindoline (XIII). It should be noted that the benzyl group in the 1 position and the

nitrile function in the 7 position are not affected in the course of the indicated reactions and that the reactivities of 4-unsubstituted and 4-dimethylamino derivatives do not differ substantially.

EXPERIMENTAL

The IR spectra of Vaseline oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Perkin–Elmer 402 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The molecular masses were determined by mass spectrometry with an MAT-112 spectrometer (with direct introduction of the samples) at 70 eV.

1-Benzyl-2-[cyanobis(N-dimethylamino)methylenecarbamoylmethylene]pyrrolidine (III). A mixture of 6.5 g (27 mmole) of 1-benzyl-2-(cyanocarbamoylmethylene)pyrrolidine (I) [6] and 12.96 g (81 mmole) of freshly distilled tetramethylurea diethylacetal [11] was refluxed at 120-125°C (in the bath) for 1.5 h. The ethanol formed during the reaction was removed by vacuum distillation and the residue was treated with 50 ml of heptane. The precipitate was removed by filtration, washed with 50 ml of heptane, and recrystallized from benzene to give 7.75 g (85%) of pyrrolidine III as colorless crystals with mp 138-139°C. The product was soluble in alcohol and benzene but only slightly soluble in heptane and water. IR spectrum: 2170 (C≡N) and 1595 cm^{-1} (C=C, C=N). Found: C 67.4; H 7.4; N 20.7%; M^+ 339. $C_{19}H_{25}N_5O$. Calculated: C 67.2; H 7.4; N 20.6%; M 339.

1-Benzyl-4-dimethylamino-6-hydroxy-7-cyano-5-azaindoline (IV). A 6.12-g (18 mmole) sample of pyrrolidine III was heated in an argon atmosphere at 200-205°C for 1 h, after which it was cooled and treated with 50 ml of isopropyl alcohol to give 3.4 g (64%) of IV in the form of a colorless crystalline powder that was only slightly soluble in water and ordinary organic solvents but soluble in DMF and had mp 275-276°C. IR spectrum: 2192 (C≡N) and 1603 cm^{-1} (CONH). UV spectrum, λ_{max} (ε): 212 (11,800), 244 (24,400), 285 (10,400), 327 nm (23,600). Found: C 69.1; H 6.0; N 19.1%. M^+ 294. $C_{17}H_{18}N_4O$. Calculated: C 69.4; H 6.2; N 19.1%; M 294.

1-Benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindoline (V). A mixture of 10.21 g (32.6 mmole) of azaindoline IV and 100 ml of freshly distilled phosphorus oxychloride was refluxed for 10 min, after which it was evaporated *in vacuo*. Water (30 ml) was added to the residue with cooling, and the mixture was made alkaline with potassium carbonate and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated *in vacuo* to give 10.7 g (100%) of V as light yellow crystals with mp 131-132°C (from benzene–cyclohexane). The product was quite soluble in ether, acetone, chloroform, alcohols, benzene, and toluene but only slightly soluble in cold heptane and cyclohexane and in water. UV spectrum, λ_{max} (ε): 208 (22,400), 253 (18,000), 273 (22,680), 323 nm (14,960). Found: C 65.3; H 5.7; Cl 11.2; N 17.8%. $C_{17}H_{17}ClN_4$. Calculated: C 65.3; H 5.5; Cl 11.3; N 17.8%.

1-Benzyl-4-dimethylamino-6-methoxy-7-cyano-5-azaindoline (VI). A solution of 1 g (3.2 mmole) of chloroazaindoline V in 20 ml of anhydrous DMF was added to a freshly prepared solution of sodium methoxide [from 1 g (44 mmole) of sodium in 30 ml of methanol], and the mixture was stirred at 80°C for 6 h. It was then evaporated *in vacuo*, and the residual DMF was removed by the addition of three portions (20 ml each) of xylene with subsequent removal by vacuum distillation. Water (20 ml) was added to the reaction mixture, and the aqueous mixture was extracted with chloroform (five 30-ml portions). The chloroform extract was dried with magnesium sulfate and evaporated, and the residue was crystallized from benzene–hexane to give 0.9 g (91%) of methoxyazaindoline VI as light yellow crystals with mp 142–143°C. The product was quite soluble in chloroform, benzene, and alcohols but only slightly soluble in hexane and water. IR spectrum: 2210 cm^{-1} (C≡N). UV spectrum, λ_{max} (ε): 206 (17,200), 248 (24,400), 285 (15,000), 320 nm (18,200). Found: C 70.2; H 6.6; N 18.3%. $C_{18}H_{20}N_4O$. Calculated: C 70.1; H 6.5; N 18.2%.

1-Benzyl-6-methoxy-7-cyano-5-azaindoline (XIII). This compound was similarly obtained from 5 g (20 mmole) of chloroazaindoline X and sodium methoxide, prepared from 0.92 g (40 mmole) of sodium and 20 ml of methanol. The process was carried out in 26 ml of DMF at 80°C for 6 h. Methoxy derivative XIII was extracted with ether and recrystallized from heptane to give 3.59 g (73%) of XIII as colorless crystals with mp 110-111°C. The product was quite soluble in ether, ethyl acetate, alcohols, and chloroform but only slightly soluble in heptane and water. IR spectrum: 2210 cm^{-1} (C≡N). UV spectrum, λ_{max} (ε): 244

(35,800), 260 (25,000), 326 nm (28,400). PMR spectrum: 1.18, 1.24 (two t, 2H + 2H, J = 10 Hz, CH_2CH_2—N); 3.95 (s, 3H, CH_3O); 4.88 (s, 2H, $CH_2C_6H_5$); 7.26 (s, 5H, C_6H_5); 7.32 ppm (s, 1H, 4-CH). Found: C 72.3; H 6.0; N 15.8%; M^+ 265. $C_{16}H_{15}N_3O$. Calculated: C 72.4; H 5.7; N 15.8%; M 265.

1-Benzyl-4-dimethylamino-6-(N-piperidino)-7-cyano-5-azaindoline (VIIb). A mixture of 2.13 g (6.8 mmole) of chloroazaindoline V and 15 ml of distilled piperidine was heated in a 55 ml bomb at 180-190°C (bath temperature) for 13 h, after which it was cooled and treated with 30 ml of water. The aqueous mixture was made alkaline with potassium carbonate and extracted with chloroform (six 30-ml portions). The chloroform extract was dried with magnesium sulfate and evaporated *in vacuo*. The residual piperidine was removed by the addition of fresh portions of xylene with subsequent vacuum distillation until the odor of piperidine vanished. This procedure gave 2.4 g (98%) of piperidinoazaindoline VIIb as light yellow crystals with mp 133-134°C (from benzene). The product was quite soluble in alcohols, acetone, and chloroform but only slightly soluble in ether, benzene, heptane, and water. Found: C 73.4; H 7.5; N 19.3%. $C_{22}H_{27}N_5$. Calculated: C 73.1; H 7.5; N 19.4%.

1-Benzyl-6-(N-piperidino)-7-cyano-5-azaindoline (XIV). This compound was similarly obtained in 76% yield from 2.5 g (10 mmole) of chloroazaindoline X and 15 ml of distilled piperidine. The colorless crystals had mp 109.5-110.5°C (from ethyl acetate). The product was quite soluble in alcohols, chloroform, and acetone but only slightly soluble in ether, ethyl acetate, heptane, and water. Found: C 75.2; H 7.0; N 17.5%. $C_{20}H_{22}N_4$. Calculated: C 75.4; H 7.0; N 17.6%.

1-Benzyl-6-chloro-7-carboxamido-5-azaindoline (XI). A suspension of 10.41 g (38.6 mmole) of nitrile X in 400 ml of a 7% aqueous solution of sodium hydroxide was refluxed for 100 h, after which it was cooled and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated *in vacuo* to give 10.7 g (95.5%) of XI as colorless crystals with mp 164.5-165.5°C (from benzene). The product was only slightly soluble in water and heptane, more soluble in benzene, ethyl acetate, and chloroform, and quite soluble in alcohols and acetone. IR spectrum: 1685 ($CONH_2$); 3190, 3290, 3400 cm^{-1} (NH_2). Found: C 62.6; H 4.7; Cl 12.3; N 14.5%. $C_{15}H_{14}ClN_3O$. Calculated: C 62.6; H 4.9; Cl 12.3; N 14.6%.

Starting V, which was identified from its IR spectrum and a mixed-melting-point determination with a genuine sample of V, was recovered quantitatively in a similar reaction with 5 g (16 mmole) of nitrile V, as well as in a reaction with the use of a 7% solution of sodium hydroxide in 50% aqueous ethanol instead of a 7% aqueous solution of sodium hydroxide in order to improve the solubility of nitrile V.

6-Chloro-5-azaindoline (XII). A mixture of 4 g (14.8 mmole) of 1-benzyl-6-chloro-7-cyano-5-azaindoline (X) and 20 g of 100% phosphoric acid was heated at 190-210°C for 30 min, after which it was cooled and neutralized with 70 ml of ammonium hydroxide. The mixture was extracted with chloroform, and the chloroform extract was dried with magnesium sulfate and evaporated. The residue was recrystallized from benzene—hexane to give 1.5 g (66%) of XII as colorless crystals with mp 113-114°C. The product did not depress the melting point of a sample of XII obtained by the method described in [12].

In a similar reaction 1-benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindoline (V) underwent complete resinification after only 15 min.

1-Benzyl-4-dimethylamino-7-cyano-5-azaindoline (VIII). A solution of 1 g (3.2 mmole) of chloroazaindoline V in 200 ml of alcohol was shaken with 2 g of a 6% palladium catalyst on carbon in a hydrogen atmosphere under standard conditions for 40 h, after which the catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. Water (20 ml) was added to the residue, and the aqueous mixture was made alkaline with potassium carbonate and extracted with chloroform (five 20-ml portions). The chloroform extract was dried with magnesium sulfate and evaporated *in vacuo*. The residue (0.8 g) was chromatographed with a column (l = 15 cm, d = 4 cm) filled with 200 g of silica gel (40/100 μ). Elution with chloroform gave initially 0.2 g (20%) of starting chloroazaindoline V followed by 0.35 g (39%) of azaindoline VIII as colorless crystals with mp 108-109°C. The product was quite soluble in benzene, chloroform, acetone, and alcohols but only slightly soluble in water and hexane. Found: C 73.5; H 6.4; N 20.0%. $C_{17}H_{18}N_4$. Calculated: C 73.4; H 6.5; N 20.1%. Elution with methanol—ammonium hydroxide (100:1) gave 0.25 g of a mixture of substances, which was not subjected to further study.

1-Benzyl-7-cyano-5-azaindoline (XV). This compound was obtained by reduction of 3 g (11 mmole) of chloroazaindoline X in 250 ml of methanol in the presence of 3 g of 5% palladium on charcoal, as described in the preceding experiment. The isolated base was chromatographed with a column filled with silica gel by elution with chloroform with monitoring of the separation of X and XV by thin-layer chromatography (TLC) on Silufol in chloroform (detection in UV light) [R_f 0.25 (dark spot) for X, and R_f 0.05 (blue luminescence) for XV]. This procedure gave 0.64 g (21.4%) of chloroazaindoline X and 1.31 g (50%) of azaindoline XV as colorless crystals with mp 95-96°C (from benzene–hexane). The product was quite soluble in acetone, benzene, chloroform, and alcohols but only slightly soluble in hexane and water. Found: C 76.7; H 5.4; N 17.9%; M^+ 235. $C_{15}H_{13}N_3$. Calculated: C 76.6; H 5.6; N 17.9%; M 235.

1-Benzyl-4-dimethylamino-6-chloro-7-cyano-5-azaindole (IX). A 3.3-g sample of γ-manganese dioxide was added to a solution of 0.37 g (1.2 mmole) of azaindoline V in 150 ml of carbon tetrachloride, and the mixture was stirred at 20°C for 10 h. The precipitate was removed by filtration, and the solution was evaporated *in vacuo* to give 0.26 g (70%) of azaindole IX as light yellow crystals with mp 150-151°C (from benzene–hexane). UV spectrum, λ_{max} (ε): 212 (28,200), 239 (22,800) 322 nm (20,800). Found: C 65.7; H 4.7; Cl 11.3; N 18.2%; M^+ 310. $C_{17}H_{15}ClN_4$. Calculated: C 65.7; H 4.9; Cl 11.4; N 18.0%; M 310.

1-Benzyl-6-chloro-7-cyano-5-azaindole (XVI). This compound was similarly obtained by oxidation of 3 g (11.1 mmole) of azaindoline X with γ-manganese dioxide. The colorless crystals had mp 107-108°C (from cyclohexane). The product was quite soluble in benzene, xylene, and chloroform but only slightly soluble in cyclohexane and water. UV spectrum, λ_{max} (ε): 241 (29,400) and 302 nm (3530). Found: C 67.3; H 4.0; Cl 13.0; N 15.9%. $C_{15}H_{10}ClN_3$. Calculated: C 67.3; H 3.8; Cl 13.2; N 15.7%.

1-Benzyl-6-isopropoxy-5-azaindole (XVIII). A 14-g sample of γ-manganese dioxide was added to a solution of 1.84 g (7.1 mmole) of 1-benzyl-6-isopropoxy-5-azaindoline (XVII) [9] [UV spectrum, λ_{max} (ε): 215 (50,200), 258 (16,050), and 290 nm (6700)] in 200 ml of benzene, and the mixture was stirred at 20°C for 30 h. The precipitate was removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was chromatographed with a column filled with activity II aluminum oxide by elution with hexane–benzene (1:3) to give 1.32 g (72%) of azaindole XVIII as light pink crystals with mp 71-72°C. UV spectrum, λ_{max} (ε): 223 (38,100), 267 (3770), and 300 nm (3480). Found: C 76.9; H 7.1; N 10.4%; M^+ 266. $C_{17}H_{18}N_2O$. Calculated: C 76.7; H 6.8; N 10.5%; M 266.

1-Benzyl-6-methoxy-7-cyano-5-azaindole (XIX). This compound was obtained from 2.18 g (8 mmole) of azaindoline XIII as in the preceding experiment (the reaction time was 7 h) and was recrystallized from heptane without chromatographic purification to give 1.12 g (52%) of azaindole XIX as colorless crystals with mp 134-135.5°C. The product was quite soluble in ether, ethyl acetate alcohols, and chloroform, less soluble in benzene, and insoluble in water and petroleum ether. IR spectrum: 2210 cm^{-1} (C≡N). UV spectrum, λ_{max} (ε): 234 (78,800), 296 (24,800), and 326 nm (25,600). Found: C 72.8; H 4.9; N 16.0%. $C_{16}H_{13}N_3O$. Calculated: C 73.0; H 5.0; N 16.1%.

LITERATURE CITED

1. V. A. Azimov, A. A. Prokopov, I. S. Zhivotovskaya, M. K. Polievktov, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 11, 1489 (1979).
2. C. Ducroq, E. Bisagni, J.-M. Choste, J. Mispelter, and J. Defaye, Tetrahedron, 32, 773 (1976).
3. A. Ducruix, C. Riche, and C. Pascard, Tetrahedron Lett., No. 1, 51 (1976).
4. L. N. Yakhontov and E. I. Lapan, Khim. Geterotsikl. Soedin., No. 1, 27 (1970).
5. L. N. Yakhontov and M. F. Marshalkin, Khim. Geterotsikl. Soedin., No. 12, 1638 (1972).
6. V. A. Azimov, V. G. Granik, R. G. Glushkov, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 355 (1978).
7. S. W. Schneller and R. S. Hosmane, J. Heterocycl. Chem., 14, 1291 (1977).
8. V. G. Granik, N. B. Marchenko, T. F. Vlasova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1509 (1976).
9. L. N. Yakhontov, D. M. Krasnokut-skaya, and A. M. Akalaev, Dokl. Akad. Nauk SSSR, 192, 118 (1970).
10. L. N. Yakhontov and E. I. Lapan, Khim. Geterotsikl. Soedin., No. 8, 859 (1972).
11. H. Meerwein, W. Florian, N. Schön, and J. Stopp, Ann. 641, 1 (1961).
12. L. N. Yakhontov and E. I. Lapan, Khim. Geterotsikl. Soedin., No. 3, 550 (1969).