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PYRROLOINDOLES. 22.* OPTIMIZATION OF PREPARATIVE METHODS FOR SOME ISOMERIC PYRROLOINDOLES

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Convenient methods have been developed for the synthesis of derivatives of angular and linear pyrroloindoles. The first such method involves the bicyclization of m-phenylenebishydrazone of ethyl pyruvate in polyphosphates through the Fischer reaction with simultaneous formation of two pyrrole rings. The second method is based on attaching a pyrrole ring to an indoline molecule.

Keywords: pyrroloindole, pyrroloindoline, *m*-phenylenebishydrazone of ethyl pyruvate, cyclization.

Synthetic methods for pyrroloindoles now permit the preparation of similar bifunctional analogs of biologically active indole compounds [5]. Some of these compounds have bactericidal, antimicrobial, and antitumor properties [6-8]. The well-known natural antibiotic, CC-1065, which contains pyrroloindoline fragments, is many times more active than reported antitumor preparations [9]. Thus, the development of new synthetic methods and the synthesis of new pyrroloindole derivatives hold great interest.

An angular isomer of diethoxycarbonylpyrroloindole **2** has been synthesized in 20% yield by the bicyclization of the *m*-phenylenebishydrazone of ethyl pyruvate (**1**) by heating this compound in 20% ethanolic HCl [10]. In our previous work [11], this yield was improved to 60% and compound **3**, which is a linear isomer of diester **2**, was obtained in 8% yield. The saponification of compounds **2** and **3** gave the corresponding diacids **4** and **5**, whose decarboxylation led to angular and linear pyrroloindole isomers **6** and **7**, respectively [10, 11].

In the present work, two methods are described for the synthesis of isomeric pyrroloindoles **6** and **7** and their derivatives, which we developed with the aim of increasing the yields of already reported and new compounds of this group.

The first method is based on the abovementioned bicyclization of bishydrazone **1** according to the Fischer indole synthesis with the simultaneous formation of two pyrrole rings (Scheme 1), while the second involves the construction of a pyrrole ring in an indoline derivative (Scheme 2).

Various condensing agents were studied as catalysts for the bicyclization of bishydrazone **1**. Considerable tar formation occurs under rigorous conditions in the presence of $ZnCl_2$, PPA, or $AcOH/H_2SO_4$. As noted above, the reaction in 20% ethanolic HCl is not very efficient [10]. A mixture of ethyl esters of PPA

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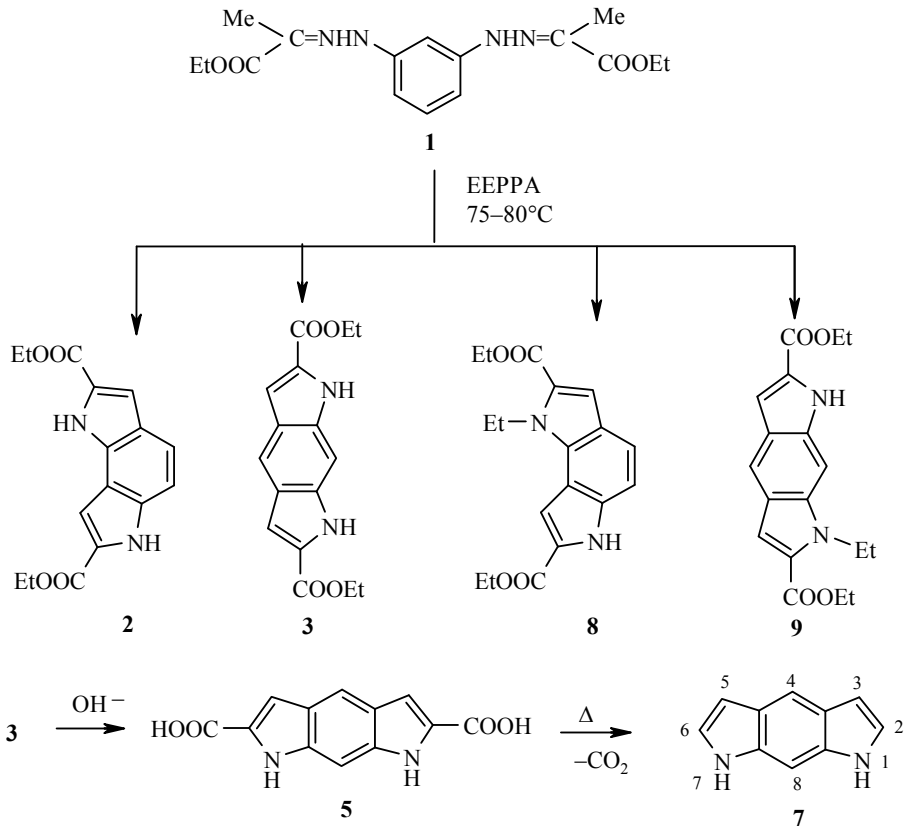
(EEPPA) proved the most successful condensing agent for the bicyclization of **1**. We should note that neither EEPPA nor the other reagents listed proved efficient for the cyclization of *m*-phenylenebishydrazone of pyruvic acid itself.

Scheme 1



The reaction with bishydrazone **1** at 75-80°C gives a mixture of angular and linear pyrroloindole derivatives **2**, **3**, **8,** and **9** (total yield 69-74%) with predominance of angular isomer **2** obtained in 65% yield. It is well known that the angular structure of multicyclic condensed aromatic systems is energetically more favored than the linear structure [12, 13]. The major isomer **2** is readily purified by heating the isomer mixture obtained in 2-propanol at reflux for 2-3 min.

Column chromatography of the impurities removed by 2-propanol gave linear isomer **3** in 8% yield as well as previously unreported N-ethylpyrroloindoles **8** (0.5% yield) and **9** (0.5% yield). These compounds are not obtained by heating pure samples of diesters **2** and **3** with EEPPA at reflux under the indicated conditions. Products **8** and **9** are probably obtained as a result of the alkylation of the amine nitrogen in bishydrazone **1** by products of the decomposition of EEPPA [14] with subsequent cyclization, which is in accord with previous findings [15, 16]. Indolization of the pure stereoisomers of *m*-phenylenebishydrazone **1** occurs with the same yields.

Thus, the method described above is both simple and efficient for obtaining angular isomer **2**, which can be used to obtain other angular pyrroloindole derivatives **6**.

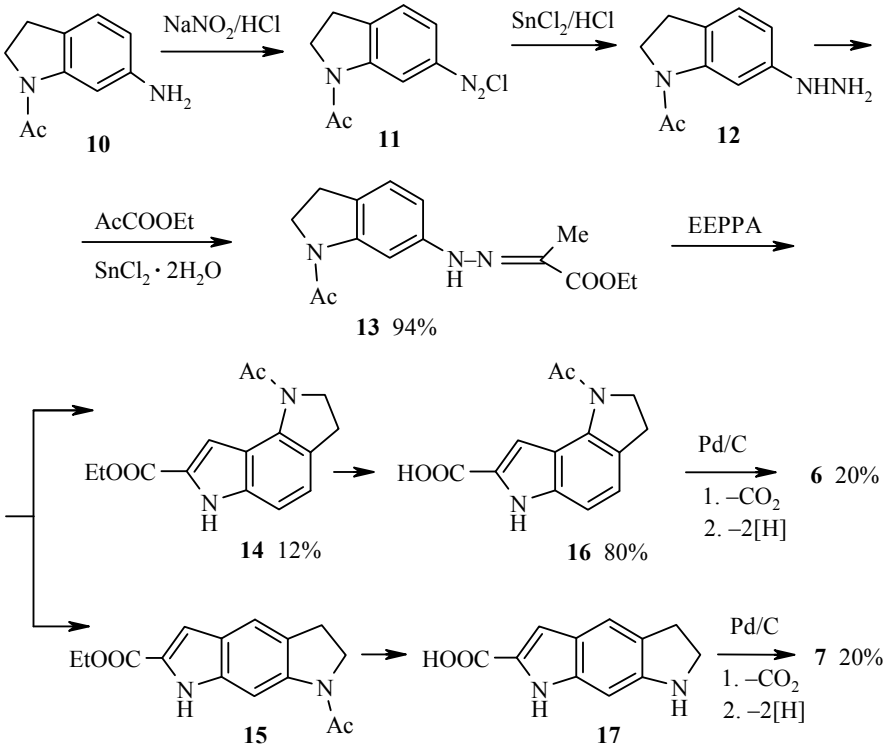
Diacid **5** was obtained in high yield by the saponification of diester **3**. The thermal decarboxylation of diacid **5** proceeds with considerable loss and tar formation. The yield of linear pyrroloindole **3** is only 20%.

The second method is a new general approach to the preparation of pyrroloindoles **6** and **7** and their derivatives starting from 1-acetyl-6-aminoindoline (**10**) (Scheme 2).

The diazotization of aminoindoline **10** was carried out by the usual procedure with subsequent reduction of diazonium salt **11** to give hydrazine **12**.

The condensation of hydrazine **12** with ethyl pyruvate gave hydrazone **13** as a mixture of the *syn* and *anti* isomers (94% total yield). A 1:5 mixture of angular **14** and linear pyrroloindolines **15** is formed upon cyclization of the mixture of *syn*- and *anti*-**13** in EEPPA. The low yield of the angular isomer **14** is probably due to spatial influence on the N-acetyl group.

Scheme 2



Hydrolysis of the ester and acetyl groups in **14** and **15** with subsequent concurrent decarboxylation and dehydrogenation of the resultant carboxylic acids **16** and **17** gave unsubstituted pyrroloindoles **6** and **7**, respectively.

Thus, the second method is convenient for the preparation of linear pyrroloindole and its derivatives.

The composition and structure of newly synthesized products **8**, **9**, **14**, and **15** were supported by elemental analysis, IR, UV, ^{1}H NMR, and mass spectral data.

EXPERIMENTAL

The IR spectra were taken on a THERMO NICOLET AVATAR 370 spectrometer. The UV spectra were taken on a Specord-UV spectrophotometer for solutions in ethanol. The ^{1}H NMR spectra were taken on a Varian Mercury-300 VX spectrometer at 300 MHz in acetone-d_6 (for **8, 9**, and **14**), and DMSO-d_6 (for **15**) with TMS as the internal standard. The mass spectra were taken on a RIBERMAG R-10-10B GC/MS. The ionizing electron energy was 70 eV. The reaction course and purity of the products were monitored on Silufol UV-254 plates. Silica gel 100-160 μ was used for preparative column chromatography.

Bishydrazone **1** was synthesized according to our previous procedure [10]. N-Acetylaminoindoline **10** was obtained according to Kost [17].

Diethyl Ester of 1H,6H-Pyrrolo[2,3-*e*]indole-2,7-dicarboxylic Acid (2), Diethyl Ester of 1H,7H-Pyrrolo[3,2-*f*]indole-2,6-dicarboxylic Acid (3), Diethyl Ester of 1-Ethyl-1H,6H-pyrrolo-[2,3-*e*]indole-2,7-dicarboxylic Acid (8), and Diethyl Ester of 1-Ethyl-1H,7H-pyrrolo[3,2-*f*]indole-2,6-dicarboxylic Acid (9). Bishydrazone **1** (10.69 g, 32 mmol) was added to 106 g EEPPA at 60°C and stirred. The temperature of the mixture rapidly rose to 90°C and the transparent solution obtained was maintained for 20 min at 75-80°C, cooled, and poured into cold water. The residue was filtered off, washed with water, and dried. Then, 50 ml 2-propanol was added to the dry residue, heated at reflux for 2-3 min, and filtered without cooling. The procedure with 2-propanol was repeated trice to give 5.85 g (61%) diester **2**, which was purified by column chromatography using 10:1 benzene–ether as the eluent. After evaporation of the fraction with R_f 0.52 (5:1 benzene–ethyl acetate), the residue was diester **2** with mp 266-267°C (mp 266-267°C [10]).

The combined filtrate after the treatment with 2-propanol was evaporated and the residue was separated by column chromatography using 4:1 petroleum ether–diethyl ether as the eluent. Evaporation of the eluate with R_f 0.65 (6:1 benzene–ethyl acetate) gave 0.05 g (0.5%) diester **8** as light-yellow crystals; mp 157-159°C. IR spectrum in chloroform, ν, cm^{-1}: 3460 (N–H), 1700 (C=O). UV spectrum, λ_{max}, nm (log ε): 207 (4.36), 294 (4.68). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (6H, t, *J* = 7.3, 2C$\underline{H}_3$CH$_2$O); 1.50 (3H, t, *J* = 7.1, C$\underline{H}_3$CH$_2$N); 4.27 (2H, q, *J* = 7.3, CH$_3$C$\underline{H}_2$O); 4.36 (2H, q, *J* = 7.3, CH$_3$C$\underline{H}_2$O); 4.91 (2H, q, *J* = 7.1, CH$_3\underline{CH}_2$N); 7.35 (1H, s, H-3); 7.39 (1H, dd, $J_{4,5}$ = 8.8, $J_{5,8}$ = 0.7, H-5); 7.55 (1H, d, $J_{4,5}$ = 8.8, H-4); 7.59 (1H, dd, $J_{5,8}$ = 0.7, $J_{6,8}$ = 2.1, H-8); 11.5 (1H, br. s, H-6). Found, %: C 66.16; H 6.42; N 8.38. $C_{18}H_{20}N_2O_4$. Calculated, %: C 65.84; H 6.14; N 8.53.

Evaporation of the eluate with R_f 0.54 (6:1 benzene–ethyl acetate) gave 0.052 g (0.5%) diester **9**; mp 187-188°C. IR spectrum in chloroform, ν, cm^{-1}: 3465 (N–H), 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 219 (4.52), 231 (4.38), 300 (4.77), 336 (4.24) sh, 350 (4.41). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (6H, t, *J* = 7.3, 2C$\underline{H}_3$CH$_2$O); 1.55 (3H, t, C$\underline{H}_3$CH$_2$N); 4.36 (4H, q, *J* = 7.3, 2CH$_3$C$\underline{H}_2$O); 4.64 (2H, q, *J* = 7.1, CH$_3$C$\underline{H}_2$N); 7.25 (1H, dd, $J_{5,7}$ = 2.1, $J_{5,8}$ = 0.9, H-5); 7.36 (1H, d, $J_{3,8}$= 0.9, H-3); 7.50 (1H, q, *J* = 0.9, H-8); 8.00 (1H, d, $J_{4,8}$ = 0.9, H-4); 10.45 (1H, br. s, H-7). Found, %: C 66.72; H 6.15; N 8.36. $C_{18}H_{20}N_2O_4$. Calculated, %: C 65.84; H 6.14; N 8.53.

Elution was continues with 10:1 benzene–diethyl ether. Evaporation of the eluate with R_f 0.52 (5:1 benzene–acetone) gave 0.38 g (4%) diester **2**, identical to the sample obtained after treatment of the precipitate from the reaction mixture in its thin-layer chromatographic mobility and melting point.

Evaporation of the eluate with R_f 0.55 (3:1 benzene–ethyl acetate) gave 0.76 g (8%) diester **3**; mp 227-228°C (mp 227-228°C [11]).

1H,7H-Pyrrolo[3,2-*f*]indole-2,6-dicarboxylic Acid (5). A solution of KOH (45 g) in water (330 ml) was added to a suspension of diester **3** (3 g, 10 mmol) in 1-butanol, (50 ml) and the mixture was heated at reflux for 1.5 h with stirring and then cooled. The aqueous layer was separated, brought to pH 1 by adding hydrochloric acid, and maintained for 12 h at room temperature. The precipitate formed was filtered off, washed with water until the wash water was neutral, and dried in vacuum to give 1.65 g (68%) diacid **5**; dec. 240°C (dec. 240°C [11]).

1-Acetylindolin-6-ylhydrazone of ethyl pyruvate (13). A solution of diazonium salt **11** obtained by the diazotization of 1-acetyl-6-aminoindoline (**10**) (1 g, 6 mmol) was added slowly with stirring to a solution of $SnCl_2 \cdot 2H_2O$ (6 g, 24 mmol) in 18% hydrochloric acid (10 ml) cooled to -8°C. The suspension obtained was stirred for 2 h at from -8 to 0°C, diluted with 100 ml water, heated to 70°C, brought to pH 3-4 by adding sodium acetate, and rapidly filtered. A solution of ethyl pyruvate (1 ml, 9 mmol) in ethanol (1-2 ml) was added slowly with stirring to the cooled solution and stirred for 2 h. The yellow precipitate obtained was filtered off, washed with water, and dried to give 1.38 g (94%) mixture of isomers of hydrazone **13**, which was separated by column

chromatography using 6:1 benzene–acetone as the eluent. Evaporation of the eluate with R_f 0.55 (3:1 benzene–acetone) gave 0.15 g (11%) *syn*-**13**; mp 155-156°C (mp 155-156°C [18]). Evaporation of the eluate with R_f 0.33 (3:1 benzene–acetone) gave 1 g (71%) *anti*-**13**; mp 198-199°C (mp 198-199°C [18]).

Ethyl Ester of 1-Acetyl-2,3-dihydro-1H,6H-pyrrolo[2,3-*e*]indole-7-carboxylic Acid (14) and Ethyl Ester of 7-Acetyl-5,6-dihydro-1H,7H-pyrrolo[3,2-*f*]indole-2-carboxylic Acid (15). A suspension of hydrazone **13** (10 g, 35 mmol) in EEPPA (100 g) was stirred for 1 h at 70-80°C, then cooled, and poured onto ice. The precipitate formed was filtered off, washed with water until the wash water was neutral, and dried to give 7.13 g (75%) of a mixture of esters **14** and **15**, which was separated by column chromatography using 6:1 benzene–acetone as the eluent. Evaporation of the eluate with R_f 0.25 (9:1 benzene–acetone) gave 1.3 g (12%) ester **14**; mp 185-186°C. IR spectrum (vaseline mull), ν, cm^{-1}: 3320 (N–H), 1730, 1620 (C=O). UV spectrum, λ_{max}, nm (log ε): 204.5 (4.14), 245 (4.43), 294 (4.08), 306 (4.19), 340 (3.84). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.0, $C\underline{H}_3CH_2O$); 2.20 (3H, s, CH_3CO); 3.22 (2H, t, *J* = 8.1, $C\underline{H}_2CH_2N$); 4.12 (2H, t, *J* = 8.1, $CH_2C\underline{H}_2N$); 4.27 (2H, q, *J* = 7.0, $CH_3C\underline{H}_2O$); 7.09 (1H, dd, $J_{4,5}$ = 8.6, $J_{5,8}$ = 0.7, H-5); 7.29 (1H, d, $J_{4,5}$ = 8.6, H-4); 7.62 (1H, dd, $J_{5,8}$ = 0.7, $J_{6,8}$ = 1.6, H-8); 11.40 (1H, br. s, H-6). Found, %: C 66.5; H 6.1; N 10.1; *m/z* 272 $[M]^+$. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92; N 10.29; M = 272.2991.

Evaporation of the eluate with R_f 0.14 (9:1 benzene–acetone) gave 6 g (63%) ester **15**; mp 291-292°C. IR spectrum (vaseline mull), ν, cm^{-1}: 3230 (N–H), 1760, 1690 (C=O). UV spectrum, λ_{max}, nm (log ε): 202 (4.27), 205 sh (3.39), 229.8 (4.20), 252 (4.25), 260 sh (4.02), 311 sh (4.02), 328 (4.27), 339 (4.32). ^{1}H NMR spectrum, δ, nm (*J*, Hz): 1.34 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2O$); 2.19 (3H, s, CH_3CO); 3.20 (2H, t, *J* = 8.3, $C\underline{H}_2CH_2N$); 4.14 (2H, t, *J* = 8.3, $CH_2C\underline{H}_2N$); 4.30 (2H, q, *J* = 7.1, $CH_3C\underline{H}_2O$); 6.95 (1H, dd, $J_{5,7}$ = 1.8, $J_{5,8}$ = 0.8, H-5); 7.32 (1H, d, $J_{4,8}$ = 0.7, H-4); 8.20 (1H, m, H-8); 11.34 (1H, br. s, H-7). Found, %: C 66.5; H 6.0, N 10.2; *m/z* 272 $[M^+]$. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92; N 10.29; M = 272.2991.

1H,6H-Pyrrolo[2,3-*e*]indole (6). A mixture of KOH (6 g), water (24 ml), and ester **14** (3.4 g, 12.5 mmol) was heated at reflux for 2 h, then cooled, filtered, and acidified to pH 5. The precipitate formed was filtered off and dried to give 2 g (80%) acid **16**, which was maintained for 10 min with 0.7 g Pd/C at 250-300°C in an argon atmosphere. Column chromatography using benzene as the eluent gave 0.31 g (20%) indole **6**; mp 134-135°C (mp 134-135°C [10]).

1H,7H-Pyrrolo[3,2-*f*]indole (7). A. Diacid **5** (1.22 g, 5 mmol) was heated in an argon atmosphere at 240-245 for 10 min. Column chromatography of the reaction product with benzene as the eluent gave 0.16 g (20%) indole **7**; mp 215-217°C (octane) (mp 215-217°C [11]).

B. The procedures described above for the saponification of ester **14** and decarboxylation of acid **16** were used to convert ester **15** (3.4 g, 12.5 mmol) through acid **17** into 0.31 g (20%) indole **7**; mp 216-217°C. A mixed melting point with the sample by procedure A was undepressed.

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REFERENCES

1. I. Sh. Chikvaidze, Sh. A. Samsoniya, N. Sh. Lomadze, N. L. Targamadze, and Z. B. Saliya, *Khim. Geterotsikl. Soedin.*, 1656 (2000). [*Chem. Heterocycl. Comp.*, **36**, 1421 (2000)].
2. Sh. A. Samsoniya, M. V. Trapaidze, and N. A. Kuprashvili, *Izv. Akad. Nauk Gruzii, Ser. Khim.*, **27**, 253 (2001).
3. D. O. Kadzhrishvili, Sh. A. Samsoniya, N. N. Suvorov, N. Sh. Samsoniya, and S. Kh. Kiladze, *Georgian Engng. News*, No. 4, 165 (2005).

4. D. O. Kadzhrishvili, Sh. A. Samsoniya, N. M. Yashvili, and A. Sh. Samsoniya, *Georgian Engng. News*, No. 4, 168 (2005).
5. Sh. A. Samsoniya, N. L. Targamadze, and N. N. Suvorov, *Usp. Khim.*, **63**, 866 (1994).
6. Sh. A. Samsoniya, M. V. Trapaidze, N. L. Targamadze, I. Sh. Chikvaidze, N. N. Suvorov, N. N. Ershova, and V. A. Chernov, *Soobshch. Akad. Nauk GruzSSR*, **100**, 337 (1980).
7. Sh. A. Samsoniya, B. A. Medvedev, D. O. Kadzhrishvili, D. M. Tabidze, M. D. Mashkovskii, and N. N. Suvorov, *Khim.-farm. Zh.*, **16**, 1335 (1982).
8. Sh. A. Samsoniya, Z. Sh. Lomtatidze, S. V. Dolidze, and N. N. Suvorov, *Khim.-farm. Zh.*, **18**, 1452 (1984).
9. V. H. Rawal, R. J. Jones, and M. P. Gava, *Heterocycles*, **25**, 701 (1987).
10. Sh. A. Samsoniya, N. L. Targamadze, L. G. Tret'yakova, T. K. Efimova, K. F. Turchin, I. M. Gverdtsiteli, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 938 (1977). [*Chem. Heterocycl. Comp.*, **13**, 757 (1977)].
11. Sh. A. Samsoniya, N. L. Targamadze, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 849 (1980).
12. D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.*, 1 (1958).
13. N. N. Suvorov, Zh. F. Sergeeva, A. P. Gryaznov, V. P. Shabunova, L. G. Tret'yakova, G. K. Ershova, T. A. Volodina, I. A. Morozova, R. N. Akhvlediani, A. Sh. Vasil'ev, and T. K. Trubytsina, *Trudy Moskovsk. Khim. Tekhn. Inst. im. D. I. Mendeleeva*, **94**, 23 (1977).
14. I. Kanaoka, I. Ban, O. Yonemitsu, K. Tanie, and K. Miyashita, *Chem. Ind.*, 473 (1965).
15. Yu. P. Kitaev and B. I. Buzykin, *Hydrazones* [in Russian], Nauka, Moscow (1974), p. 121.
16. I. I. Grandberg, D. V. Sibiryakova, and L. V. Brovkin, *Khim. Geterotsikl. Soedin.*, 94 (1969). [*Chem. Heterocycl. Comp.*, **5**, 75 (1969)].
17. G. I. Zhutgietu, B. A. Budilin, and A. N. Kost, *The Preparative Chemistry of Indole* [in Russian], Shtinitsa, Kishinev (1975), p. 160.
18. N. A. Kuprashvili, M. V. Trapaidze, D. O. Kadzhrishvili, Sh. A. Samsoniya, and N. N. Suvorov, *Soobshch. Akad. Nauk GruzSSR*, No. 2, 118 (1985).