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SYNTHESIS AND PROPERTIES OF 2-AMINO-6-NITROINDOLES

Yu. M. Volovenko and T. A. Volovnenko

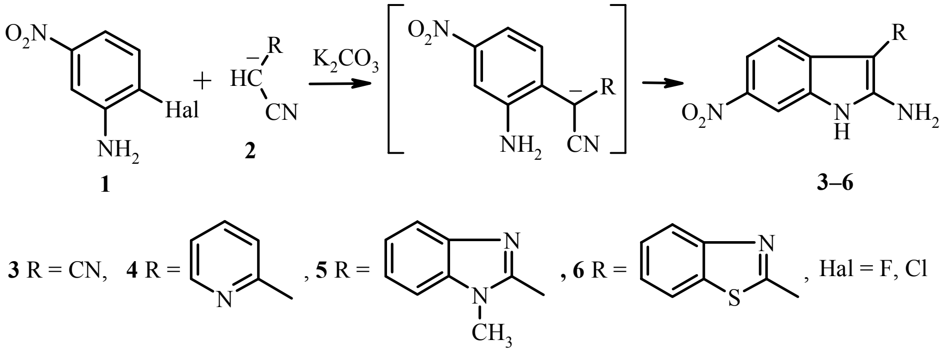
A new method is proposed for the synthesis of 2-amino-6-nitroindoles, based on the reaction of 2-haloanilines and substituted acetonitriles. The reaction of 2-amino-6-nitroindoles with β-dicarbonyl compounds was studied.

Keywords: 2-aminoindoles, pyrimido[1,2-*a*]indoles.

Many derivatives of 2-aminoindole have a wide range of biological activity [1, 2], and for this reason the synthesis of new compounds of this series and study of their characteristics represent an actual task.

Classical methods for the synthesis of derivatives of 2-aminoindole – the Pschorr synthesis [3] and its various modifications [4] and also the Kost reaction [5] – always lead to 2-aminoindoles substituted at position 1.

We have developed a simple method for the synthesis of 2-amino-6-nitroindoles based on the reaction of 2-halo-5-nitroanilines **1** with substituted acetonitriles **2**. The reaction starts with nucleophilic substitution of the halogen atom by the carbanion generated from the substituted acetonitriles **2** by the action of a base. Subsequent intramolecular reaction of the amino and nitrile groups leads to the formation of 2-amino-6-nitroindoles **3-6**.



The reaction is conducted in aprotic solvents, such as acetonitrile, dioxane, and dimethylformamide. The ease with which the reaction occurs is determined by the nature of the leaving halogen. As expected, 2-fluoro-5-nitroaniline (**1a**) reacts with acetonitrile **2** more rapidly than 2-chloro-5-nitroaniline (**1b**). It should be noted that the higher reactivity of fluoroaniline **1a** manifests itself in the fact that it enters into the reaction in acetonitrile, whereas chloroaniline **1b** does not react with nitriles **2** in this solvent. By comparing a series of

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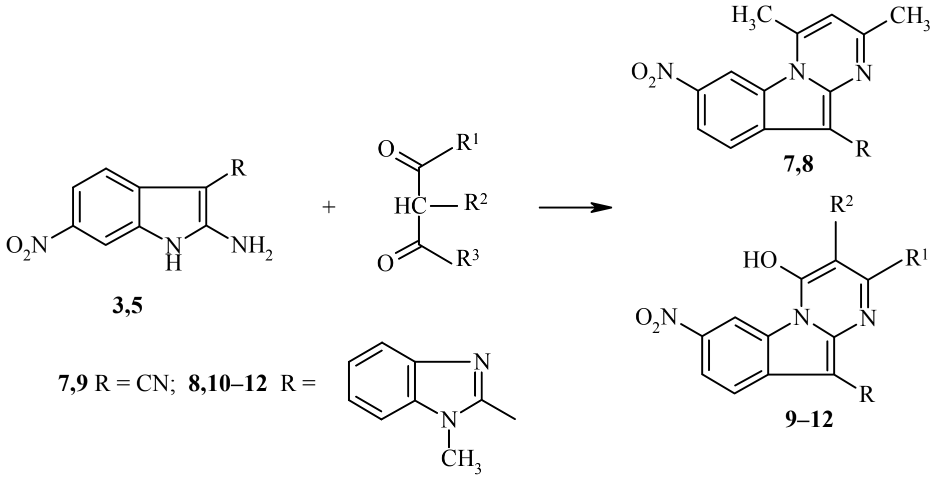
Taras Shevchenko Kiev University, Kiev, Ukraine; e-mail: atver@mail.univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1191-1194, September, 2001. Original article submitted January 27, 1999. Revision submitted June 29, 2000.

bases – sodium, cesium, and potassium carbonates – we came to the conclusion that the last compound was the best. Potassium carbonate is significantly more effective than sodium carbonate and is more readily available than cesium carbonate.

It is well known [6] that 2-aminoindoles as free bases exist predominantly in the indolenine form and are easily oxidized by atmospheric oxygen to form the 3-hydroxy derivatives. The presence of a substituent at position 3 of 2-aminoindole stabilizes its molecule. In fact 3-substituted 2-amino-6-nitroindoles **3-6** that we obtained are high-melting crystalline substances stable in air.

Their structure was confirmed by the IR and ^{1}H NMR spectra. Thus, the IR spectra of indoles **3-6** contain bands for the stretching vibrations of the primary amino group in the region of 3370-3345 cm^{-1} and the NH group of the indole ring in the region of 3480-3450 cm^{-1}, while the spectrum of compound **3** contains a further band for the stretching vibrations of the nitrile group at 2200 cm^{-1}. The ^{1}H NMR spectra of indoles **3-6**, recorded in DMSO-d$_6$, contain a two-proton singlet for the primary amino group in the region of 6.97-7.7 ppm, a singlet for the proton of the NH group at 11.20-11.30 ppm (which disappears with the addition of D$_2$O), and a doublet in the region of 8.00-8.10 ppm assigned to the proton at position 7 of the molecule. A doublet of doublets at 7.92-7.94 ppm (J_1 = 2.6, J_2 = 9.3 Hz) corresponds to 5-H while a doublet at 7.2 ppm (J = 9.3 Hz) corresponds to 4-H.

Pyrimido[1,2-*a*]indoles **7-12**, characterized by IR and ^{1}H NMR spectra are formed in the reaction of 2-aminoindoles **3** and **4** with β-dicarbonyl compounds, such as acetylacetone, acetoacetic ester, and ethyl trifluoroacetoacetate.



3,5

7,8

9–12

7,9 R = CN; **8,10–12** R =

7–10,12 R^1 = CH$_3$; **11** R^1 = CF$_3$; **7–11** R^2 = H; **12** R^2 = C$_2$H$_5$; **7,8** R^3 = CH$_3$; **9–12** R^3 = OC$_2$H$_5$

Thus, in the IR spectrum of 10-cyano-2,4-dimethyl-7-nitropyrimido[1,2-*a*]indole (**7**) there are bands for the stretching vibrations of the NO$_2$ group in the region of 1520-1510 cm^{-1} and those of the nitrile group at 2200 cm^{-1}, and there is no band for the stretching vibrations of the NH bond in the region of 3300-3310 cm^{-1}. In the IR spectra of compounds **9-12** the stretching vibrations of the OH group form a broad band at 3300 cm^{-1}. In the ^{1}H NMR spectra of compounds **7** and **8** (in CF$_3$COOD) there are three-proton singlets for the two methyl groups at 3.10 and 3.54 ppm (compound **7**) and at 2.98 and 3.59 ppm (compound **8**) and also a singlet for the proton at the C$_{(3)}$ atom in the region of 7.37-7.38 ppm and a singlet for the proton at the C$_{(6)}$ atom at 9.52 ppm. The ^{1}H NMR spectra of pyrimidoindoles **9-12**, recorded in DMSO-d$_6$, contain a singlet for the hydroxyl proton at position 4 at 6.28 ppm, a singlet for the proton at the C$_{(3)}$ atom in the region of 7.69-7.71 ppm (compounds **9-11**), a singlet for the methyl group at position 2 of the molecule at 2.37-2.57 ppm (compounds **9**, **10**, **12**), and a triplet at 1.5 and a quartet at 3.5 ppm for the protons of the ethyl group (compound **12**).

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %	mp, °C	Solvent for recrystallization	Yield, %
4	$C_{13}H_{10}N_4O_2$	21.90 22.04	249	Acetonitrile	60
5	$C_{16}H_{13}N_5O_2$	22.80 22.79	>300	Acetic acid	65
6	$C_{15}H_{10}N_4O_2S$*	18.25 18.05	>300	Dimethylformamide	55
7	$C_{14}H_{10}N_4O_2$	20.98 21.04	>300	Chlorobenzene	52
8	$C_{21}H_{17}N_5O_2$	19.03 18.96	>300	Dimethylformamide	50
9	$C_{13}H_8N_4O_3$	21.01 20.89	>300	Dimethylformamide	50
10	$C_{20}H_{15}N_5O_3$	18.81 18.75	>300	Nitromethane	51
11	$C_{20}H_{12}F_3N_5O_3$	16.41 16.39	>300	Dimethylformamide	53
12	$C_{22}H_{19}N_5O_3$	17.49 17.45	281	Dimethylformamide	51

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* Found, %: S 10.40. $C_{15}H_{10}N_4O_2S$. Calculated, %: S 10.33.

EXPERIMENTAL

The IR spectra were recorded on a Pye Unicam SP 3-300 instrument in tablets with potassium bromide. The ^1H NMR spectra were recorded in DMSO-d_6 and deuterotrifluoroacetic acid on a Bruker WP-100 spectrometer at 100 MHz with TMS as internal standard. The purity of the obtained substances and the course of the reactions were monitored by TLC on Silufol UV-254 plates in the 9:1 chloroform–methanol system.

2-Amino-3-cyano-6-nitroindole (3). To solution of 2-fluoro-5-nitroaniline (5 mmol) and malononitrile (5 mmol) in dry dimethylformamide (30 ml) well-ground calcined potassium carbonate (10 mmol) was added, and the mixture was boiled for about 3 h. The solvent was removed under vacuum, water (30 ml) was added to the residue, and the mixture was acidified with acetic acid. The precipitate was filtered off, washed with water, dried, and crystallized from dioxane; mp 258-260°C. Found, %: N 27.80. $C_9H_6N_4O_2$. Calculated, %: N 27.71. $R_f = 0.40$, eluent 9:1 chloroform–methanol.

2-Amino-3-(2-azahetaryl)-6-nitroindoles (4-6). To solution of the respective 2-haloaniline (5 mmol) and 2-azaheteroarylacetonitrile (5 mmol) in an aprotic solvent (acetonitrile, dioxane, dimethylformamide) (30 ml) calcined ground potassium carbonate (10 mmol) was added, and the mixture was boiled for 3-5 h. The end of the reaction was determined by TLC. The solvent was removed under vacuum, water (30 ml) was added to the residue, and the mixture was acidified with acetic acid. The precipitate was filtered off, washed with water, dried, and recrystallized from the appropriate solvent. The physicochemical characteristics of the compounds **4-6** are given in Table 1.

2,4-Dimethylpyrimido[1,2-*a*]indoles (7, 8). To the respective 2-aminoindole (0.01 mol) acetylacetone (20 ml) was added, and the mixture was boiled for 3-5 h until the initial 2-aminoindole had disappeared according to TLC. The precipitate was filtered off, washed with a small amount of 2-propanol, and recrystallized from an appropriate solvent. The yields and the constants of compounds **7**, **8** are given in Table 1.

10-Cyano-4-hydroxy-2-methyl-7-nitropyrimido[1,2-*a*]indole (9), 4-Hydroxy-2-methyl-10-(N-methyl-2-benzimidazolyl)-7-nitropyrimido[1,2-*a*]indole (10), 4-Hydroxy-10-(N-methyl-2-benzimidazolyl)-7-nitro-2-trifluoromethylpyrimido[1,2-*a*]indole (11), and 3-Ethyl-4-hydroxy-2-methyl-10-(N-methyl-2-

benzimidazolyl)-7-nitropyrimido[1,2-*a*]indole (12). These compounds were obtained by a similar method from the corresponding 2-aminoindoles and β-dicarbonyl compounds. The characteristics of the pyrimidoindoles **9-12** are given in Table 1.

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