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SYNTHESIS OF 3-DIMETHYLPHENYLSILYL-SUBSTITUTED PYRIDO[1,2-*a*]BENZIMIDAZOLES

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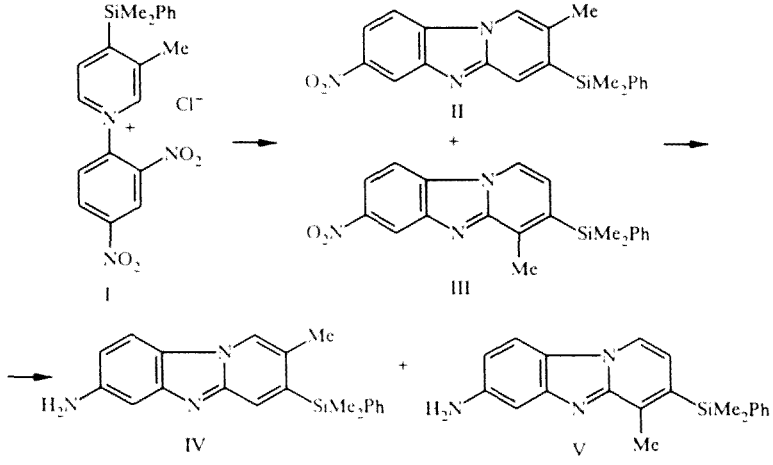
Reductive cyclization of 1-(2,4-dinitrophenyl)-3-methyl-4-dimethylphenylsilylpyridinium chloride by the action of phenylhydrazine or hydrogen in the presence of Pd/C gave, for the first time, 7-nitro(amino)-3-dimethylphenylsilylpyrido[1,2-a]benzimidazoles.

The cyclization of α-nitrophenylamino-substituted pyridines is one of the main methods for the synthesis of nitro-substituted pyrido[1,2-*a*]benzimidazoles [1, 2]. Reductive cyclization of N-(2,4-dinitrophenyl)pyridinium chloride in the presence of Pt/C or Pd/C leads to 7-amino-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole [3]. The last was also obtained by the reductive cyclization of N-(2,4-dinitrophenyl)piperidinium chloride using tin(II) chloride in hydrochloric acid [4]. Phenylhydrazine in acetic acid may be utilized as the cyclization agent. When this reagent acts on N-(2,4-dinitrophenyl)- and N-(2,4,6-trinitrophenyl)pyridinium chloride and picolinium chloride, mono- and dinitro-substituted pyrido[1,2-*a*]benzimidazoles are formed [3]. We utilized this method to synthesize the previously unknown silyl-substituted pyrido[1,2-*a*]benzimidazoles. The last present interest as compounds with potential biological activity [5].

The initial 1-(2,4-dinitrophenyl)-3-methyl-4-dimethylphenylsilylpyridine chloride (I) was synthesized from 2,4-dinitrochlorobenzene and 3-methyl-1-dimethylphenylsilylpyridine in boiling acetone with the yield of 85%. When this reaction is carried out in ether at 20°C, the yield of the salt (I) decreases twofold.



When the salt (I) undergoes reaction with phenylhydrazine in boiling glacial acetic acid, intramolecular reductive cyclization occurs at both α-positions of the pyridine ring with the formation of the mixture of 7-nitro-2-methyl- and 7-nitro-4-methyl-3-dimethylphenylsilylpyrido[1,2-*a*]benzimidazoles, (II) and (III) respectively, in the ratio of 1.2:1 according to the PMR data. Also occurring in the process of the reaction, besides the cyclization, is the cleavage of the salt (I) into the silylpyridine and dinitrochlorobenzene, as well as the formation of N-phenyl-N'-acetylhydrazine.

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TABLE 1. PMR Spectral Parameters of the Silyl-substituted Pyrido[1,2-*a*]benzimidazoles (II)-(V)

Compound	Chemical shift, δ, ppm (J, Hz)										
	1-H	2-H	4-H	6-H	8-H	9-H	$SiCH_3$	2-CH_3	4-CH_3	NH_2	SiPh
II*	8,17	—	7,96	8,82 (2,1)	8,26 (2,1, 8,3)	7,92	0,705	2,30	—	—	7,52, m
III	8,32 (3,5)	6,96 (3,5)	—	8,88 (2,1)	8,24 (1,5, 8,6)	7,91	0,710	—	2,70	—	7,40, m
IV	8,05	—	7,84	7,11	6,68	7,56	0,63	2,20	—	3,66	7,33, m
V*	8,32	6,98	—	7,19	6,76	7,63	0,63	—	2,70	3,66	7,33, m

*The spectrum of the mixture of isomers was analyzed.

The compound (III) was separated chromatographically in the discrete form. In contrast to the data of the work [3], the 1,2,3,4-tetrahydro derivatives of the compounds (II) and (III) were not isolated in any of the experiments. The IR spectrum of the compounds (II) and (III) contains bands of the NO_2 vibrations at 1525 and 1345 cm^{-1}. Their mass spectra show the peak of the molecular ion 361,* of maximal intensity, corresponding with their empirical formula. The main routes of the fragmentation of the M^+ ion are associated with the elimination of NO_2 as well as CH_3 and C_6H_5 from the silicon atom; this leads to the formation of the 315 (6%), 346 (45%), and 284 (8%) ions correspondingly. The cleavage of the Si—heterocycle bond is accompanied by the localization of charge on the silyl-containing substituent and the appearance of the $[SiMe_2Ph]^+$ ion 135 (10%) in the mass spectrum. The PMR spectrum (Table 1) of the compounds (II) and (III) shows the signals of all the protons present in the molecule. The PMR spectrum of compound (III) is characterized by the signal of the protons of the CH_3 group, at lower field than found in compound (II), and two doublets from the 1-H and 2-H protons. In the PMR spectrum of compound (II), the signal of the protons of the 2-CH_3 group is split into a doublet (J = 1 Hz) due to the spin—spin interaction of the protons of the methyl group with the 1-H proton. The assignment of the signals of the 6-H, 8-H, and 9-H protons was performed taking into account their position, multiplicity, and integral intensity.

The reduction of the mixture of nitro derivatives (II) and (III) by iron in hydrochloric acid gave the mixture of 7-amino-2-methyl- and 7-amino-4-methyl-3-dimethylphenylsilylpyridines, (IV) and (V) respectively of the same composition, with the yield of 67%. The compound (IV) was also synthesized with an insignificant yield by the reductive cyclization of the salt (I) in methanol saturated with hydrogen chloride in the presence of Pd/C or Pd/Al_2O_3. The separation of the mixture of amino derivatives, (IV) and (V), into the individual isomers could not be managed using column chromatography. The chemical shifts of the protons of the compounds (IV) and (V), presented in Table 1, were obtained by the analysis of the PMR spectrum of the mixture of these compounds. The IR spectrum of the mixture of the compounds (IV) and (V) contains the band of the stretching vibrations of the amino group at 3450 cm^{-1}. Their mass spectrum shows the peak of the molecular ion 331 (100%), of maximal intensity, corresponding with the empirical formula. The M^+ ions of the amino derivatives are characterized by high stability. The main route for their decomposition is the elimination of the methyl group from the silicon atom, which leads to the fragment ion 316 (38%). The intensity of the peak of the ion 254, corresponding with the cleavage of phenyl, does not exceed 1%.

Therefore, the synthesis of silyl-substituted pyrido[1,2-*a*]benzimidazoles was accomplished for the first time.

EXPERIMENTAL

The PMR spectra of the compounds (II) and (III) were recorded on the Bruker WM-400 spectrometer, and those of the compounds (IV) and (V) were recorded on the Bruker WP-80 instrument in $CDCl_3$ using TMS as the internal standard.

The mass spectra were obtained on the MX-1303 instrument with the system of the direct introduction of the sample at the ion source using the ionizing voltage of 70 eV. The IR spectra were taken on the VR-20 spectrometer using KBr tablets.

*Here and further, the m/z values are given for the peaks of the ions.

Column chromatography was performed on Al_2O_3 of grade Brockmann II. The thin layer chromatography was performed on plates with a fixed layer of Al_2O_3 of type Alufol. Development was effected with iodine vapor.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

3-Methyl-1-(2,4-dinitrophenyl)-4-dimethylphenylsilylpyridinium Chloride (I) ($C_{20}H_{20}ClN_3O_4Si$). A. The mixture of 2.27 g (0.01 mole) of 3-methyl-4-dimethylphenylsilylpyridine and 2.03 g (0.01 mole) of 2,4-dinitrochlorobenzene in 10 ml of abs. acetone is boiled for 2 h. The residue obtained after the distillation of the acetone is triturated in abs. ether. The salt (I) is obtained with the yield of 3.65 g (85%) as a dark brown bright powder, darkening in air, and having the mp 138-141°C (from ether, decomp.).

B. The solution of 6.68 g (29 mmole) of 3-methyl-4-dimethylphenylsilylpyridine and 5.95 g (29 mmole) of dinitrochlorobenzene in 100 ml of abs. ether is held for 3 days at 20°C. The salt (I) is obtained with the yield of 5.48 g (44%). The mixed test with the sample obtained according to the method A does not give a depression of the melting temperature. Found, %: C 56.2, H 4.7, N 9.7, and Cl 8.0. Calculated, %: C 55.9, H 4.7, N 9.6, and Cl 8.3.

7-Nitro-2-methyl- and 7-Nitro-4-methyl-3-dimethylphenylsilylpyrido[1,2-a]benzimidazoles (II) and (III). ($C_{20}H_{19}N_3O_2Si$). To the solution of 3.62 g (8.4 mmole) of the salt (I) in 20 ml of glacial acetic acid at 70°C are added 7.06 g (65 mmole) of freshly distilled phenylhydrazine, and the mixture is boiled for 2 h. The residue remaining after the distillation of the acetic acid is chromatographed on a column, 50 by 1.5 cm, with Al_2O_3 using the 3:1 mixture of ether—heptane as the eluent. The following compounds are separated sequentially: 0.5 g of 3-methyl-4-dimethylphenylsilylpyridine with the R_f 0.7 (Alufol, the 3:1 mixture of ether—heptane) and the mass spectrum characterized by the M^+ 227, 0.35 g of the mixture of the silylpyridine and dinitrochlorobenzene with the mass spectrum characterized by the M^+ 227 and 202 (for the isotope ^{35}Cl), and 1.45 g (48%) of the mixture of compounds (II) and (III) with the R_f values 0.53 and 0.50 (Alufol, the 3:1 mixture of ether—heptane) as yellow crystals with the mp 162-165°C (the 1:3 mixture of ether—hexane) and the mass spectrum characterized at 361 (100, M^+), 346 (32), 315 (5), 300 (20), 284 (5), 283 (15), and 135 (8). Found, %: C 66.3, H 5.4, and N 11.4. Calculated, %: C 66.5, H 5.3, and N 11.6. Ether is utilized to elute 10 mg of acetylphenylhydrazine with the R_f 0.05 (Alufol, the 3:1 mixture of ether—hexane), identical in its chromatographic mobility to a known sample, and the mass spectrum is characterized by the M^+ 150. The separated mixture (1 g) of the compounds (II) and (III) is chromatographed repeatedly on a column, 60 by 0.8 cm, using the 2:1 mixture of ether—hexane as the eluent.The finish of the chromatography leads to the isolation of 50 mg of compound (III) with the R_f 0.5, being yellow crystals with the mp 169-170°C (the 1:3 mixture of ether—hexane). Found, %: C 66.7, H 5.1, and N 11.5.

7-Amino-2-methyl- and 7-Amino-4-methyl-3-dimethylphenylsilylpyrido[1,2-*a*]benzimidazoles (IV) and (V). ($C_{20}H_{21}N_3Si$). A. The mixture of 1.35 g (3.7 mmole) of the mixture of the nitro compounds (II) and (III), 1.74 g (18 mmole) of iron filings, and 60 ml of hydrochloric acid (1:1) is boiled for 1 h. To the reaction mixture are added 10 ml of ethanol, and the solution is decanted and extracted with 3 portions of 10 ml of ether. The aqueous layer is rendered alkaline with sodium carbonate to the pH 10-12, and the reduction products are extracted with 3 portions of 60 ml of chloroform. The residue remaining after the distillation of the chloroform is purified chromatographically on a column, 50 by 1.5 cm, with Al_2O_3 using chloroform as the eluent. The mixture of the compounds (IV) and (V) is isolated with the yield of 0.83 g (67%), and has the R_f 0.5 (Alufol, the 100:1 mixture of chloroform—ethanol), being bright brown crystals with the mp 70-72°C (hexane—benzene). The mass spectrum is as follows: 331 (100, M^+), 330 (30), 316 (39), 315 (2), 314 (5), and 300 (2). Found, %: C 72.6, H 6.4, and N 12.8. Calculated, %: C 72.5, H 6.4, and N 12.7.

B. To the solution of 1.65 g (3.8 mmole) of the salt (I) in 50 ml of methanol, saturated with hydrogen chloride, is added 0.5 g of 1% Pd/C (or 1% Pd/Al_2O_3). Hydrogen is passed through the reaction mass for 4 h at 40°C. The residue remaining after the distillation of the methanol *in vacuo* is neutralized with the aqueous solution of sodium carbonate and extracted with benzene. The residue remaining after the distillation of the benzene is triturated with ether. Chromatography of the ether extract on a column, 40 by 1.5 cm, with aluminum oxide using the 3:1 mixture of ether—hexane as the eluent leads to the isolation of 0.15 g of the mixture of the nitro derivatives (II) and (III), as yellow crystals with the mp 160-163°C. In the mixed test with the standard, it melts without the depression of the temperature. The residue which did not dissolve in ether is crystallized repeatedly from the 10:1 mixture of hexane—benzene. The compound (IV) is isolated with the yield of 40 mg (4%) as brown crystals with the mp 78-80°C (hexane—benzene). The mass spectrum is characterized as the M^+ 331.

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