NEW METHOD FOR THE SYNTHESIS OF PYRIDO[1,2-a]BENZIMIDAZOLE

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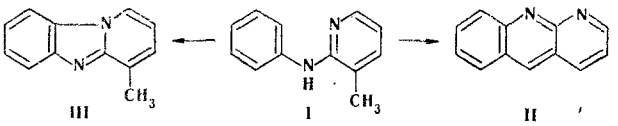
A catalytic method for the conversion of α-(phenylamino)pyridines to pyrido-[1,2-a]benzimidazoles was developed.

The methods for the preparation of pyrido[1,2-a]benzimidazole described in the literature are either multistep methods [1] or involve the preparation of starting compounds that are difficult to obtain [2, 3], as a consequence of which insufficient study has been devoted to its chemical and other properties. Pyridobenzimidazole derivatives are of interest for the study of their physiological activity, since pyrido[1,2-a]benzimidazole itself has analgesic and antipyretic properties [3].

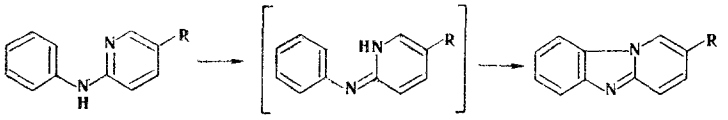
We undertook a study of the transformations of α-(phenylamino)-substituted pyridine bases on a K-16 dehydrogenating catalyst at 560-580°C. We found that under these conditions the dehydrocyclization of 3-methyl-2-phenylaminopyridine (I) proceeds via two pathways. In addition to benzo[b]-1,8-naphthyridine (II) (in 8% yield), in the reaction products we detected for the first time 4-methylpyrido[1,2-a]benzimidazole (III), which is formed by intramolecular cyclization of starting I with the participation of the pyridine ring nitrogen atom.



III I II

The data from the PMR spectrum of III confirm its structure. Approximately equal $J_{1,2}$ and $J_{2,3}$ values, which are characteristic for the indolizine fragment, are observed in the spectrum. The location of the methyl group in the $C_{(4)}$ position is confirmed by the constants of spin-spin coupling of the 1-H and 3-H protons with the methyl protons (Table 1).

The generality of the new method for the construction of the pyridobenzimidazole system was further confirmed in the case of the dehydrocyclization of 2-phenylaminopyridine (IV) and 5-methyl-2-phenylaminopyridine (V). In the first case we obtained unsubstituted pyrido-[1,2-a]benzimidazole (VI) [2], whereas in the second case we obtained the previously unknown 2-methylpyrido[1,2-a]benzimidazole (VII).



IV, V VI, VII

IV, VI R=H; V, VII R=CH_3

The structures of polycyclic II, III, VI, and VII were proved by interpretation of their PMR spectra with the aid, where necessary, of iteration calculations of the questionable spectra with a computer (Table 1).

Thus the catalytic transformation of α-aminopyridines open up a pathway to the synthesis of substituted pyrido[1,2-a]benzimidazoles, as well as benzo[b]-1,8-naphthyridines.

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TABLE 1. PMR Spectra of Benzonaphthyridine and Pyridobenzimidazoles (II, III, VI, and VII)

Compound	Chemical shifts, δ, ppm									SSCG, J, Hz
	ring protons								CH_3 protons	
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	
II	—	9,17	7,34	8,23	8,54	7,88	7,73	7,47	8,27	—	(6—7) 8,3; (6—8) 1,5; (6—9) 0,8; (7—8) 6,7; (7—9) 1,1; (8—9) 8,7; (5—9) 0,9; (5—4, 5—6) 0,2—0,3[a]
III	8,29	6,67	7,20	—	—	7,96	7,33	7,50	7,83	2,62	(1—2) 6,8; (1—3) 1,2; (2—3) 6,7; (6—7) 8,1; (6—9) 0,7; (7—8) 7,2; (7—9) 1,1; (8—9) 8,8; (1—4-CH_3) 0,6; (3—4-CH_3) 1,3[b]
VI	8,37	6,80	7,36	—	—	7,91	7,33	7,50	7,83	—	(1—2) 6,6; (1—3) 1,2; (1—4) 1,2; (2—3) 6,7; (2—4) 1,0; (3—4) 9,0; (6—7) 8,1; (6—8) 1,0; (6—9) 0,5; (7—8) 6,9; (7—9) 0,9; (8—9) 8,3
VII	8,15	—	—	—	—	—	—	—	—	2,36 br	—

[a]Double resonance (5-H) was used in the analysis. [b]Iteration analysis with a computer for systems of the ABC and ABCD types and double resonance (4-CH_3).

EXPERIMENTAL

The PMR spectra were obtained with BS-497 (100 MHz, CW), BS-467 (60 MHz), and Brucker WP-80 Fourier (80 MHz) spectrometers with tetramethylsilane as the internal standard. Iteration analysis and calculations of the complex spectra were realized by means of the ITR CAL program. The mass spectra were obtained with an MKh-1303 spectrometer. The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a UV-vis spectrophotometer. Activity II (Brockmann classification) aluminum oxide was used for thin-layer chromatography (TLC) and column chromatography. Data from the PMR spectra of the compounds obtained are presented in Table 1.

4-Methylpyrido[1,2-a]benzimidazole (III), Pyrido[1,2-a]benzimidazole (VI), and 2-Methylpyrido[1,2-a]benzimidazole (VII). A solution of 0.012 mole of pyridine I, IV, or V in 20 ml of benzene was passed at 560-580°C at a constant rate in the course of 40 min through a quartz reactor of the flow type containing 5 ml of K-16 catalyst. At the end of the reaction, the reactor was washed with 100 ml of benzene, the benzene was removed from the catalyzate by distillation, and the residue was chromatographed. Initial elution with hexane—ether (10:1) gave starting pyridine I, IV, or V, after which elution with the same mixture in a ratio of 5:1 gave pyridobenzimidazoles III, VI, and VII. Benzonaphthyridine II was eluted from the products of dehydrocyclization of pyridine base I by means of the 5:1 solvent mixture.

4-Methylpyrido[1,2-a]benzimidazole (III). This compound, with mp 134.5-136°C (from hexane), was obtained as colorless crystals in 9.4% yield. UV spectrum, λ_{max} (log ε): 214 (4.16), 240 (4.70), 245 (4.66), 258 (4.32), 266 (4.18), 298 (3.74), 310 (3.78), 338 (3.88), 352 (3.86), and 372 nm (3.62). Found: N 15.4%; M^+ 182. $C_{12}H_{10}N_2$. Calculated: N 15.4%; M 182.

Pyrido[1,2-a]benzimidazole (VI). This compound, with mp 180.5-182°C (from ether), was obtained as colorless crystals in 27% yield. UV spectrum, λ_{max} (log ε): 206 (4.84), 242 (4.82), 246 (4.84), 258 (4.26), 268 (4.18), 300 (3.76), 312 (3.78), 330 (3.76), 342 (3.94), 360 (3.79), and 380 nm (3.48). Found: C 78.4; H 4.4; N 16.3%; M^+ 168. $C_{11}H_8N_2$. Calculated: C 78.6; H 4.7; N 16.6%; M 168.

2-Methylpyrido[1,2-a]benzimidazole (VII). This compound, with mp 141-143°C (from hexane), was obtained as colorless crystals in 22% yield. UV spectrum, λ_{max} (log ε): 210 (3.92), 240 (4.26), 247 (4.33), 261 (3.82), 270 (3.72), 302 (3.28), 314 (3.34), 337 (3.30), 346 (3.32), 364 (3.32), and 384 nm (3.04). Found: N 15.4%; M^+ 182. $C_{12}N_{10}N_2$. Calculated: N 15.4%; M 182.

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FORMATION OF DERIVATIVES OF PYRAZINE 1,4-DIOXIDE AND 1-HYDROXYIMIDAZOLE IN THE CONDENSATION OF 1,2-HYDROXYAMINO OXIME ACETATES WITH 1-PHENYL- AND 1-(2-HETARYL)-1,2-DICARBONYL COMPOUNDS

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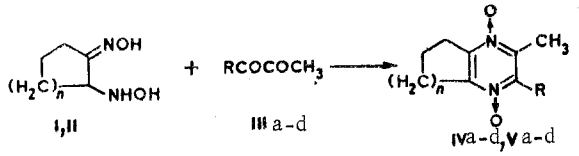
The condensation of acetates of 2-hydroxyaminocyclohexanone and 2-hydroxyaminopentanone oximes with 1-phenyl and 1-(2-hetaryl) 1,2-diketones leads to pyrazine 1,4-dioxide derivatives, whereas the condensation of 2-hydroxyaminocyclohexanone oxime acetate with 1-phenyl- and 1-(2-hetaroyl)glyoxals gives mixtures of pyrazine 1,4-dioxide and 1-hydroxyimidazole derivatives.

We have previously shown that the reaction of secondary 2-hydroxyaminocycloalkanone oximes with aliphatic 1,2-dicarbonyl compounds leads to pyrazine 1,4-dioxide derivatives [1], whereas tertiary 1,2-hydroxyamino oximes condense with diacetyl to give 1-hydroxy-2-acetyl-3-imidazoline 3-oxide derivatives [2]. In the present research we studied the reaction of acetates of 2-hydroxyaminocycloalkanone oximes with 1-phenyl and 1-(2-hetaryl) 1,2-dicarbonyl compounds, viz., both glyoxals and diketones.

2-Hydroxyaminocyclopentanone and 2-hydroxyaminocyclohexanone oximes (I, II) react with 1-phenyl- and 1-(2-hetaryl)-1,2-propanediones (IIIa-d) to give IVa-d and Va-d, the compositions of which correspond to products of condensation with splitting out of two water molecules (Table 1). The IR spectra of IVa-d and Va-d contain intense absorption of an N → O group at 1300-1380 cm^{-1}, and the UV spectra coincide with the spectrum of a pyrazine 1,4-dioxide derivative [3]. The PMR spectra are also in agreement with the proposed formulas (Table 2).



I, IV $n=1$; II, V $n=2$; III a R=Ph; b R=2-furyl; c R=2-thienyl, d R=5-methyl-2-furyl

Only the starting compounds were isolated in an attempt to realize the condensation of hydroxyamino oximes I and II with bifuroyl and bibenzoyl under the same conditions.

The available information on direct methods for the synthesis of pyrazine and quinoxaline 1,4-dioxide derivatives without the use of oxidation is limited [4]. At the same time, a number of pyrazine and quinoxaline dioxide derivatives are biologically active substances, particularly when there is a hetaryl substituent in the 2 position [5]. Phenyl- and hetarylglyoxals were therefore subjected to condensation in order to increase the number of pyrazine 1,4-dioxides obtained from 2-hydroxyaminocycloalkanone oximes.

In contrast to 1,2-diketones, phenyl- and hetarylglyoxals VIa-c react with hydroxyamino oximes II via two pathways to give mixtures of 1-hydroxyimidazole derivatives VIIa-c and pyrazine 1,4-dioxide derivatives VIIIa-c. Thus the condensation of II with phenylglyoxal hydrate in alcohol at 20°C for 12 h leads to a mixture of 1-hydroxy-2-benzoyl-4,5,6,7-tetra-

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