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SYNTHESIS OF INDOLE DERIVATIVES OF PYRIDO[2,3-d]PYRIMIDINE

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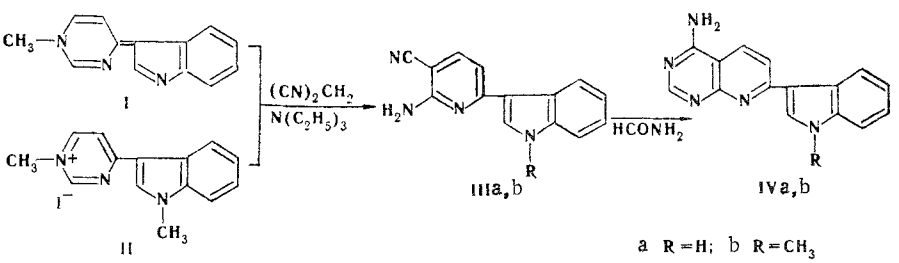
Recyclization of the pyrimidine ring with inclusion of the reagent in the newly formed ring to give indole derivatives of 2,3-disubstituted pyridines occurs in the reaction of the anhydro base of 4-(3-indolyl)pyrimidine with CH acids in the presence of triethylamine. The products react with formamide to give the pyrido[2,3-d]pyrimidine heterocyclic system.

Indole derivatives of condensed heterocyclic systems with nitrogen atoms in different rings are difficult to obtain and are limited to a few representatives, since there is no convenient method for their preparation. Isomeric indolyl-1,2-dihydro-1,5-naphthyridines and indolyl-1,2-dihydro-1,8-naphthyridines, which are obtained by direct reaction of indole with naphthyridines in the presence of benzoyl chloride [1], and the indole derivative of 2,3-dihydropurine, which is formed via a similar pathway [2], constitute exceptions. These dihydro structures could not be aromatized, whereas both indole and condensed heterocycles, viz., purine, pteridine, etc., are important structural fragments of many natural and synthetic physiologically active substances. In this connection the search for new convenient methods for the synthesis of such structures is an urgent task.

We have previously reported [3] the synthesis of 2-amino-3-cyano-6-(3-indolyl)pyridines (III) in the recyclization of anhydro base I or quaternary salt II under the influence of the anion of malonic acid dinitrile. The ortho orientation of the functional groups in pyridylindoles III makes it possible to regard these compounds as promising starting compounds for the subsequent construction of new heterocyclic systems. It is known that o-amino nitriles readily give condensed 4-aminopyrimidines in high yields when they are heated briefly in excess formamide [4]. This reaction lies at the foundation of one of the rather widely used methods for the synthesis of a pyrimidine ring and is regarded as a qualitative reaction for vicinal amino nitriles.

Compounds III [3] also react readily with formamide to give indole derivatives (IV) of pyridopyrimidine:



Absorption bands at 3300 cm^{-1}, which correspond to ν_{NH_2} vibrations, and a series of intense absorption bands at 1650-1670 cm^{-1}, which we assigned to the absorption ($\nu_{C=N}$) of the

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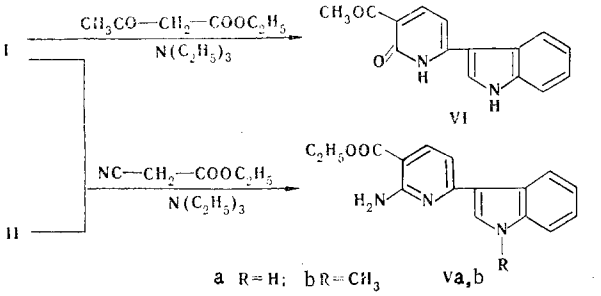
C=N bonds in the molecules, and a signal at 3496 cm^{-1} (ν_{NH}) from the indole ring are present in the IR spectra of IVa, b. The latter peak is absent in the IR spectrum of IVb. Two singlets of indole 7-H and 2-H protons at 9.16 and 8.87 ppm, respectively, two doublets at 8.92 and 8.48 ppm, which were assigned, respectively, to the protons attached to the $C_{(3)}$ and $C_{(4)}$ atoms of the pyridine ring with $J_{3,4}$ = 8 Hz and $J_{4,5}$ = 7 Hz (an AB system), and a multiplet of aromatic protons of the indole ring at 7.63 ppm are observed in the PMR spectrum of pyridopyrimidine IVa. Similar signals are also observed in the PMR spectrum of IVb: 9.03 (1H, s, indole 7-H), 8.83 (1H, s, indole 2-H), 8.71 (1H, d) and 8.37 (1H, d) [protons attached to the $C_{(3)}$ and $C_{(4)}$ atoms of the pyridine fragment with $J_{3,4}$ = 7.8 Hz and $J_{4,5}$ = 7.5 Hz], and a multiplet of aromatic protons of the benzene ring of indole centered at 7.56 ppm. In addition to the indicated signals, a singlet signal of three protons of the N-methyl group at 4.05 ppm appears in the PMR spectrum of IVb.

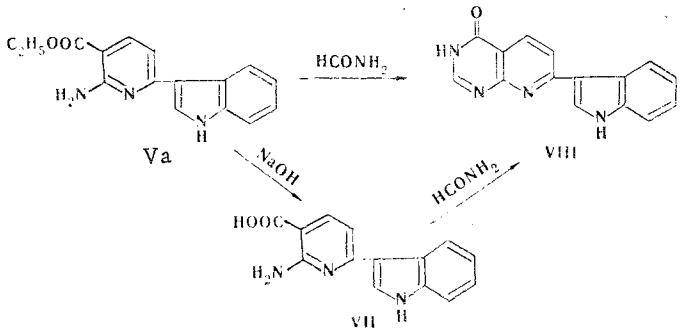
An M^+ peak, which corresponds to the calculated molecular mass, is recorded in the mass spectrum of IVa. The pattern of the fragmentation of M^+ is typical for heterocyclic compounds with structures of the biphenyl type [5]: the interannular C–C bond is not cleaved, but a hydrogen atom is split out with cyclization of the rings in the $[M - H]^+$ ion to give a condensed system. The three-stage successive elimination of an HCN particle from the $[M - H]^+$ ion demonstrates the presence of a pyridopyrimidine fragment in the molecule. A peak of doubly charged molecular ions (M^{++}) is also observed in the spectrum.

The ease of recyclization of the indolylpyrimidine derivatives (I or II) under the influence of the anion of malonic acid dinitrile provides a basis for the assumption that other CH acids, the pK_a values of which are close to the pK_a value of malonic acid dinitrile (~11), could cause recyclization of the pyrimidine ring, which is included in the ring formed in this case to give pyridylindoles with a set of various functional groups in the pyridine ring. We selected ethyl cyanoacetate, diethyl malonate, and ethyl acetoacetate, the pK_a values of which are, respectively, 9, 11, and 11, as the CH acids. We found that anhydro base I does not react with diethyl malonate, whereas it does react with ethyl cyanoacetate to give 2-amino-3-carbethoxy-6-(3-indolyl)pyridine (V). In the formation of the pyridine ring in this case cyclization proceeds with the participation of the nitrile group of ethyl cyanoacetate rather than with participation of the carbonyl group. Anhydro base I reacts with ethyl acetoacetate under similar conditions to give 3-acetyl-6-(3-indolyl)-2-pyridone (VI):



Salt II behaves similarly in this reaction to give pyridylindole Vb. Triplets centered at 1.39 and 1.42 ppm, respectively, and quartets at 4.45 ppm, which are due to the presence of protons of an ethyl substituent of an ester residue, and a weakly resolved multiplet of aromatic protons centered at 7.64 ppm, among which the signal of the α-carbon atom of the indole substituent at 8.33 ppm is isolated, are observed in the PMR spectra of Va, b. A signal of an N-methyl group of indole at 4.03 ppm is additionally present in the spectrum of Vb. We also confirmed the structure of Va, b by mass spectrometry. These compounds can also be classified as bisheterocycles with structures of the biphenyl type. However, the position of the substituents (the ortho effect [6]) and the presence of an ester grouping in the pyridine ring change somewhat the fragmentation pattern that is characteristic for bisheterocycles, primarily because of the possibility of localization of the charge in M^+ on the carbonyl group [7]. Processes that are characteristic for ketones and esters take place in the first step of fragmentation of M^+: as a result of the McLafferty rearrangement, an olefin molecule is split out, and "ester" fragmentation with the ejection of OC_2H_5 and $COOC_2H_5$ radicals and a neutral $COOC_2H_4$ fragment also takes place. The $[M - OC_2H_5]^+$ and $[M - C_2H_4COO]^+$ ions can subsequently undergo dehydrogenation to give charged condensed heteroresidues or can successively eliminate HCN molecules (ions with m/z 182, 181, and 164). The formation of doubly charged fragment ions is observed.

When pyridylindoles IIIa and Va are refluxed in an aqueous alcohol solution of alkali, they are readily hydrolyzed to nicotinic acid derivative VII. Both acid VII and esters V (for example, Va), like vicinal amino nitriles, readily undergo condensation with formamide to give the same compounds, viz., 2-(3-indolyl)pyrido[2,3-d]-4-pyrimidinone (VIII):



In a study of the mass spectrum of VIII we established that it has high resistance to electron impact (W_M = 15.5). Under electron impact a hydrogen atom is split out from M^+, and cyclization occurs due to the formation of a four-membered ring at the hetaryl nitrogen atom, which has a great deficiency of π electrons; intense peaks of doubly charged M^{++} and $[M - H]^{++}$ ions are also present. Peaks of ions that characterize the pyridopyrimidine part of the molecule, viz., $[M - CO]^+$ (F), $[F - HCN]^+$, and $[F - H_2CH]^+$, are additionally recorded in the mass spectrum. The structure is in the S-cis conformation [7], as evidenced by the extremely intense $[M - H]^+$ ion peak. The elimination of a molecule of CO from M^+ constitutes evidence in favor of the oxo form of 4-pyrimidinone VIII.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform and suspensions in mineral oil were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Varian MAT-311A spectrometer at an accelerating voltage of 3 kV, a cathode emission current of 300 μA, and an ionizing voltage of 70 eV. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla-80 spectrometer with tetramethylsilane as the internal standard. Chromatography in a loose thin layer of Al_2O_3 was realized by elution with chloroform–benzene–hexane (30:6:1) (system A) and chloroform–benzene–hexane–methanol (30:6:1:1) (system B).

2-Amino-3-carbethoxy-6-(3-indolyl)pyridine (Va). A mixture of 0.9 g (4 mmole) of 1-methyl-4-(indolen-3-ylidene)-1,4-dihydropyrimidine, 0.7 g (6 mmole) of ethyl cyanoacetate, and 1 ml of triethylamine in 25 ml of acetonitrile was refluxed for 10 h, after which water was added to the reaction mixture, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 0.7 g (58%) of a product with mp 190-191°C and R_f 0.4 (A). IR spectrum: 1710 (C=O), 3330 (NH_2), and 3490 cm^{-1} (indole NH). PMR spectrum: 1.39 (t, C_2H_5), 4.45 (q, C_2H_5), 7.64 (m, aromatic protons), and 8.33 ppm (s, indole 2-H). Mass spectrum, m/z (%): 140.5 (8.3), 152 (6.3), 164 (14.4), 181 (19.1), 182 (12.2), 208 (24.4), 209 (8.9), 234 (18.6), 236 (29.7), 253 (27.4), 281 (100). W_M = 9.2. Found, %: C 68.2; H 5.5; N 14.8. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.3; H 5.3; N 15.1

TABLE 1. Indole Derivatives of Pyridine and Pyrido[2,3-d]pyrimidine

Compound	mp,[a] °C	R_f[b]	IR spectrum, ν, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IVb	320—321	—	1630 (C=N), 3410 (NH_2)	69,8	4,6	25,6	$C_{16}H_{13}N_5$	69,8	4,7	25,5	91
Vb	174—175[c]	0,38	3400 (NH_2), 1660 (C=O)	69,3	5,6	14,1	$C_{17}H_{17}N_3O_2$	69,2	5,8	14,2	14
VI	309—310	0,27	3380 (indole NH), 3480 (indole NH), 3610 (OH), 1690 (C=O)	71,4	4,8	11,1	$C_{16}H_{12}N_2O_2$	71,6	4,9	11,1	17
VIII	350—351	0,50	3380 (amide NH), 3490 (indole NH), 1590, 1660 (C=N)	68,8	3,6	21,3	$C_{15}H_{10}N_4O$	68,7	3,8	21,4	89

[a]From DMF. [b]In system B. [c]From ethanol.

The other pyridylindoles, the principal characteristics of which are presented in Table 1, were similarly obtained.

2-Amino-6-(3-indolyl)nicotinic Acid (VII). A suspension of 0.3 g (1.4 mmole) of 2-amino-3-cyano-6-(3-indolyl)pyridine in a 10% aqueous methanol solution of KOH was refluxed for 30 min, after which it was cooled and neutralized with 10% HCl. The resulting precipitate was removed by filtration and recrystallized from ethanol to give 0.2 g (74%) of a product with mp 275-276°C. IR spectrum: 1690 (C=O), 3300 (NH_2), 3495 (indole NH), and 3600 cm^{-1} (OH). Found, %: C 66.2; H 4.3; N 16.7. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.4; H 4.3; N 16.6.

2-(3-Indolyl)-5-aminopyrido[2,3-d]pyrimidine (IVa). A mixture of 0.7 g (3 mmole) of 2-amino-3-cyano-6-(3-indolyl)pyridine and 10 ml of formamide was heated at 140°C for 2 h, after which water was added to the reaction mixture, and the precipitate was removed by filtration and recrystallized from DMF to give 0.4 g (51%) of a product with mp 376-377°C. IR spectrum: 1650 (C=N), 3300 (NH_2), and 3496 cm^{-1} (indole NH). PMR spectrum: 9.16 (1H, s, indole 7-H), 8.87 (1H, s, indole 2-H), 8.92 (1H, d), 8.48 (1H, d, 3-H–4-H), and 7.63 ppm (4-H, m, aromatic protons). Mass spectrum, m/z (%): 77 (5.3); 130.5 (6.7), 152 (5.8), 179 (12.3), 180 (6.3), 207 (7.1), 233 (17.1), 234 (8.8), 260 (60.4), 261 (100); W_M = 14.7. Found, %: C 69.1; H 4.3; N 26.7. $C_{15}H_{11}N_5$. Calculated, %: C 69.0; H 4.2; N 26.8.

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