SYNTHESIS OF 9H-PYRIMIDO[4,5-b]INDOLES FROM 2-AMINO-3-CYANOINDOLES

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The rearrangement of N-substituted N-phenylhydrazides of cyanoacetic acid under the ocnditions of the Kost reaction gave 2-amino-3-cyanoindoles, starting substances for the synthesis of pyrimido[4,5-b]indoles.

The Kost reaction has opened a route for the synthesis of 2-aminoindoles containing functional groups in the β position, in particular an amino group and an ω -haloalkyl group [1, 2]. In [3] we described an approach to the synthesis of 2-aminoindoles with a nitrile group in the 3 position, which are difficult to obtain by other methods. It was determined that N-substituted N-phenylhydrazides of cyanoacetic acid Ia-b facilely undergo rearrangement to 2-amino-3-cyanoindoles IIa and IIb in a reaction with POCl₃.



Va, VIa $R = CH_3$, Vb, VIb $R = CH_2C_6H_5$

We should note that the formation of 2-amino-3-cyanoindoles II is accomplished by their phosphorylation, and the resulting salts are difficult to purify. Therefore, for analytical purposes and spectral investigations, salts II were converted to free bases III by alkalizing their aqueous solutions.

The PMR spectrum of compound IIIa (in DMSO-D₆) contained an unresolved multiplet of aromatic protons at 6.00-6.42 ppm and a singlet of three methyl-group protons at the nitrogen atom in the region of 3.11 ppm. The IR spectrum of compound IIIa contained absorption bands of the amino group in the region of 3460-3270 and the nitrile group at 2230 cm⁻¹. The mass spectrum of base IIIa contained a peak of the molecular ion with M⁺ 171, corresponding to that calculated for this compound. In this case, there is no autooxidation at the β position of 2-amino-3-cyanoindole (IIIa), although it is known that 2-aminoindoles containing alkyl radicals in this position in the form of free bases are facilely oxidized by oxygen or air with the formation of 3-peroxy or 3-hydroxy derivatives [4]. Apparently, the introduction of electron-acceptor substituents into the β position of 2-amnoindole IIIa promotes stabilization of the 2-aminoindole form with respect to oxidation.

The presence of two functional groups in compounds III opens up wide synthetic possibilities for the construction of new heterocyclic systems based on them [5, 6]. Thus, in the reaction of unpurified salts of 2-amino-3-cyanoindoles IIa-b with formic acid in the presence of sodium acetate, we obtained compounds that, on the basis of all the spectral data, were assigned the structure of 9-substituted 4-oxo-9H-pyrimido[4,5-b]indoles IVa-b. The IR spectrum of compound IVb contained an absorption band of a carbonyl group at 1670 cm⁻¹ and a band of NH stretchng vibrations in the region of 3070 cm^{-1} . The PMR spectrum of compound IVb (in DMSO-D₆) contained not only a singlet of the methylene group (5.62) and a multiplet of aromatic protons (6.67-7.57), but also a peak of the NH group at 8.23 ppm.

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Com- pound	PMR spectrum δ, ppm (in CDC1 ₃)	Mass spectrum, M ⁺
Va	4.03(s , 3H, NCH ₃); 7.13 (s , 1H, 2-H); 7.269,03 (m , 4H, CH arom.)	217
Vb *	5.09(s , 2H, NCH ₂); 6.226,93 (m , 10H, CH arom.)	293
Vla*	3.86(s , 3H, NCH ₃); 4.26 (s , 3H, OCH ₃); 7.17,5 (m , 5H, CH arom.)	213
Vlb	4.16(s , 3H, OCH ₃); 5.52 (s , 2H, NCH ₂); 6.5 (s , 1H, 2-H); 7.68,8 (m , 9H, CH arom.)	289

TABLE 1. Spectral Characteristics of Pyrimido[4,5-b]indoles V and VI

*The peak of the 2-H proton is in the region of aromatic protons.

The mass spectrum of compound IVb contained a peak of a molecular ion with M⁺ 275, corresponding to that calculated for the given compound. Compound IVb can also exist in the tautomeric 4-hydroxy form, the presence of which was confirmed by reactions of the obtained pyrimidoindoles IVa and IVb with phosphorus oxychloride with the formation of the corresponding 4-chloro-9H-pyrimido[4,5-b]indoles Va and Vb, the structure of which was confirmed by all the spectral data (see Table 1). During reaction with sodium methylate, compounds Va and Vb were facilely converted in high yield to the corresponding 4-methoxypyrimido[4,5-b]indoles VIa and VIb. Singlets of the OCH₃ group (4.16 and 4.26 ppm) appeared in the PMR spectra of compounds VIa and VIb (see Table 1). The UV spectrum of compound VIb (in CH₃COOH) had absorption maxima at 257 and 270 nm (log ε 4.46 and 3.67) and differed significantly from the UV spectrum of 4-oxopyrimido[4,5-b]indole (IVb), in which there was also absorption at 314 nm.

Thus, 2-amino-3-cyanoindoles can be successfully used as starting substances for the synthesis of new heterocyclic structures.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 instrument (in white mineral oil), and the UV spectra were recorded on a Perkin-Elmer 402 instrument (in acetic acid). The PMR spectra were recorded on Tesla BS-587A (90 MHz) and Tesla BS-467 (60 MHz) instruments. The mass spectra were obtained on an MI-1201 instrument by bombardment with nuclei of neutral argon in a glycerin matrix. The course of the reaction was monitored by chromatography on Silufol UV-254 in a 10:1 benzene-isopropyl alcohol system.

The data of the elemental analyses for C, H, and N corresponded to the calculated values.

Cyanoacetic N-Methyl-N-phenylhydrazide (Ia, C_{10}H_{11}N_3O). A solution of 5.9 g (28 mmoles) of dicyclohexylcarbodiimide in 10 ml of tetrahydrofuran was added with stirring and cooling to a solution of 3.1 g (28 mmoles) of N-methyl-N-phenylhydrazine and 2.4 g (28 mmoles) of cyanoacetic acid in 20 ml of tetrahydrofuran. The whole was stirred for 0.5 h, the precipitate was filtered, the filtrate was evaporated, ether was poured onto the residue, the whole was left for 10 h with cooling, and the resulting precipitate was washed with ether and crystallized from a 20:1 petroleum ether—isopropyl alcohol mixture. We obtained 3.5 g (97%) of compound Ia with mp 85°C. IR spectrum: 3270 (NH), 2260 (CN), 1670 cm⁻¹ (CO).

Cyanoacetic N-Benzyl-N-phenylhydrazide (Ib, $C_{16}H_{15}N_3O$). This compound was prepared similarly to hydrazide Ia in 96% yield with mp 116°C (from 2-propanol). IR spectrum: 3060, 3220 (NH), 2250 (C=N), 1675 cm⁻¹ (CO).

2-Amino-1-methyl-3-cyanoindole (IIIa, $C_{10}H_9N_3$). For 4 h, 1 g (5.3 mmoles) of compound Ia in 10 ml of dioxane was boiled with 0.73 ml (8.0 mmoles) of phosphorus oxychloride. The solvent and the excess phosphorous oxychloride were evaporated, the obtained precipitate was suspended in 60 ml of water, alkalized to pH 9, extracted with chloroform, and evaporated, and 0.3 g (34%) of compound IIIa with mp 166-167°C was obtained. IR spectrum: 3460-3270 (NH), 2230 (C=N), 1650 cm⁻¹.

9-Methyl-4-oxo-9H-pyrimido[4,5-b]indole (IVa, $C_{11}C_9N_3O$). A mixture of 5 g (26 mmoles) of compound Ia and 3.7 ml (40 mmoles) of phosphorus oxychloride in 50 ml of absolute dioxane was boiled for 2.5 h and cooled, and the resulting precipitate of the 2-amino-3-cyanoindole salt IIa was filtered and washed with ether. We heated 1 g of the obtained precipitate (without preliminary purification) and 2 g of sodium acetate at 80°C in 20 ml of formic acid for 4 h, cooled the whole, filtered the resulting precipitate, and washed it with water and alcohol. Recrystallization was carried out from a 1:10 dimethylformamide (DMFA)—methanol mixture. We obtained 0.73 g (91%) of pyrimidoindole IVa with mp 255-260°C. IR spectrum: 1675 cm⁻¹.

9-Benzyl-4-oxo-9H-pyrimido[4,5-b]indole (IVb, $C_{17}H_{13}N_3O$). This compound was prepared similarly to pyrimidoindole IVa in 89% yield with mp 220°C (from a 1:10 DMFA-methanol mixture). IR spectrum: 1660 cm⁻¹.

9-Methyl-4-chloro-9H-pyrimido [4,5-b] indole (Va, $C_{11}H_8ClN_3$). For 1 h, 1 g (5 mmoles) of compound IVa was boiled in 5 ml of POCl₃. The phosphorus oxychloride was evaporated in vacuo, water was poured onto the residue,

and the resulting precipitate was filtered, thoroughly washed with water, and dried. Crystallization was carried out from hexane. We obtained 0.7 g (64%) of indole Va with mp 128-130°C; according to the data of [7], mp 128-130°C.

9-Benzyl-4-chloro-9H-pyrimido[4,5-b] indole (Vb, $C_{17}H_{12}ClN_3$). This compound was prepared similarly to compound Va in 84% yield with mp 126-127°C (from hexane). IR spectrum: 1700 cm⁻¹.

9-Methyl-4-methoxy-9H-pyrimido[4,5-b]indole (VIa, $C_{12}H_{11}N_3O$). A solution of 1 g (4.6 mmoles) of indole Va in 20 ml of a 1 N solution of sodium methylate in methanol was boiled for 2 h and evaporated, water was added to the residue, and the precipitate of compound VIa was filtered and recrystallized from a 1:10 DMFA-methanol mixture with mp 95-97°C. IR spectrum: 1640 cm⁻¹. The yield was 0.72 g (73%).

9-Benzyl-4-methoxy-9H-pyrimido[4,5-b]indole (VIb, $C_{18}H_{15}N_3O$). This compound was prepared similarly to pyrimidoindole VIa in 78% yield with mp 117-118°C (from alcohol). IR spectrum: 1630 cm⁻¹.

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