ANHYDRO BASE OF 4-(3-INDOLYL)PYRIMIDINE*

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The reaction of 4-(3-indolyl)pyrimidine methiodide with alkali gives a stable anhydro base, which reacts under mild conditions with methyl iodide to give 1-methyl-4-(1-methyl-3-indolyl)pyrimidinium iodide. On the basis of the calculated molecular diagrams of both compounds it was concluded that they have high reactivities. The reaction of the anhydro base with an aqueous methanol solution of KOH, concentrated NH_4OH, hydrazine hydrate, and a mixture of malonic acid dinitrile with triethylamine leads to 3-acetylindole, 4-(3-indolyl)pyrimidine, 3(5)-(3-indolyl)pyrazole, and 2-amino-3-cyano-6-(3-indolyl)pyridine, respectively. 1-Methyl-4-(1-methyl-3-indolyl)pyrimidinium iodide under the same conditions gives similar compounds that contain a methyl group attached to the indole nitrogen atom. The structures of the synthesized compounds were confirmed by their IR, UV, PMR, and mass spectra.

The quaternized pyrimidine ring reacts readily with various nucleophilic reagents, and several pathways of the chemical transformations are possible. The action of a nucleophile leads either to dealkylation of the pyrimidine ring (through a step involving the open form or as a result of direct attack by the hydroxide ion on the α-carbon atom of the N-alkyl group) or to its destruction [2, 3]. In a number of cases the nucleophile that gives rise to opening of the pyrimidine ring is included in the resulting ring in the step involving the open form [4, 5]. Methylamine in alcohol solution upon heating in a sealed ampul with quaternary salts of alkylpyrimidines also causes opening of the pyrimidine ring with subsequent reformation of a ring, not with the reagent but rather with a fragment of the molecule itself — specifically with the side alkyl or aralkyl group [6]. This recyclization leads to aminopyridine derivatives and is one of the special cases of isomerization recyclization of nitrogenous heteroaromatic systems [7]. In addition, quaternary salts of alkylpyrimidine under the influence of hydroxide ion under mild conditions are capable of splitting out a proton from the side alkyl group to give unstable anhydronium bases [8]. When an indole fragment is present in the N-alkylpyrimidinium salt, the corresponding anhydro base may prove to be completely stable, as we have previously observed in the case of quaternary salts of various pyridyl- and benzopyridylindoles [9-11]. Such stable anhydro bases may be of interest as intermediates in the synthesis of preparations with antitremor, soporific, or anesthetizing character [12]. In addition, the presence of a π-electron-donor indole fragment in the pyrimidinium salt may, when it is treated with nucleophiles, promote isomerization recyclization and the formation of a new heterocyclic system, as has been previously observed for quaternary salts of nicotyrine and 2-(3-pyridyl)indole [13, 14].

However, one should take into account the effect of aza substitution on the formation of the anhydro base of 4-(3-indolyl)pyrimidine, if one conceives of the starting cation as a derivative of the 4-(3-indolyl)pyridine cation in which one of the methylidyne groups of the pyridine ring is replaced by a nitrogen atom. Our previous studies have shown that the presence of aza substitution in the pyridine ring of the 2-(3-indolyl)quinoline cation has a pronounced effect on its reaction with alkali: Only dealkylation of the pyridine nitrogen atom occurs under the influence of alkali, and an anhydro base is not formed in even trace amounts [15]. The ratio of the dealkylation and deprotonation processes is dictated by the difference in the partial positive π-electron charges on the nitrogen atoms in the pyridine and pyrrole rings of the indolylpyridinium cations.

*See [1] for our preliminary communication.

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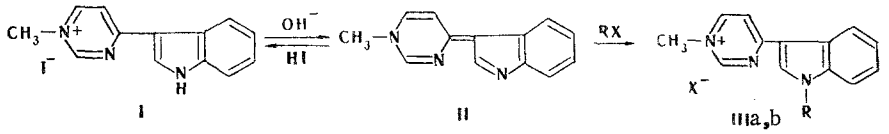
Calculation of the π-electron density in the 4-(3-indolyl)pyrimidine cation within the framework of the Pariser–Parr–Pople (PPP) method [16, 17] shows (Fig. 1) that the greatest positive π-electron charge is concentrated on the nitrogen atom in the indole ring, which exceeds that on the pyrimidine nitrogen atom (0.36098 and 0.33056, respectively). This difference, taking into account the results of our previous studies [10, 15], in combination with the high polarity of the N–H bond and the facile solvation of the proton should promote deprotonation, which terminates with the formation of the corresponding anhydro base.

In fact, when we treated 4-(3-indolyl)pyrimidine methiodide (I) under mild conditions with an alcohol solution of KOH, we obtained colored anhydro base II (λ_{max} 395 nm) in quantitative yield, which upon treatment with hydriodic acid is again converted to starting salt I:



I II IIIa,b

a R = CH_3, X = I; b R = COC_6H_5, X = Cl

The IR spectrum of anhydro base II does not contain the absorption band at 3300-3500 cm^{-1} that is characteristic for the NH group of indole, but a series of intense bands at 1610-1650 cm^{-1}, which correspond to the stretching vibrations of the C=N and C=C bonds in the molecule, is observed. A singlet of an N-methyl group at δ = 4.11 ppm, as well as a weakly resolved multiplet of aromatic protons of an indole fragment centered at δ = 7.50 ppm, is observed in the PMR spectrum recorded in trifluoroacetic acid. The singlet at weak field (δ = 8.93 ppm) is related to the most deshielded proton attached to the C_2 atom of the pyrimidine ring, while the two doublets at 8.27 and 7.93 ppm are related to the protons attached to the C_4 and C_5 atoms, respectively (J_{HCCH} = 6.9 Hz). We assigned the doublet (δ = 8.47 ppm) to the proton attached to the α-carbon atom of the indole ring. Splitting is due to spin–spin coupling with the proton attached to the indole nitrogen atom (J_{HCNH} = 3.5 Hz), since strong base II (pK_a 9.65) exists in the protonated form in trifluoroacetic acid. A molecular-ion peak (M^+) with m/z 209,* which corresponds to the calculated molecular mass, was recorded in the mass spectrum of II. The character of its fragmentation is typical for anhydro bases [18]. The following fragment ions are observed: $[M-H]^+$, which evidently has the structure of an immonium cation, $[M-CH_2]^+$ and $[M-CH_3]^+$, which characterize the presence of an N-methyl group in the molecule, and ions, the formation of which is associated with the successive splitting out of two neutral HCN particles from the $[M-CH_2]^+$ and $[M-CH_3]^+$ daughter ions (ions with m/e 168, 167, 141, and 140, respectively); this is due to the presence of nitrogen-containing hetaryls in the II system under consideration. The absence of ions, the formation of which would be due to cleavage of an interannular bond, proves its π character.

The presence of several reaction (both electrophilic and nucleophilic) centers in the II molecule (Fig. 1) makes it possible to assume the possibility of participation of anhydro base II in reactions with compounds with different chemical natures. Thus, the high δ-negative charge on the indolenine nitrogen atom (Fig. 1) explains the fact that anhydro base II reacts under mild conditions with alkyl and acyl halides to give 4-(3-indolyl)pyrimidinium quaternary salts (III) that are substituted at the indole nitrogen atom.

The electron-deficient pyrimidine ring in anhydro base II is responsible for its high activity with respect to nucleophilic reagents. Brief refluxing of base II in an aqueous methanol solution of alkali leads to opening of the pyrimidine ring and solvolytic cleavage of the open form to 3-acetylindole (IV). The action of ammonium hydroxide leads to dealkylation of the pyrimidine ring and liberation of the free base (V). A stronger base (an aqueous solution of methylamine), like a solution of alkali, gives rise to hydrolysis to give 3-acetylindole. Ring contraction, as was previously observed in [19], and the formation of 3(5)-(3-indolyl)pyrazole (VII), which we also obtained by an independent method [20], occur when anhydro base II is treated with hydrazine hydrate in alcohol solution. The reaction evidently proceeds through a step involving the intermediately formed dihydro derivative (VI):

*Here and subsequently, the numbers that characterize the ions are the mass-to-charge ratios.

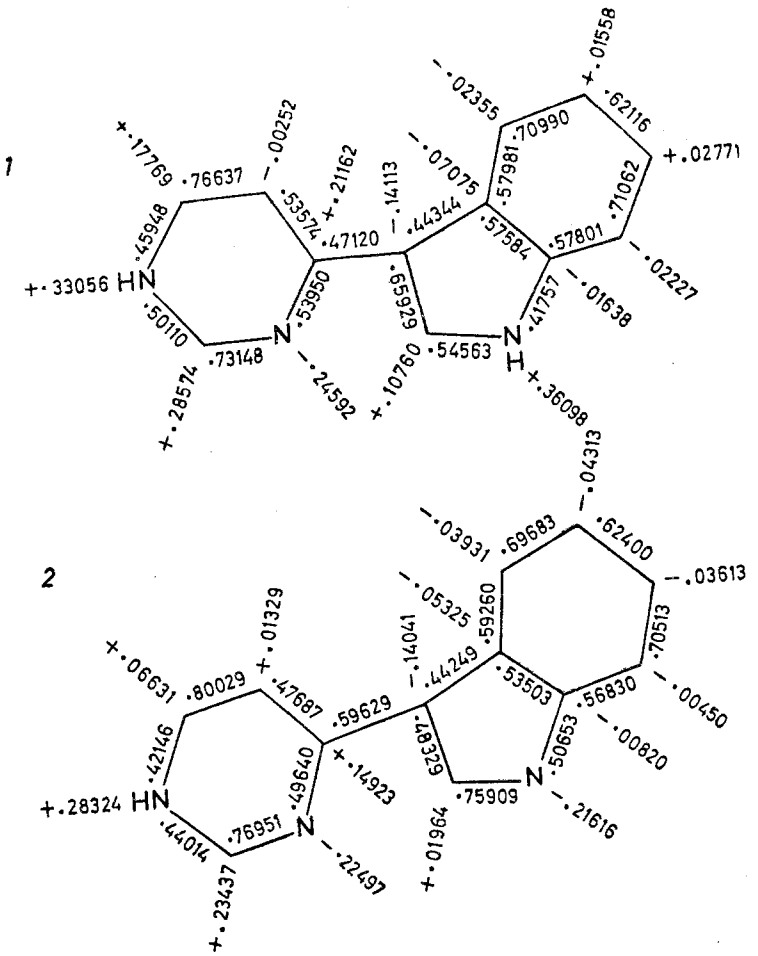
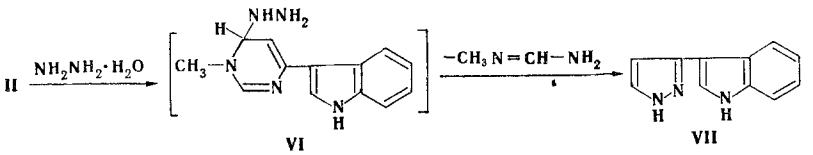


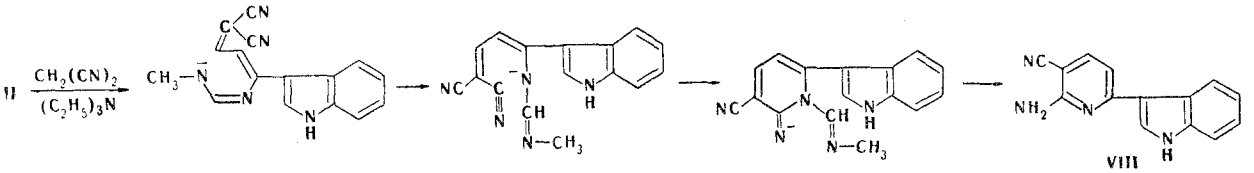
Fig. 1. Molecular diagrams: 1) 4-(3-indolyl)pyrimidine cation; 2) 1H-4-(3-indolenylidene)-1,4-dihydropyrimidine.



Compound VII behaves like other dihetaryls under electron impact. It is known [21] that hetaryl compounds with structures of the diphenyl type have rather high stability with respect to electron impact (W_M) and that the M^+ peak is, as a rule, the maximum peak in the mass spectrum. Cleavage of the interannular bond does not occur (peaks of the indole and pyrazole fragments were not observed in the mass spectrum). The presence of a pyrazole fragment in the system is confirmed by the $[M-N_2]^+$ and $[M-NH_2]^+$ ions. The elimination of an HCN particle from the $[M-N_2]^+$ and $[M-HN_2]^+$ ions constitutes evidence for the presence of a second hetaryl ring.

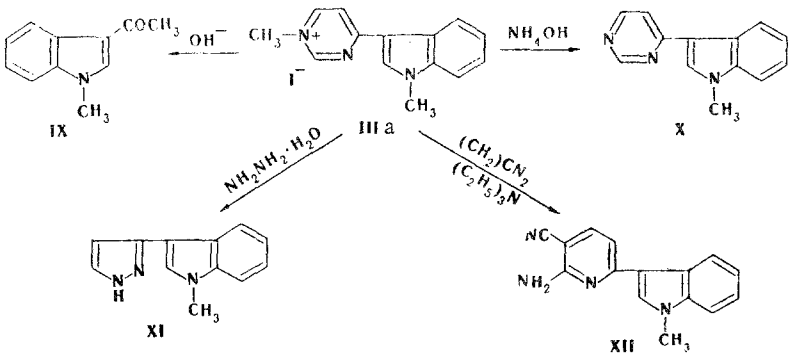
We attempted to carry out the recyclization of the pyrimidine ring by ring closure of the open form not with the reagent but rather with a fragment of anhydro base II itself, i.e., in the α position of the π-electron-surplus indole ring. However, recyclization was not observed even in the case of heating with an anhydrous alcohol solution of methylamine under the conditions described in [5], and IV and V were isolated.

In an aprotic solvent (acetonitrile), which excludes competitive solvolysis processes, the reaction of anhydro base II with malonic acid dinitrile in the presence of triethylamine leads to recyclization with the incorporation of the reagent in the resulting ring, and 2-amino-3-cyano-6-(3-indolyl)pyridine (VIII) is liberated in accordance with the scheme:



Two distinct maxima at 3410 and 3490 cm^{-1}, which are due to stretching vibrations of a 2-amino group and an indole imino group, an intense absorption band corresponding to stretching vibrations of a C≡N bond at 2210 cm^{-1}, and a series of intense bands related to the vibrations of the C=N and C–N bonds in the molecule in the region of 1400-1650 cm^{-1}, are observed in the IR spectrum of VIII. An M^+ peak is recorded in the mass spectrum of pyridylindole VIII. A calculation made from the relative intensities of the M^+ peaks and the monoisotopic $[M+1]^+$ ion proves the presence of 14 carbon atoms in the compound. As noted above, compounds of this type have increased stability with respect to electron impact (W_M = 18.4), the ability to undergo ring cyclization due to dehydrogenation processes, no ions that characterize cleavage of the interannular bond, and an intense M^{2+} peak. The noted fragmentation peculiarities are also observed in the spectrum of VIII. Ion peaks that characterize the substituents in the pyridine ring are observed in the mass spectrum in addition to the indicated peak: $[M - NH_2]^+$ (218), $[M - CN]^+$ (208), $[M - HCN]^+$ (207), $[M - H, -HCN]^+$ (206), and $[M - H, -2HCN]^+$ (179).

Salt IIIa, which was obtained by alkylation of anhydro base II, can behave in the following two ways under the influence of nucleophilic reagents: Like II, it may add a hydroxide on to the C_6 atom with subsequent opening of the pyrimidine ring and further transformations, or, as a result of attack by the hydroxide ion on the carbon atom of the N-methyl group in the indole ring, it may undergo dealkylation to anhydro base II, which subsequently reacts independently with nucleophiles, as described above. We made the latter assumption on the basis of a quantum-chemical calculation of the 4-(3-indolyl)-pyrimidine cation (Fig. 1), which shows that the greatest positive π-electron charge in it is concentrated on the nitrogen atom of the indole ring, to which attack by the nucleophilic reagent should also be primarily directed. However, we found that in the case of nucleophilic attack the methyl group attached to the indole nitrogen atom is retained, and reaction with alkali in an aqueous alcohol solution leads to 1-methyl-3-acetylindole (IX), reaction with ammonium hydroxide leads to 4-(1-methyl-3-indolyl)pyrimidine (X), reaction with hydrazine hydrate leads to 3(5)-(1-methyl-3-indolyl)pyrazole (XI), and reaction with malonic acid dinitrile under the conditions described above leads to 2-amino-3-cyano-6-(1-methyl-3-indolyl)pyridine (XII):



We also obtained X by an independent method by condensation of 1-methyl-3-acetylindole with formamide by the method described in [12].

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. 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, an ionizing voltage of 75 V, and an ion-source temperature of 250-300°C. The pK_a values were determined potentiometrically with a pH-340

meter by titration of aqueous methanol solutions of the compounds (c 10^{-2} mole/liter, 10% methanol) with a 0.1 N solution of HCl. The pK_a values were assumed to be equal to the pH values at the half-neutralization points. Chromatography in a loose thin layer of aluminum oxide (Brockmann activity) was realized by elution with chloroform–benzene–hexane (30:6:1).

1-Methyl-4-(3-indolenylidene)-1,4-dihydropyridine (II). A 1.5-g (0.007 mole) sample of I was heated in 15 ml of a saturated methanol solution of KOH until the solid dissolved completely (2-3 min), after which water was added to the reaction mixture, and the resulting precipitate was removed by filtration and recrystallized from acetonitrile to give 0.9 g (98%) of a product with mp 115-116°C and pK_a 9.65. UV spectrum, λ_{max} (log ε): 208 (3.92), 277 (3.53), 283 (3.65), and 395 nm (3.90). IR spectrum: 1650 (C=N) and 1410 cm^{-1} (C–N). PMR spectrum: 4.11 (s, N–CH_3), 8.93 (s, pyridine C_2), 8.27 (d, pyridine C_4), 7.93 (d, pyridine C_5) (J = 6.9 Hz), and 8.47 ppm (d, indole C_2). Mass spectrum, m/z (%): 57 (7.0); 63 (8.5); 89 (6.2); 91 (7.5); 97 (3.0); 104.5 (4.0); 113 (8.4); 114 (10.4); 140 (19.8); 141 (16.2); 142 (6.0); 167 (21.8); 168 (10.3); 193 (7.0); 194 (29.1); 195 (13.3); 208 (9.2); 209 (100.0); 210 (16.7); W_M = 18.5. Found: C 74.3; H 5.5; N 20.0%. $C_{13}H_{11}N_3$. Calculated: C 74.6; H 5.3; N 20.1%.

1-Methyl-4-(1-methyl-3-indolyl)pyrimidinium Iodide (IIIa). A mixture of 0.5 g (0.002 mole) of II and 0.3 g (0.002 mole) of methyl iodide in 20 ml of acetonitrile was refluxed for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration and recrystallized from methanol to give 0.2 g (25%) of a product with mp 220-221°C. Found: C 47.7; H 4.0; I 36.2; N 12.2%. $C_{14}H_{14}IN_3$. Calculated: C 47.9; H 4.0; I 36.2; N 12.0%.

Compound IIIb, with mp 260-261°C (from methanol), was similarly obtained in 25% yield. Found: C 65.4; H 4.6; Cl 10.1; N 11.1%. $C_{20}H_{14}ClN_3O$. Calculated: C 65.6; H 4.4; Cl 9.8; N 11.5%.

Reaction of 1-Methyl-4-(3-indolenylidene)-1,4-dihydropyrimidine with an Aqueous Methanol Solution of KOH. A mixture of 1 g (0.005 mole) of II in 10 ml of a 10% aqueous methanol solution of KOH (containing 50% methanol) was refluxed for 4 h, after which 30 ml of water was added, and the resulting precipitate was removed by filtration and recrystallized from benzene–ethyl acetate (1:1) to give 0.2 g (26%) of 3-acetylindole with mp 190-191°C. No melting-point depression was observed for a mixture of this product with a genuine sample.

The reaction with an aqueous methanol solution of KOH and salt IIIa proceeded similarly to give 38% 1-methyl-3-acetylindole with mp 108-109°C (from hexane). No melting-point depression was observed for a mixture of this product with a genuine sample.

Reaction of 1-Methyl-4-(3-indolenylidene)-1,4-dihydropyrimidine with NH_4OH. A suspension of 1 g (0.005 mole) of II in 20 ml of concentrated NH_4OH was refluxed for 3 h, after which water was added to the reaction mixture, and the resulting mixture was extracted several times with chloroform. The chloroform extract was dried, the chloroform was removed by distillation, and the residue was recrystallized from benzene–ethyl acetate (1:1) to give 0.7 g (70%) of 4-(3-indolyl)pyrimidine with mp 164-165°C. No melting-point depression was observed for a mixture of this product with a genuine sample.

The demethylation of salt IIIa proceeded similarly to give 69% 4-(1-methyl-3-indolyl)pyrimidine with mp 90-91°C (from cyclohexane) (mp 90-91°C [12]) and R_f 0.48.

3(5)-(3-Indolyl)pyrazole (VII). A mixture of 1 g (0.005 mole) of II and 1 ml of hydrazine hydrate in 10 ml of methanol was refluxed for 1 h, after which water was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The chloroform extract was dried, the chloroform was removed by distillation, and the residue was recrystallized from benzene to give 0.3 g (33%) of a product with mp 160-161°C (from benzene) (mp 160-161°C [20]).

3(5)-(1-Methyl-3-indolyl)pyrazole (XI) was similarly obtained in 74% yield from salt IIIa and had mp 128-129°C (from methanol) and R_f 0.60. IR spectrum: 3460 (pyrazole N–H), 1650 (C=N), and 1410 cm^{-1} (C–N). Found: C 71.1; H 6.0; N 22.9%. $C_{12}H_{11}N_3$. Calculated: C 71.4; H 5.9; N 22.7%.

2-Amino-3-cyano-6-(3-indolyl)pyridine (VIII). A mixture of 1 g (0.005 mole) of II, 0.4 g (0.006 mole) of malonic acid dinitrile, 1 ml of triethylamine, and 25 ml of acetonitrile was refluxed for 6 h, after which water was added to the reaction mixture, and the resulting precipitate was removed by filtration and recrystallized from n-butanol to give 0.6 g (50%)

of a product with mp 194-195°C and R_f 0.25. IR spectrum: 3490 (indole NH), 3410 (NH_2), 2210 (C≡N), 1650 (C=N), and 1410 cm^{-1} (C–N). UV spectrum, λ_{max} (log ε): 220 (4.50), 230 (4.49), 270 (4.10), and 370 nm (4.43). Mass spectrum, m/z (%): 43 (25.2); 55 (10.7); 57 (36.0); 71 (22.8); 85 (12.5); 90 (5.3); 103 (4.6); 117 (4.6); 179 (3.5); 206 (33.3); 207 (35.0); 208 (10.9); 217 (5.8); 218 (5.1); 232 (3.2); 233 (26.7); 234 (100.0) – M^+; 235 (17.2); W_M = 18.4. Found: C 72.1; H 4.4; N 23.5%. $C_{14}H_{10}N_4$. Calculated: C 71.9; H 4.3; N 23.9%.

2-Amino-3-cyano-6-(1-methyl-3-indolyl)pyridine (XII) was similarly obtained in 60% yield from salt IIIa and had mp 139-140°C (from methanol) and R_f 0.40. IR spectrum: 3410 (NH_2), 1630 (C=N), and 2212 cm^{-1} (C≡N). Found: C 72.2; H 4.7; N 22.8%. $C_{15}H_{14}N_4$. Calculated: C 72.6; H 4.8; N 22.6%.

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