THE 2-(4-PYRIDYL)INDOLE ANHYDRO BASE

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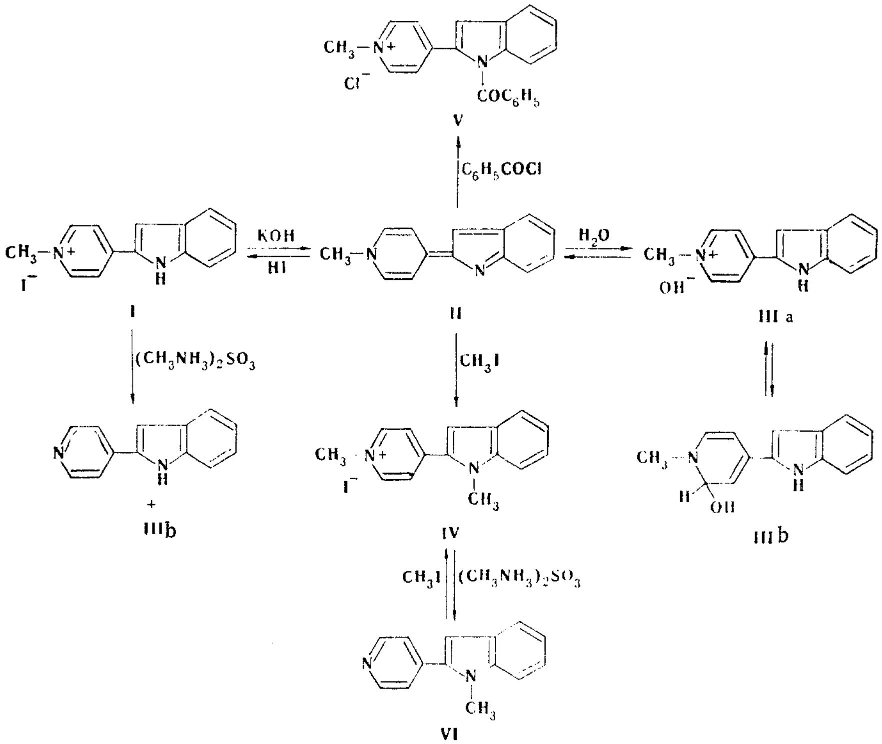
A stable anhydro base, which reacts readily with various electrophiles (the proton and alkyl or acylium cations), is formed in the reaction of 2-(4-pyridyl)indole methiodide with an alcohol solution of alkali.

We have previously reported that the quaternary salts of 3-(4-pyridyl)indole split out a molecule of hydrogen halide under the influence of alkali and are converted to stable anhydro bases [1]. In the opinion of Gray and Archer [2], the formation of anhydro bases from the quaternary salts of the isomeric 2-(4-pyridyl)indole is impossible, since the aromatic character of not only the pyrrole ring but also that of the benzene ring condensed with it will be disrupted in it. In fact, attempts to obtain the anhydro base of this structure by the action of aqueous NaOH solution on 2-(4-pyridyl)indole methiodide (I) were unsuccessful [3]; however, when methiodide I is heated briefly in a saturated alcohol solution of potassium hydroxide, it is converted smoothly in quantitative yield to the corresponding anhydro base (II), which on treatment with hydriodic acid is converted to starting salt I. Anhydro base II is a blue compound, and its formation is accompanied by a pronounced bathochromic shift of the principal band of the $\pi-\pi^*$ transitions in the UV spectrum from 380 to 440 nm (Fig. 1). When the synthesis of this compound is carried out in an aqueous or aqueous alcohol solution of alkali, only hydration product III, in which the hydroxide ion may be ionic or covalently bonded, can be isolated in low yield:



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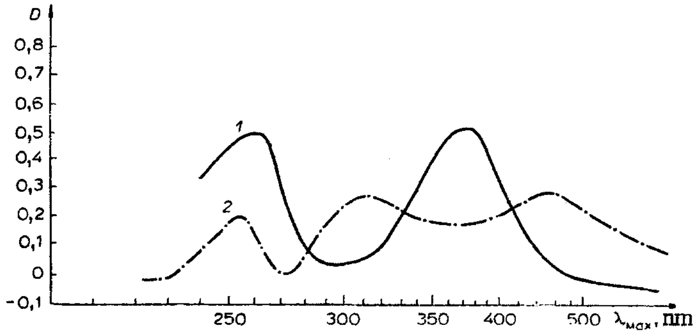

Fig. 1. UV spectra: 1) 1-methyl-4-(2-indolyl)-pyridinium iodide (I); 2) 1-methyl-4-(2-indolenylidene)-1,4-dihydropyridine (II).

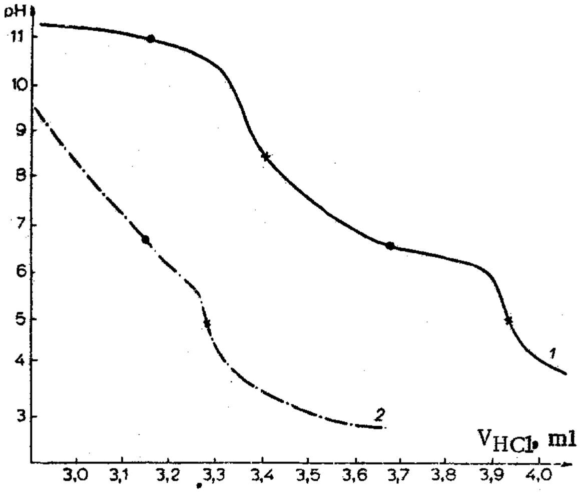

Fig. 2. Curves of the tritration of 1-methyl-4-(2-indolenylidene)-1,4-dihydropyridine (II) with 0.1 N HCl: 1) c = 10^{-2} M; 2) c = 10^{-3} M.

Anhydro base II is a very strong base with pK_a 11. Two sharp drops in the pH are observed on the titration curve (Fig. 2) of an aqueous alcohol solution of II, and this indicates the presence in the system of two bases, viz., anhydro base II and its hydrated form III. When the titration solution is diluted, one of the inflections disappears (with pK_a 11), and this constitutes evidence in favor of complete hydration of the anhydro base in aqueous media. We isolated the hydrated form (both by the action of water on base II and by treatment of salt I with aqueous or aqueous alcoholic alkali) in the form of a yellow crystalline substance that is quite soluble in water and other polar solvents and only slightly soluble in organic nonpolar solvents. Its UV spectra in various polar solvents (water, methanol, and acetonitrile) are completely similar to the UV spectrum of salt I, and this constitutes evidence in favor of dissociation of carbinol IIIb in polar media, as observed in some similar cases in [4, 5]. We were unable to record the UV spectra of III in nonpolar solvents because of its low solubility.

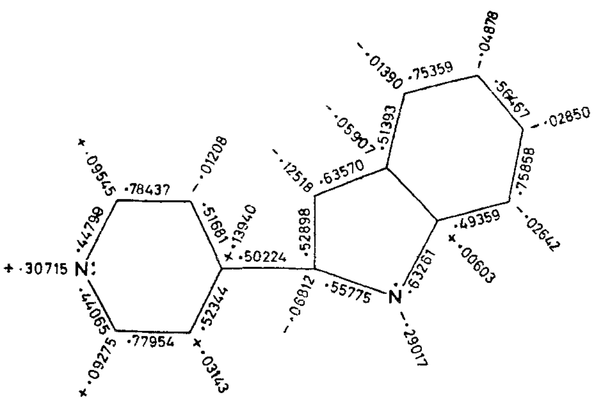

Fig. 3. Molecular diagram of 1-methyl-4-(2-indolenylidene)-1,4-dihydropyridine (II).

One inflection with pK_a 6.55, which coincides completely with respect to its position and form with the second inflection on the titration curve of an aqueous alcohol solution of anhydro base II, was observed in the potentiometric titration of an aqueous alcohol solution of III (Fig. 2). Two diffuse maxima, which are related to the stretching vibrations of the NH and OH groups in the molecule, are observed in the IR spectrum of III at 3300-3600 cm^{-1}.

Anhydro base II, despite the several nucleophilic centers in the molecule, is protonated only at the indolenine nitrogen atom (by the action of mineral acids and water) and also adds strong electrophiles (alkyl and acylium cations) in this position. Quaternary salts of the substituted (at the NH group of the indole ring) of pyridylindole (IV and V) are formed by reaction of II with methyl iodide and benzoyl chloride. A calculation within the framework of the Pariser—Parr—Pople (PPP) method* shows that the highest negative π-electron charge is located on the indolenine nitrogen atom (Fig. 3), which dictates the direction of electrophilic attack.

In both anhydro base II and in starting quaternary salt I we assumed opening of the electron-deficient pyridine ring with subsequent ring closing in the nucleophilic β-position of the indole ring with the formation of a new heterocyclic system, as in the recyclization of the quaternary salts of nicotyrine to indole [6] and of 2-(3-pyridyl)indole to carbazole [7]. However, the desired result was not obtained even under severe conditions (by the action of methylammonium sulfate at 150°C). Instead of this, two competitive processes, viz., N-dealkylation with the liberation of the nonquaternized base and hydration of intermediate anhydro base II, occurred in the case of salt I. In an attempt to recyclize the anhydro base itself the only product was III. In the absence of water, i.e., in an alcohol solution of methylamine, the process stops at the step involving the anhydro base, which does not undergo subsequent transformations. We assumed that by blocking the NH group of indole we would be able to exclude deprotonation, which leads to the anhydro base, and direct the reaction via the other pathway. For this, we subjected IV, in which the NH group of the indole ring is substituted with a methyl group, to recyclization. However, in this case also we realized only N-dealkylation with the formation of pyridylindole VI. Compound VI reacts with methyl iodide to give starting salt IV.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of 10^{-5} M solutions of the compounds in methanol, water, acetonitrile, and a solution of KOH in methanol were recorded with a Specord UV-vis spectrophotometer. Potentiometric determination of the pK_a values was realized with a pH-340 apparatus by titration of 10^{-2}-10^{-3} M aqueous methanol solutions (the percentage of methanol was 10%) of the bases with 0.1 N HCl. The pK_a values were assumed to be equal to the pH values at the half-neutralization points.

1-Methyl-4-(2-indolenylidene)-1,4-dihydropyridine (II). A suspension of 1.7 g (5 mmole) of 1-methyl-4-(2-indolyl)pyridinium iodide in 15 ml of a 10% methanol solution of KOH was

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*The calculations were performed with the assistance of B. P. Zemskii and Yu. B. Vysotskii.

heated until the salt dissolved completely, after which the solution was cooled. The precipitate was removed by filtration, washed with small portions of ether, and recrystallized from a 5% methanol solution of KOH to give 0.95 g (95%) of a product with mp 210-212°C. IR spectrum: 1660 (C=N) and 1610 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 250 (4.17), 325 (4.22), and 440 nm (4.07); pK_a 11.0. Found %: C 80.6; H 6.1; N 13.2. $C_{24}H_{12}N_2$. Calculated %: C 80.8; H 5.8; N 13.5.

1-Methyl-2-hydroxy-4-(2-indolyl)-1,2-dihydropyridine (IIIb). A) A suspension of 0.7 g (5 mmole) of 1-methyl-4-(2-indolyl)pyridinium iodide in 15 ml of a 10% methanol solution of KOH was heated until the salt dissolved completely, after which the solution was cooled and poured into 50 ml of water. The resulting yellow precipitate was removed by filtration and washed with acetonitrile to give 0.3 g (27%) of a product with mp 205°C (dec.). IR spectrum: 1610 (C=C), 3440 (NH), and 3510 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 205 (3.98), 225 (3.76), 255 (3.57), and 380 nm (3.84); pK_a 6.55. Found %: C 74.2; H 5.9; N 12.6. $C_{14}H_{13}N_2O$. Calculated %: C 74.4; H 5.8; N 12.4.

B) A solution of 1 g (5 mmole) of II in 20 ml of 50% methanol was allowed to stand at room temperature for 1 h, after which the solvent was removed by vacuum distillation, and the residue was washed with ether to give 0.8 g (73%) of a product with mp 205°C (dec.). No melting-point depression was observed for a mixture of this product with the compound obtained by method A.

1-Methyl-4-(1-methyl-2-indolyl)pyridinium Iodide (IV). A mixture of 1 g (5 mmole) of II and 0.7 g (5 mmole) of methyl iodide in 10 ml of dry DMF was heated at 100°C for 30 min, after which it was cooled and poured into 50 ml of ether. The precipitate was removed by filtration and recrystallized from DMF to give 1 g (55%) of a product with mp 199-200°C. IR spectrum: 1655 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 220 (4.09), 245 (3.65), and 388 nm (4.12). Found %: C 51.2; H 4.2; N 8.2. $C_{15}H_{15}N_2I$. Calculated %: C 51.4; H 4.3; N 8.0.

1-Methyl-4-(1-benzoyl-2-indolyl)pyridinium Chloride (V). This compound was similarly obtained by the reaction of 1 g (5 mmole) of II and 0.7 g (5 mmole) of benzoyl chloride in 10 ml of dioxane. Workup gave 1.3 g (85%) of a product with mp 294-295°C (from DMF). IR spectrum: 1658 (C=N) and 1665 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 215 (3.85), 238 (3.02), and 390 nm (4.07). Found %: C 57.1; H 3.6; N 6.2. $C_{21}H_{17}N_2ClO$. Calculated %: C 57.3; H 3.9; N 6.4.

Reaction of 1-Methyl-4-(2-indolyl)pyridinium Iodide with Methylammonium Sulfite. A mixture of 1.7 g (5 mmole) of 1-methyl-4-(2-indolyl)pyridinium iodide, 10 ml of a 25% aqueous solution of methylamine, and 5 ml of a solution of methylammonium bisulfite, obtained by saturation of a 25% solution of methylamine with gaseous SO_2, was heated in a sealed ampul at 150°C for 40 h. The precipitate was removed by filtration and washed several times with small portions of water and hot chloroform to give 0.8 g (73%) of III, which was identified by comparison with a genuine sample. Workup of the chloroform filtrate yielded 0.2 g (25%) of 2-(4-pyridyl)indole with mp 240-241°C (from n-butanol) and R_f 0.25 [chloroform—benzene—hexane (30:6:1), on aluminum oxide]. No melting-point depression was observed for a mixture of this product with a genuine sample.

1-Methyl-2-(4-pyridyl)indole (VI). This compound was obtained as a result of the reaction of 1-methyl-4-(1-methyl-2-indolyl)pyridinium iodide with a solution of methylammonium sulfite, as described above. Workup gave a product with mp 104-105°C (from methanol) and R_f 0.56 [chloroform—benzene—hexane (30:6:1), on aluminum oxide] in 80% yield. IR spectrum: 1662 cm^{-1} (C=N). Found %: C 80.6; H 5.9; N 13.4. $C_{14}H_{12}N_2$. Calculated %: C 80.0; H 5.8; N 13.5.

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