INDOLES

# XXIX.* STRUCTURE OF THE INTERMEDIATE IN THE SYNTHESIS OF 2-METHYL-7-AZATRYPTAMINE

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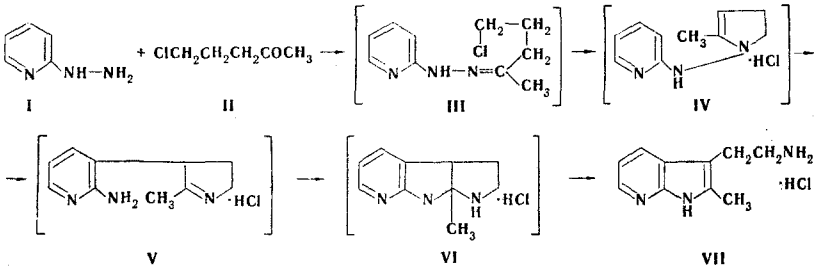
UDC 547.822.7'829'83'743:543.422.4

An intermediate, which proved to be a dimer of N-(α-methylpyrrolino)-2-aminopyridine, was isolated during the synthesis of 2-methyl-7-azatryptamine from 2-pyridylhydrazine and γ-chloropropyl methyl ketone under mild conditions.

We have previously [1] reported that 2-methyl-7-azatryptamine (VII) can be obtained in high yield when 2-pyridylhydrazine (I) is used as the arylhydrazine component in the synthesis of tryptamines [2]:



I II III IV V VI VII

However, the reaction proceeded under more severe conditions (150°C for 6 h) than in the case of phenylhydrazine itself or its substituted derivatives (at 70° for 6 h) [2]. When the reaction temperature was lowered, we isolated a crystalline substance with the same empirical formula as that of azatryptamine VII, $(C_{10}H_{13}N_3)_n$. It was smoothly converted to azatryptamine VII on heating with an equimolar amount of HCl in methanol (at 160° for 5 h) and underwent partial conversion during attempts to distill it in vacuo. It was natural to assume that the compound obtained is one of the intermediates of the reaction depicted in the scheme presented above.

We studied the spectral characteristics of the compound. Absorption bands at 244 nm (log ε 3.82) and 306 nm (log ε 3.43), as well as an inflection at 256 nm (log ε 3.78), are present in the UV spectrum of an alcohol solution of it. A comparison of the UV spectra with the spectra of 2,3-dimethyl-7-azaindole, 2,3,3-dimethyl-7-azaindolenine and methyl ethyl ketone 2-pyridylhydrazone demonstrated the difference between the chromophores of the compound under investigation and the chromophores of model compounds (Fig. 1).

The IR spectrum of a solution of the compound in carbon tetrachloride (Fig. 2) contained an absorption band at 3290 $cm^{-1}$, which we assigned to the stretching vibrations of the associated NH group. It should be noted that the hydrogen bond was an intramolecular one, since changing the concentration of the solution did not shift it. Also present in the spectrum were the absorption bands common to aromatic systems and a band at 1630 $cm^{-1}$, which might be assigned either to the stretching vibrations of the C=C or C=N bond or to the deformation vibrations of the NH group.

*See [1] for communication XXVIII.

K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1202-1207, September, 1972. Original article submitted July 5, 1971.

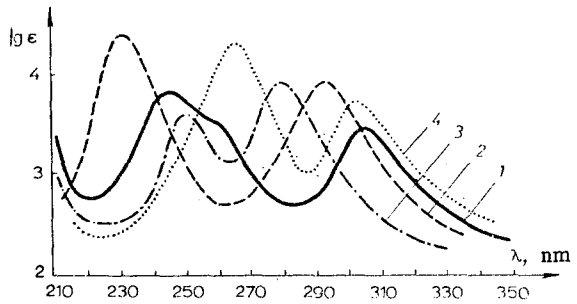



Fig. 1. UV spectra: 1) IVa; 2) 2,3-dimethyl-7-azaindole; 3) 2,3,3-trimethyl-7-azaindolenine; 4) methyl ethyl ketone 2-pyridylhydrazone.

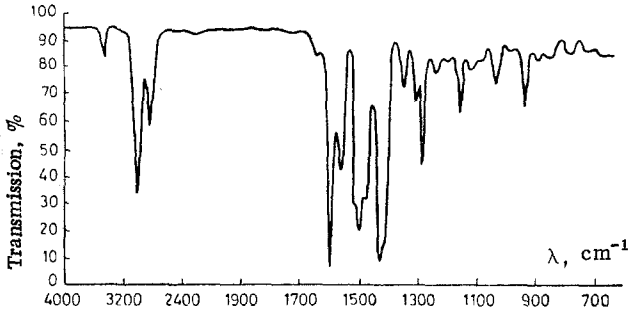
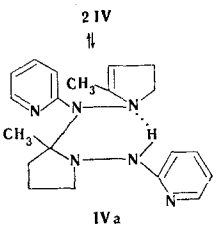



Fig. 2. IR spectrum of IVa in $CCl_4$.

We carried out deuterium exchange of the labile hydrogen atoms of the compound in neutral media and established that the band at 3290 $cm^{-1}$ is shifted to 2330 $cm^{-1}$, while the band at 1630 $cm^{-1}$ does not change its position. This enabled us to conclude that the band at 1630 $cm^{-1}$ is due to the vibrations of the C=C or C=N groups, while the band at 3290 $cm^{-1}$ is due to the stretching vibrations of the NH groups. Since the spectrum of a KBr pellet of the substance contained an absorption band at 860 $cm^{-1}$, which we assigned to the vibrations of the $R_2C=CHR$ group, we assigned the band at 1630 $cm^{-1}$ to the vibrations of the C=C bond. The PMR spectrum of a $CCl_4$ solution of the substance (Fig. 3) contained a signal at 5.7 ppm, which, according to the integration data, corresponded in intensity to half a proton. This fact suggested that we were dealing either with a mixture of tautomeric forms or with a dimeric compound. Recording of the PMR spectra in various solvents at various temperatures demonstrated that the position and form of the signals do not change appreciably when the recording conditions are changed. In addition, we recrystallized the substance from various solvents, as a result of which we isolated a substance with precisely the same characteristics in all cases (the identification was performed by means of determination of the melting points of mixtures, thin-layer chromatography, and UV and IR spectroscopy); the results obtained indicated a dimeric structure for the substance.

Groups of multiplets, related to the signals of protons of two nonequivalent 2-monosubstituted pyridine rings, were present in the region of the signals of aromatic protons in the PMR spectrum. The definitive assignment of the signals of the aromatic protons was made by comparison of the PMR spectra recorded with spectrometers with operating frequencies of 60 and 100 MHz and also by means of double-proton resonance. The chemical shifts and spin–spin coupling constants presented correspond to those for the pyridine ring [3].

On the basis of the considerations indicated above, we proposed the dimeric N-(α-methylpyrrolino)-2-aminopyridine structure (IVa) for the compound:




IVa

The mass spectra of dimer IVa also confirm the proposed structure. To identify IVa, we made preliminary investigations of the mass spectra of 2,3-dimethyl-7-azaindole, 2,3,3-trimethyl-7-azaindolenine, and 2-methyl-7-azatryptamine. A comparison of the mass spectrum of dimer IVa at 250° with the spectra of the model compounds demonstrated that the dimer is characterized by peaks that correspond to disintegration of 2-methyl-7-azatryptamine and peaks characteristic for the dimer. It was natural to assume that, under the conditions of recording at 250° with allowance for the catalytic action of the walls of the inlet system, dimer IVa is initially converted into two monomer molecules that undergo partial cyclization to form 2-methyl-7-azatryptamine. The relatively low volatility of the sample made it impossible to follow the change in the mass spectrum as the temperature was lowered, and the indicated assumption was therefore verified by recording the spectrum of dimer IVa with an apparatus with direct input into the source at 140°. It was found that the molecular weight of dimer IVa is 350, which corresponds to the dimeric structure of

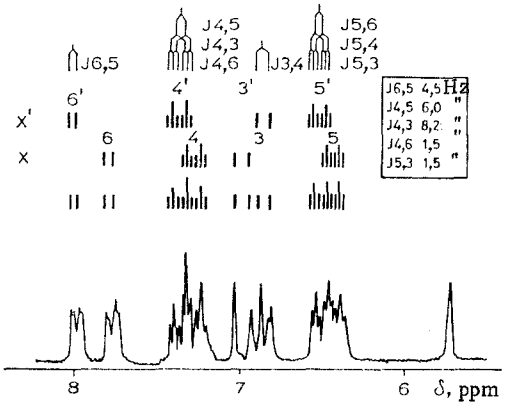



Fig. 3. Aromatic portion of the PMR spectrum of IVa.

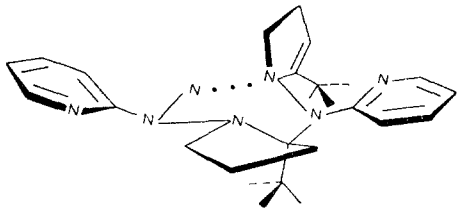


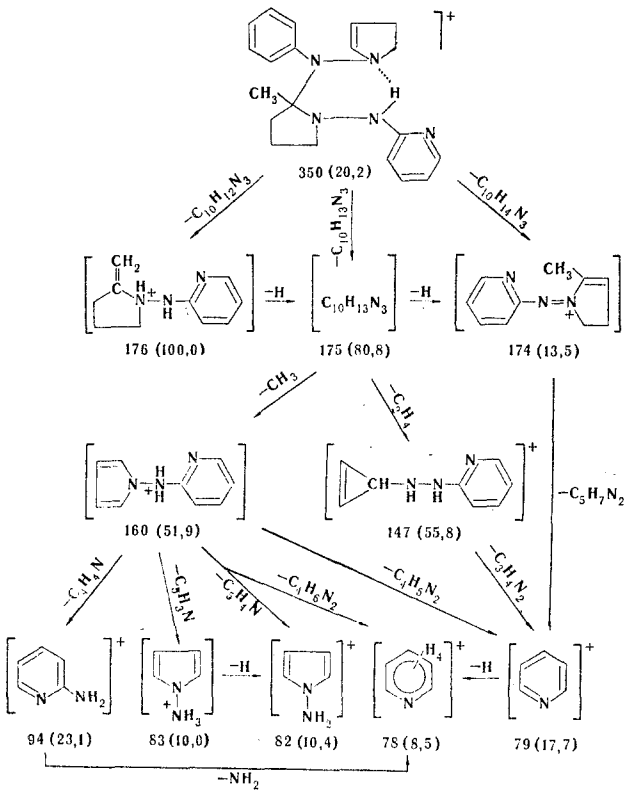
Fig. 4. Dreiding model of IVa.

the product. As seen from the scheme, IVa disintegrates in the first stages to form three fragment ions that are close in mass to half the molecular weight of the dimer and correspond to both simple cleavage of the C–N bond that joins the "aminopyridylpyrroline" portions of the molecule and to cleavage with hydrogen migration. The structure of the dimer is also confirmed by the presence of a rather intense peak of an ion with mass 94, which corresponds to the α-aminopyridine structure. The subsequent decomposition of IVa is characterized by the peaks that are usually observed for the disintegration of pyrrole and aminopyridine derivatives.

Thus it can be considered to be proved that IVa has the structure presented.

Returning to the PMR spectrum of dimer IVa, on the basis of the proposed structure it can be asserted that the broad proton signal at 5.7 ppm is related to the proton attached to the double bond of the pyrroline ring. The fact that the signal of this proton is not split should not evoke any surprise, since this sort of phenomenon occurs in similar systems, particularly in pyrazolines (3-H is rarely split by 4-H).

Conformational analysis using Dreiding models demonstrated that the dimer is stabilized by the formation of a hydrogen bond, and a boat-shaped six-membered ring, which includes four nitrogen atoms, develops (Fig. 4). An examination of this model also explains the nonequivalence of the protons of the two pyridine rings. As seen from Fig. 4, one of the rings



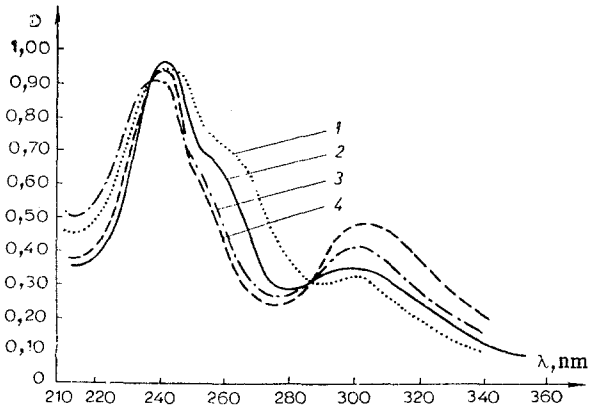
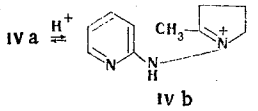



Fig. 5. UV spectra of IVa at various pH values: 1) 6.8; 2) 4.5; 3) 2.3; 4) 1.6.

falls into the region of shielding of the double bond, as a consequence of which the proton signals of this ring are shifted to stronger field.

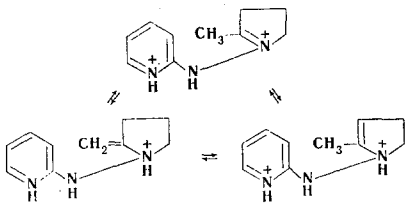
In a study of the UV and PMR spectra of dimer IVa in media with different acidities, we found that IVa undergoes monomerization under the influence of acid to form a protonated structure:



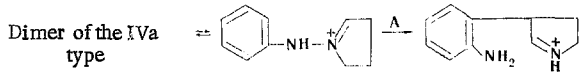

IV b

This monomerization process is complete at pH 1.6 and is reversible, which is confirmed by the presence of an isosbestic point in the set of curves of the UV spectra (Fig. 5). The PMR spectrum of dimer IVa in 20% $H_2SO_4$ also satisfactorily confirms the proposed protonated structure (IVb). The two distorted triplets at 4.1 and 4.9 ppm are related to the signals of the $\gamma$- and $\alpha$-methylene groups, while the quintet at 3.0 ppm is related to the signal of the $\beta$-methylene group. The "three-proton" singlet at 3.1 ppm is the signal of the methyl group attached to the $C=N^+$ double bond. The signals of four aromatic protons are present at weak field: the doublet of the proton in the 6 position (8.83 ppm) is superimposed on the triplet of a proton in the 4 position (8.83 ppm), and the doublet of the proton in the 3 position (7.91 ppm) is superimposed on the triplet of the proton in the 5 position (8.0 ppm). The chemical shifts of the aromatic protons correlate well with the known changes in the chemical shifts of protons of the pyridine ring that occur when it is protonated [4].

It should be noted that tautomerism of the following type occurs in acidic media:




This assertion is based on an analysis of the PMR spectrum of IVa in a 20% solution of $D_2SO_4$ in $D_2O$. Due to the indicated tautomerism, the protons of the $\gamma$-methylene and methyl groups are rapidly deuterated, a consequence of which is disappearance of the signals of these groups in the PMR spectrum.




The formation of dimer IVa occurs through nucleophilic addition of the N–H group of the monomer to the activated double bond of the other monomer molecule. In the case of arylhydrazines, the dimer cannot be isolated under the usual conditions because of the irreversible tying up of the C–C bond (A) and the subsequent formation of the tryptamine system. Since the pyridine ring undergoes electrophilic attack under more severe conditions, process A does not proceed under mild reaction conditions (70°), and a dimer, which is stabilized due to the formation of a six-membered ring with the participation of a hydrogen bond, is obtained in alkalization of the reaction mixture during workup.

## EXPERIMENTAL

N-($\alpha$-Methylpyrrolino)-2-aminopyridine Dimer (IVa). A 3.5-g (0.03 mole) sample of $\gamma$-chloropropyl methyl ketone in 20 ml of 90% methanol was added to a solution of 3.2 g (0.03 mole) of 2-pyridylhydrazine in 30 ml of 90% methanol, and the mixture was refluxed for 6 h. It was then cooled, the methanol was removed by vacuum distillation, and the residue was dissolved in 50 ml of 0.1 N hydrochloric acid. The acid solution was filtered through 0.5 g of activated charcoal, and the filtrate was made alkaline with excess

potassium hydroxide to give 4.3 g (83%) of dimer IVa with mp 140-141° (from petroleum ether) and $R_f$ 0.51.* Found: C 68.5; H 7.4%. $C_{20}H_{26}N_6$. Calculated: C 68.6; H 7.4%.

Conversion of Dimer IVa to 2-Methyl-7-azatryptamine. A. Hydrochloric acid was added to a solution of 4.5 g of dimer IVa in 50 ml of 90% methanol until the pH was 5.5. The solution was sealed in an ampule, and the ampule was heated in an autoclave at 150° for 5 h. The reaction mixture was cooled, the methanol was evaporated in vacuo, and the residue was dissolved in 30 ml of 0.1 N hydrochloric acid. The acid solution was extracted with ether, and the ether extracts were discarded. The aqueous layer was made strongly alkaline with excess potassium hydroxide, and the mixture was extracted with ether. The ether extracts were dried with potassium hydroxide, the ether was removed by distillation, and the residue was vacuum-distilled to give 3.3 g (75%) of 2-methyl-7-azatryptamine with bp 130° (1 mm). The IR, UV, and PMR spectra and the $R_f$ values of the compound obtained were identical to those of a genuine sample of 2-methyl-7-azatryptamine [1].

B. Three distillations of dimer IVa yielded a fraction with bp 180° (1 mm), the spectral characteristics of which also proved to be identical to the characteristics of 2-methyl-7-azatryptamine [1].

The IR spectra were recorded with a Jasco-IRS spectrophotometer with a NaCl prism. The PMR spectra† were recorded with JNM-4H-100, JNM-60, and T-60 (Varian) spectrometers. The mass spectra were recorded with MKh 1303 and MS 3301 spectrometers with direct introduction into the source. The UV spectra were recorded with an EPS-3T spectrophotometer (Hitachi).

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*On Silufol UV-254 with methanol as the mobile phase.


† The authors thank A. Tupchauskas for assistance in interpreting the PMR spectra.