INDOLES

VI. A Study of the Mechanism of the Formation of Tryptamines with Phenylhydrazine Labeled with the Isotope ^{15}N*

I. I. Grandberg, N. M. Przheval'skii, V. I. Vysotskii, and R. A. Khmel'nitskii

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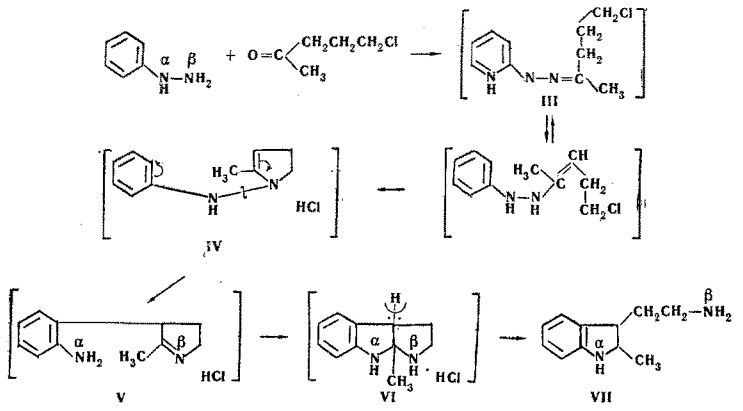
In order to elucidate the mechanism of the one-stage synthesis of tryptamines that we discovered previously, 2-methyltryptamines obtained from phenylhydrazine labeled with the isotope ^{15}N at the α- and β-nitrogen atoms have been studied by mass spectrometry. It has been shown that the β-nitrogen atom of the arylhydrazine forms the amino group of the aminoethyl moiety of tryptamine and the α-nitrogen atom of the phenylhydrazine becomes the indole nitrogen atom in the tryptamine molecule formed.

We recently discovered a new method for the synthesis of important biogenic amines of the tryptamine series [1, 2] and the following reaction scheme was proposed for its simplest case:



According to this scheme, the β-nitrogen atom of the arylhydrazine takes part in the formation of the amine group of the aminoethyl moiety of the tryptamine molecule. We have attempted to obtain confirmation of the hypothesis put forward by means of the ^{15}N nitrogen isotope.

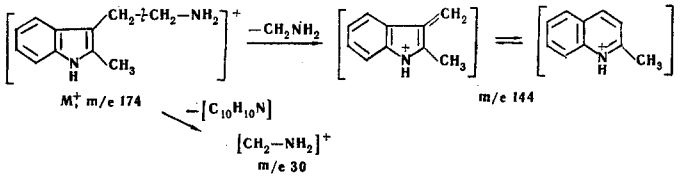
One of the analogs of 2-methyltryptamine was obtained from [α-^{15}N]phenylhydrazine. For this purpose, [^{15}N]aniline was converted by the usual method into phenylhydrazine in which, therefore, the ^{15}N isotope occupied the α-position [3]. It was heated under the usual conditions [1, 2] with γ-chloropropyl methyl ketone in ethanol to give 2-methyltriptamine. If the scheme proposed above were correct, the latter should have contained the ^{15}N isotope in position 1 of the indole nucleus.

Another analog of 2-methyltryptamine was obtained from aniline, which was treated with sodium nitrite containing the ^{15}N isotope to give phenylhydrazine. In this case, the phenylhydrazine had the ^{15}N isotope in the β-position [4], and the reaction with the same chloroketone formed (if the scheme is correct) 2-methyltryptamine labeled with the ^{15}N isotope in the amino group of the 3-(β-aminoethyl) residue.

The two labeled compounds were purified by similar methods and were absolutely identical in their constants both with one another and with ordinary 2-methyltryptamine. All three 2-methyltryptamines were studied by mass spectrometry under absolutely identical conditions.

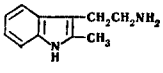
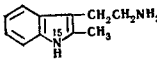
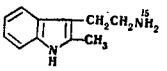
*For part V, see [7].

We have shown previously [5] that the main process for the dissociative ionization of the tryptamines, including 2-methyltryptamine, is decomposition at the β-bond of the aminoethyl group with the splitting out of $-CH_2NH_2$ and the formation of an ammonium ion with m/e 144 (the maximum ion in the spectrum), which rearranges into the stable structure of the quinolinium ion. In addition to this, in this act of degradation an ion with m/e 30, corresponding to the $[CH_2NH_2]^+$ ion is also formed.



In a study of the mass spectrum of the 2-methyltryptamine obtained from phenylhydrazine labeled in the o- position and (if the scheme is correct) containing the ^{15}N in position 1 of the nucleus, a decrease in the intensity of the peak of the ion with m/e 174 (the molecular ion in the case of unlabeled 2-methyltryptamine) and an increase in the intensity of the peak of the ion with m/e 175 corresponding to the molecular ion of the labeled compound were to be expected. In addition, since the ^{15}N isotope is present in the nucleus, the intensity of the peak of the ion with m/e 145 corresponding to the quinolinium cation with ^{15}N should increase. However, the intensity of the peak of the ion with m/e 31 corresponding to $[CH_2\ ^{15}NH_2]^+$ should remain the same as in the unlabeled 2-methyltryptamine. In actual fact, as can be seen from the table, in the mass spectrum of the 2-methyltryptamine labeled in the nucleus there was an 11.4% increase in the intensity of the peak of the ion with m/e 175 as compared with that having m/e 174, and an 11.2% increase in the peak of the ion with m/e 145 as compared with that having m/e 144. The intensities of the peaks with m/e 31 in 2-methyltryptamine and its analog labeled in the nucleus remained approximately the same (0.68-0.79).

Table 1. Intensities of the Ion Peaks (in % of the Maximum Peak in the Spectrum)

m/e			
174	15.2	13.1	14.0
175	2.1	3.3	3.3
144	100.0	100.0	100.0
145	31.7	42.9	31.6
31	0.68	0.79	1.42

In an analogous examination of the 2-methyltryptamine obtained from phenylhydrazine containing the ^{15}N isotope in the β- position and (if the scheme is correct) having the label in the side chain, an increase in the intensity of the peak of the ion with m/e 175 as compared with that having m/e 174 was again to be expected, but the intensities of the peaks of the ions with m/e 144 and 145 should remain the same as in the unlabeled compound. On the other hand, the peak of the ion with m/e 31 should increase in intensity as compared with both 2-methyltryptamine and its analog with the ^{15}N isotope in the nucleus. In actual fact the relative intensity of the ion with m/e 175 as compared with that of the ion with m/e 174 rose by 10.6%, while the intensity of the peak of the ion with m/e 145 remained equal to that in 2-methyltryptamine: 31.6 and 31.7% (see Table 1). At the same time, the intensity of the peak of the ion with m/e 31, corresponding to the $[CH_2\ ^{15}NH_2]^+$ ion was approximately twice as great as in 2-methyltryptamine and its analog labeled in the indole nitrogen (1.42%), which shows the presence of the ^{15}N isotope in the aminoethyl group of the tryptamine.

Thus, a study of the mass spectra of 2-methyltryptamine and its labeled analog has shown the presence of the ^{15}N isotope in the positions expected according to the scheme proposed previously. The contents of the ^{15}N isotope in atomic percentages in both the labeled analogs of 2-methyltryptamine proved to be very similar to those in the initial aniline and sodium nitrite, respectively.

The results obtained, besides confirming the reaction scheme given above for the formation of the tryptamines, have a more general significance, additionally confirming the mechanism of the Fischer indole synthesis since the reaction that we have found undoubtedly has much in common with it. This is all the more important since earlier attempts to elucidate the mechanism of the Fischer reaction were carried out with phenylhydrazine containing a low percentage of isotope [3, 4].

EXPERIMENTAL

[α-^{15}N]**Phenylhydrazine** was obtained by the general method for the synthesis of arylhydrazines using ordinary sodium nitrite and labeled aniline containing 14.2 atom-% of the ^{15}N isotope. The yield was 55%. Bp 126-127°C (20 mm).

[1-^{15}N]-2-Methyltryptamine was obtained as described previously [1] from [α-^{15}N]phenylhydrazine and γ-chloropropyl methyl ketone. Yield 80%. Bp 169-170°C (2 mm).

[β-^{15}N]**Phenylhydrazine** was obtained by the general method for the synthesis of arylhydrazines using ordinary aniline and labeled sodium nitrite ($Na^{15}NO_2$ containing 96.7% of the main substance and 10.4 atom-% of the isotope) with a yield of 51%. Bp 125-126°C (19 mm).

2-Methyltryptamine labelled with the ^{15}N isotope in the aminoethyl residue. The method of preparation has been given previously [1]. Yield 81%. Bp 170-171°C (2 mm).

The constants of all three samples of tryptamine after two high-vacuum sublimations were: mp 109°C, R_f 0.79 [chromatography on "rapid" paper of the Volodarskii mill in the butanol–pyridine–water (1 : 1 : 1) system with Ehrlich's reagent for revealing the spots]; the UV and IR spectra were completely identical. The picrates had mp 218°C.

The mass spectra of 2-methyltryptamine and both of its analogs labeled with the ^{15}N isotope in position 1 and in the β-aminoethyl residue were recorded, after careful purification by vacuum sublimation, on a MKh-1303 instrument with a modified recording device [6] under the following conditions. Temperature of the inlet system and ion source 250°C; ionizing voltage 50 eV, emission current 1.5 mA, accelerating voltage 2 kV.

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