INDOLES

XV.* INTERMEDIATES IN THE SYNTHESIS OF TRYPTAMINES

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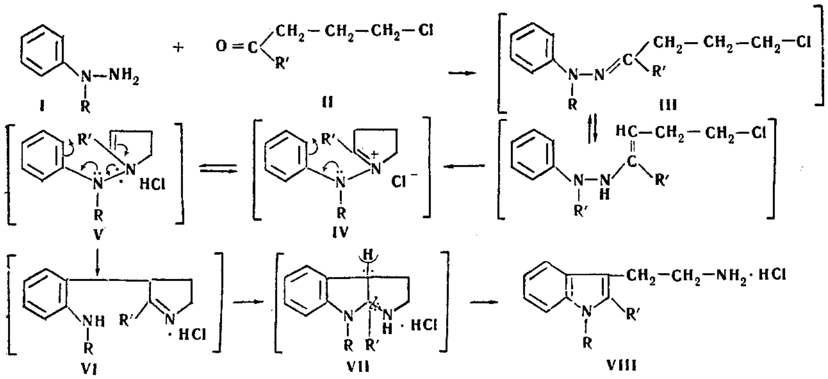
Several intermediates of the various steps of the reaction to form tryptamines were isolated and their structures were established. Additional evidence for the previously proposed reaction mechanism was thereby obtained.

The following working scheme has been proposed to explain our synthesis [2, 3] of tryptamines, homotryptamines, and eserine systems on the basis of the general assumptions of the scheme for the Fischer indole synthesis:



Partial evidence of the correctness of this scheme was obtained by means of a mass-spectrometric investigation of 2-methyltryptamines [4] containing N^{15} and by calculation of the π-electron densities for several starting systems and their conformational analysis [5].

The isolation and identification of the intermediates in the various steps of the reaction are direct and convincing evidence for any reaction mechanism; this was investigated in the present case.

The usual conditions for the synthesis of tryptamine and its derivatives are refluxing the arylhydrazine and γ-haloketone in aqueous alcohol [2, 3]. Under these conditions, it was impossible to isolate any intermediate during the synthesis of 2-methyltryptamine. However, a product, which, according to the IR, UV, and PMR spectra, is γ-chloropropyl methyl ketone phenylhydrazone – intermediate III (R = H, R' = CH_3) in the proposed reaction scheme – could be isolated by mixing equimolecular amounts of phenylhydrazine and γ-chloropropyl methyl ketone in benzene and allowing the mixture to stand at room temperature for 1 h. The hydrazone is very unstable even at room temperature. On heating, it is rapidly converted to 2-methyltryptamine. The UV spectrum of a freshly prepared sample (in ethanol) has one absorption maximum at 271 nm (log ε 4.19), which is characteristic for phenylhydrazones [6]. The PMR spectrum of γ-chloropropyl methyl ketone phenylhydrazone is rather complex because of the presence of two forms – syn and anti (see Fig. 1). The assignment of the proton signals to syn and anti isomers is based on the data in

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*See [1] for Communication XIV.

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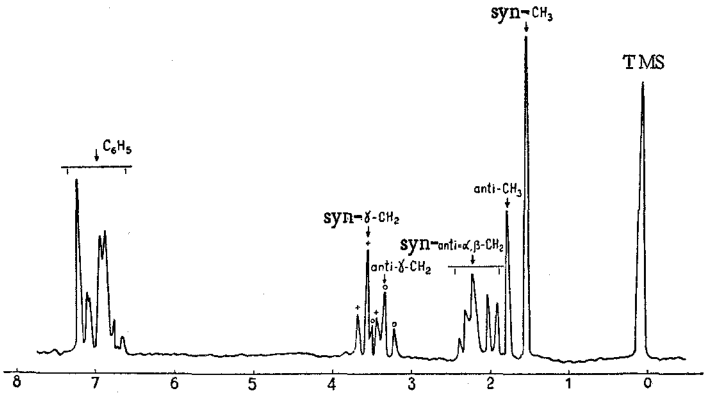


Fig. 1. PMR spectrum of γ-chloropropyl methyl ketone phenylhydrazone.

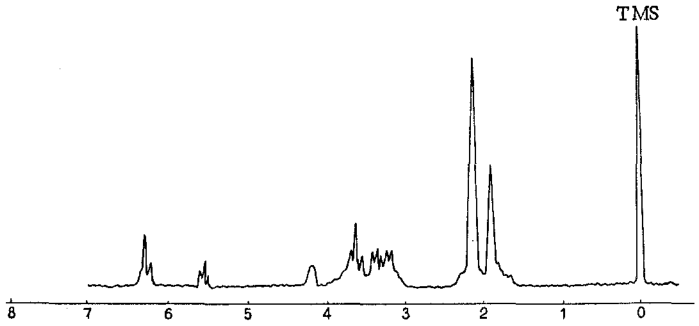


Fig. 2. PMR spectrum of 1-mesitylamino-Δ^2-2-methylpyrroline.

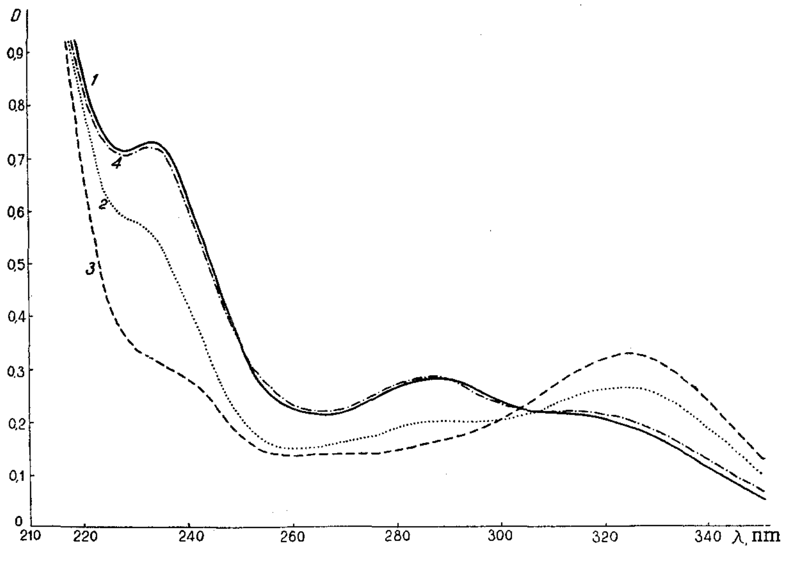


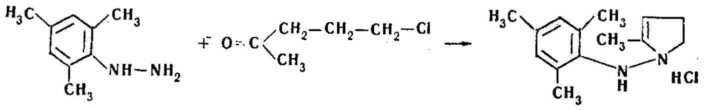
Fig. 3. UV spectra of 1-mesityl-Δ^2-2-methylpyrroline at various solution pH values (80% C_2H_5OH): 1) 11.4 (form A); 2) 3.5 (A $\rightleftharpoons$ B); 3) 1.6 (form B); 4) 7.7 (form A).

[7], during which the methyl group and the aniline residue are in the cis position in the syn isomer. The two singlets at 1.57 and 1.80 ppm are assigned to the methyl protons of the syn and anti forms, respectively. The proton signals of the γ-methylene group are manifested as triplets centered at 3.31 ppm (J = 8 Hz) for the syn form and at 3.45 ppm (J = 8 Hz) for the anti form. The complex multiplet at 1.98-2.41 ppm belongs to the proton signals of the α- and β-CH_2 groups of both forms. The aromatic protons are found at

6.90-7.10 ppm. On the basis of the integral intensity ratio of the peaks of the syn and anti forms (for the methyl group) it was found that about 70% of the hydrazone exists in the syn form for the given conditions (20°, CCl_4).

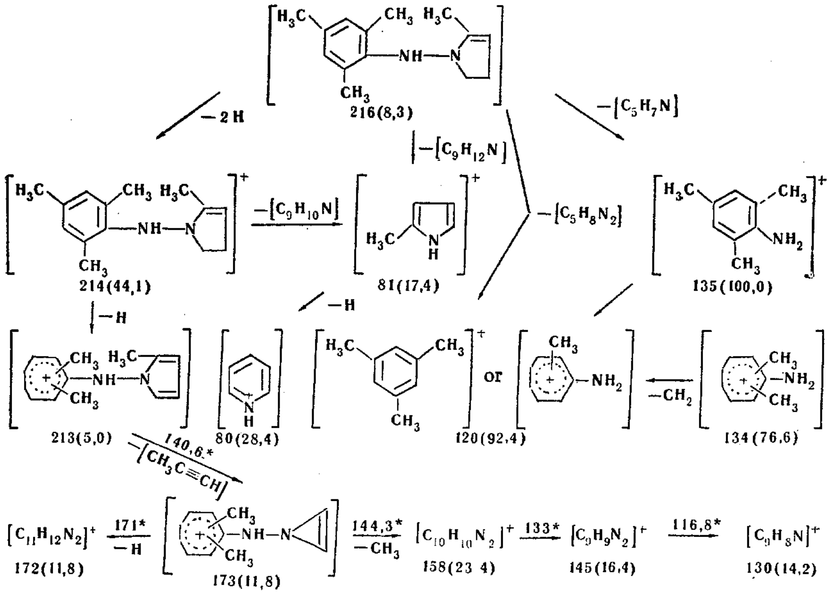
It was expressly the presence of syn and anti isomers that made it possible to previously isolate, under the usual conditions, γ-chloropropyl methyl ketone diphenylhydrazone in only the syn form [5].

According to the proposed scheme, the second step of the reaction should lead to N-anilinopyrroline (IV $\rightleftharpoons$ V) which then rearranges to β-(o-aminophenyl)pyrroline (VI). We assumed that substituents in the ortho position of the benzene ring should hinder this process (V → VI). In fact, 1-mesitylamino-Δ^2-2-methylpyrroline — an intermediate of the V type — is formed when mesitylhydrazine is refluxed with γ-chloropropyl methyl ketone under the usual conditions.

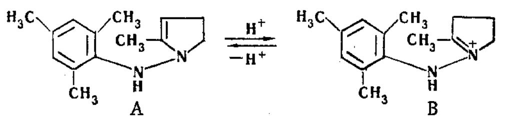


The analyses and IR, UV, PMR, and mass spectra are in complete agreement with this structure.

Thus the PMR spectrum (Fig. 2) contains 2 singlets at 1.85 and 2.10 ppm, which are assigned to the methyl groups attached to the double bond and to the benzene ring, respectively. The proton on the double bond is manifested as a triplet centered at 5.57 ppm (J = 7 Hz). The proton signals of the α- and β-methylene groups are two poorly resolved triplets centered at 3.56 ppm (J = 7 Hz) and 3.30 ppm (J = 7 Hz), respectively. The broad singlet at 4.2 ppm is assigned to the NH group. Finally, the aromatic protons are found at 6.13-6.20 ppm.



The UV spectrum of 1-mesitylamino-Δ^2-2-methylpyrroline (in ethanol) displays two absorption maxima, 235 nm (log ε 3.75) and 288 nm (log ε 3.37), and an inflection at 314 nm (log ε 3.22). On obtaining the UV spectrum of this compound in aqueous alcohol while varying the pH, it was observed that, in an acidic medium (pH 3.5), a maximum appears at 325 nm and becomes sharply pronounced at pH 1.6. Meanwhile, the absorption maxima at 235 and 288 nm almost vanish (see Fig. 3). All of this clearly indicates the conversion of 1-mesitylamino-Δ^2-2-methylpyrroline to the Δ^1 form, since the UV spectrum in this case is very characteristic for arylhydrazones [5].

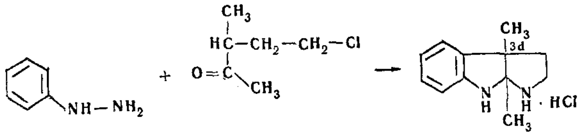


The compound is broken down in three major directions under electron impact.* First, cleavage of the N−N bond (cleavage at the β bond with respect to the aryl ring and the β bond with respect to the double bond of the pyrroline ring) with migration of hydrogen and formation of an ion (the maximum in the spectrum) with mass B_5^{135}, which corresponds to the aniline structure which, on losing a hydrogen atom, gives a very intense ion with mass 134; this corresponds completely to the cleavage of aromatic amines [8].

In addition, an ion with mass 81 (17.4%), which corresponds to the 2-methylpyrrole structure, is formed during this cleavage, either with the simultaneous loss of two hydrogen atoms or from the dehydrogenated molecular ion (m/e 214). Its cleavage with the formation of ions with masses of 80 (28.4) (pyridinium ion obtained by expansion of the pyrrole ring), 53 (11.8), 52 (6.1), 51 (7.8), 50 (2.9), 41 (12.4), 40 (3.5), and 39 (14.2) is characteristic for the behavior of 2-methylpyrrole under electron impact [9]. Finally, a molecule of the compound readily loses two hydrogen atoms to form a more stable pyrrolaniline structure (ion with mass 214), and its subsequent cleavage, as confirmed by the corresponding metastable transitions, agrees completely with the cleavage of pyrrole derivatives [10]. Thus the behavior of the compound corresponds completely to the structure of the corresponding anilinopyrroline.

It should be noted that all attempts to convert 1-mesitylamino-Δ^2-2-methylpyrroline hydrochloride to the corresponding tryptamine with cleavage of one o-methyl group were unsuccessful: pronounced resinification occurs under severe conditions (autoclave, 200°, 10 h), and under milder conditions (benzene, 80°).

If a γ-haloketone with an alkyl substituent in the α-position relative to the carbonyl group is used as a carbonyl component in the synthesis of tryptamines, a compound of the eserine series is formed, and is an intermediate of the VII type in the penultimate step of the reaction.



Further transformation of this compound into a tryptamine is impossible because of the presence of a methyl group instead of a hydrogen atom in the 3d position. Proof of the structure of the dinordeoxy-9-methyleseroline formed in the reaction is presented in [11].

Thus the isolation of intermediates in the various steps of the reaction proves the correctness of the proposed reaction scheme.

EXPERIMENTAL

The PMR spectra in CCl_4 were obtained by Yu. A. Ustynyuk with a JNM-60 spectrometer with an operating frequency of 60 MHz using tetramethylsilane (TMS) as the internal standard. The chemical shifts are given in the δ scale.

The UV spectra in ethanol were obtained with an EPS-3T spectrometer (Hitachi). The IR spectra of thin films were obtained with a JASCO-IR-S spectrophotometer with an NaCl prism. The mass spectrum of 1-mesitylamino-Δ^2-2-methylpyrroline was obtained with an MKh-1303 spectrometer with an ionizing electron energy of 50 eV, an emission current of 1.5 mA, and a source and admission system temperature of 250°.

γ-Chloropropyl Methyl Ketone Phenylhydrazone. A mixture of 3.24 g (0.03 mole) of phenylhydrazine and 3.62 g (0.03 mole) of γ-chloropropyl methyl ketone in 50 ml of benzene at 20° was allowed to stand for 1 h. The mixture was then passed through a filter with 2 g of activity II aluminum oxide, after which the solvent was removed in vacuo with a water aspirator without heating. The residual yellow oil was dried in vacuo over alkali and paraffin to give 6 g (95%) of product. Found %: C 62.73, 62.70; H 7.34, 7.33. $C_{11}H_{15}ClN_2$. Calculated %: C 62.71; H 7.17. R_f 0.73 (activity II Al_2O_3, benzene, development with iodine). IR spectrum: C=N 1620 cm^{-1}, NH 3300 cm^{-1}.

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*The numbers under the formulas in the scheme are the mass numbers, the numbers in parentheses are the peak intensities of the corresponding ions in percent of the maximum, and the numbers with crosses correspond to the masses of the metastable ions.

Mesitylhydrazine Hydrochloride. The hydrazine was obtained in the form of the hydrochloride via the method in [12] since the free base is very unstable [13]. The hydrochloride was obtained in 60% yield and had mp 305-306° (decomp., from aqueous alcohol). Found %: C 58.17, 58.11; H 7.94, 7.90. $C_9H_{14}N_2 \cdot HCl$. Calculated %: C 57.90; H 8.09.

1-Mesitylamino-Δ^2-2-methylpyrroline. A solution of 0.44 g (0.011 mole) of sodium hydroxide in 20 ml of methanol, followed by a solution of 1.33 g (0.011 mole) of γ-chloropropyl methyl ketone in 10 ml of methanol, was added to a solution of 2 g (0.011 mole) of mesitylhydrazine hydrochloride. The mixture was refluxed under nitrogen for 1 h. The solvent was then removed, the residue was dissolved in hot water, and the solution was extracted with ether to remove neutral impurities (twice with 15-ml portions). The aqueous solution was made alkaline, and the resulting oil was extracted with benzene (twice with 20-ml portions). The benzene extract was dried over potassium carbonate and distilled in vacuo under nitrogen to give 1.6 g (74%) of a product with bp 128-130° (2 mm) and R_f 0.59 [activity II aluminum oxide, benzene–isopropyl alcohol system (9 :1), development with iodine]. Found %: C 77.48, 77.40; H 9.24, 9.20. $C_{11}H_{20}N_2$. Calculated %: C 77.70; H 9.32. IR spectrum: C=C 1640 cm^{-1}, NH 3290 cm^{-1}.

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