INDOLES

XXXI.* UNSYMMETRICAL CYCLIC ENAMINES IN THE SYNTHESIS OF INDOLYLALKYLAMINES

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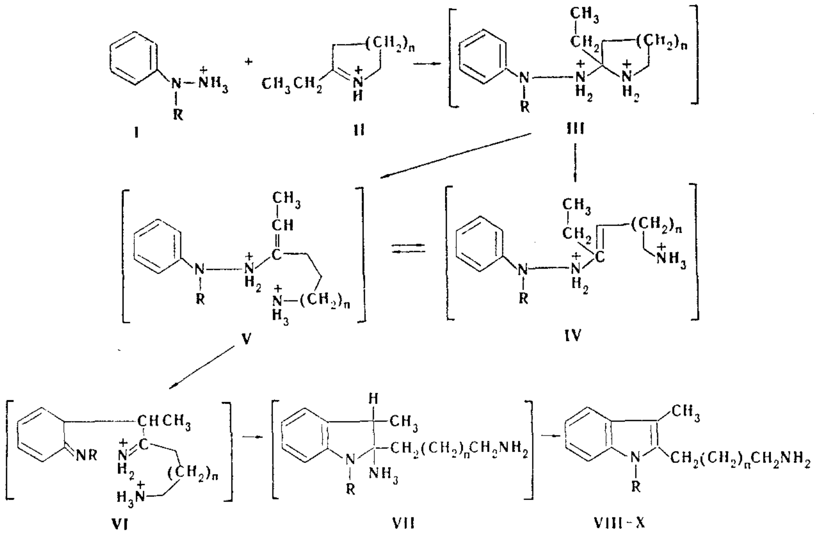
UDC 547.75.07

The reaction of 2-ethyl-Δ^1-pyrroline and 2-ethyl-Δ^1-piperideine with arylhydrazine hydrochlorides leads to the formation of "anomalous" 3-methyl-2-indolylalkylamines.

The reaction between arylhydrazine hydrochlorides and 2-methyl-Δ^1-pyrroline and 2-methyl-Δ^1-piperideine gives 2-methyltryptamines and 2-methylhomotryptamines, respectively [2].

When we introduced 2-ethyl-substituted pyrrolines and piperideines into the reaction, we observed that the reaction products are 3-methylindolylalkylamines rather than 2-ethylindolylalkylamines. Thus the product of the reaction of 2-ethyl-Δ^1-pyrroline with α-benzyl-α-phenylhydrazine hydrochlorides is 3-methyl-2-(γ-aminopropyl)indole (IX). The formation of a compound with this sort of structure is possible if the intermediate hydrazone is isomerized with the participation of the ethyl group of the substituent to enehydrazine form V rather than to IV. A singlet at 2.16 ppm, equivalent to three protons of the same methyl group (Fig. 1), is observed in the PMR spectrum of 3-methyl-2-(γ-aminopropyl)indole in deuterochloroform. The position of the signals of the protons of the α-, β-, and γ-methylene groups corresponds to that in homotryptamines [3]. In sulfuric acid, the singlet of the protons of the methyl group is converted to a doublet (2.25 ppm) with a spin-spin splitting constant of 8.2 Hz (Fig. 2). This fact may be due only to the interaction of the protons of the methyl group with the proton that is added to the 3 position of the indole ring in sulfuric acid [4]. Gas-liquid chromatography (GLC) and PMR spectroscopy were used to demonstrate the individuality of VIII-X and to confirm their structures. The formation of a single product in this reaction is an indirect confirmation that it proceeds through enehydrazine form V.



VIII R=H, n=1; IX R=$C_6H_5CH_2$, n=1; X R=$C_6H_5CH_2$, n=2

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*See [1] for communication XXX.

K. A. Timiryazeva Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1216-1219, September, 1972. Original article submitted July 5, 1971.

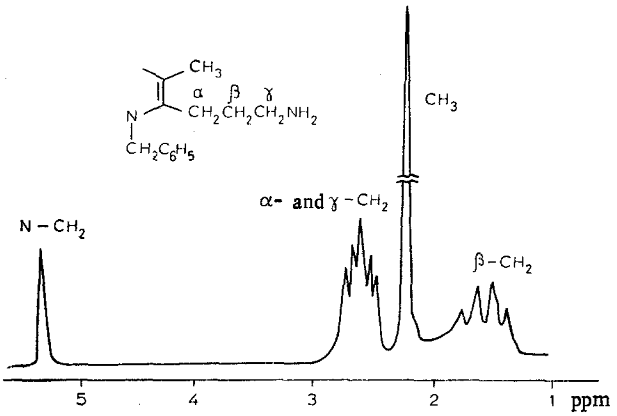

Fig. 1. PMR spectrum of 1-benzyl-2-(γ-aminopropyl)-3-methylindole in $CDCl_3$ (aliphatic portion).

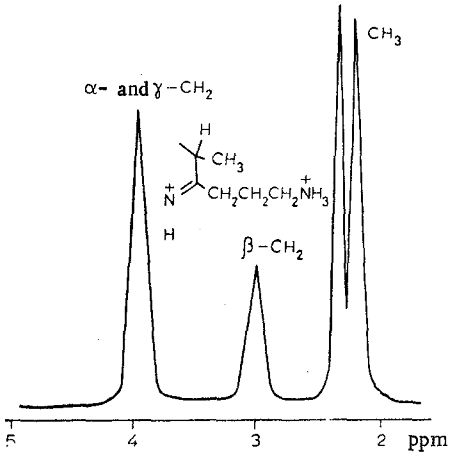

Fig. 2. PMR spectrum of 1-benzyl-2-(γ-aminopropyl)-3-methylindole in 96% H_2SO_4 (aliphatic portion).

EXPERIMENTAL

2-Ethyl-Δ^1-pyrroline. This compound was obtained via the method in [5] and had bp 52° (40 mm) and R_f 0.51 [activity II Al_2O_3, benzene–methanol (9 : 1)]. UV spectrum[*]: λ_{max} 212 nm, log ε 2.12. IR spectrum[†]: 1645 cm^{-1} ($\nu_{C=N}$). PMR spectrum[‡]: 2-CH_3 1.13 t (J = 7 Hz); 2-H 2.3 m; 3-H 2.3 m; 4-H 1.95 q (J = 7 Hz); 5-H 3.84 m. According to mass spectrometry, the molecular weight was 97.

2-Ethyl-Δ^1-piperideine. This compound was obtained by the method in [6] and had bp 138-139°; 40% NaOH was used to isolate the reaction product, and this raised the yield from 15% to 30%. R_f 0.41 [activity II Al_2O_3, benzene–methanol (9 : 1)]. According to mass spectrometry, the molecular weight was 111. IR spectrum: 1655 cm^{-1} ($\nu_{C=N}$). PMR spectrum: 2-CH_3 1.03 t (J = 7 Hz); 2-H 2.42 q (J = 7 Hz); 3- and 4-H 1.58 m; 5-H 2.12 m; 6-H 3.67 t. UV spectrum: λ_{max} 313 nm, log ε 3.90.

General Method of Condensation. A solution of 0.05 mole of enamine in 20 ml of isopropyl alcohol containing precisely 0.05 mole of hydrogen chloride was added to a solution of 0.05 mole of arylhydrazine hydrochloride in 75 ml of isopropyl alcohol, and the mixture was refluxed for 8 h. The solvent was removed by distillation, and 150 ml of water was added to the residue. The neutral impurities were extracted with benzene, and the aqueous layer was filtered through 2 g of activated charcoal and made alkaline with sodium hydroxide. The liberated indolylalkylamine was extracted with benzene and vacuum-distilled in a stream of inert gas.

The picrates were obtained in absolute ether with an equimolar amount of picric acid and were recrystallized from methanol.

2-(γ-Aminopropyl)-3-methylindole (VIII). This compound was obtained in 20% yield from phenylhydrazine hydrochloride and 2-ethyl-Δ^1-pyrroline and had bp 170-172° (1 mm), R_{f_1} 0.85, and R_{f_2} 0.61.[**] UV spectrum, λ_{max}, nm (log ε): 224 (3.50), 282 (3.84), 289 (3.78). IR spectrum: 1335, 1450, 1490, 1590 cm^{-1} (ring stretching vibrations), 3250 cm^{-1} (NH_2). PMR spectrum: NH_2 1.83 broad s; 2-β-CH_2 1.26 q;

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[*] The UV spectra in ethanol were recorded with an EPS-3T spectrophotometer.

[†] The IR spectra of thin films or CCl_4 solutions were recorded with a JASCO-IRS spectrophotometer.

[‡] Here and elsewhere, on the δ scale. The abbreviations are as follows: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.

[**] Here and elsewhere, the R_{f_1} values were obtained on "fast" chromatographic paper of the Volodarskii Leningrad factory in n-butyl alcohol–pyridine–water (1 : 1 : 1), while the R_{f_2} values were obtained on a thin layer of silica gel in isopropyl alcohol–25% ammonium hydroxide (9 : 1.5).

2-α-CH_2 2.71, two t; 3-CH_3 2.21 s; in sulfuric acid 3-CH_3 2.25 d (J = 8.2 Hz). Gas-liquid chromatography[*]. retention time 3 min. Found: C 76.8; H 8.6%. $C_{12}H_{16}N_2$. Calculated: C 76.6; H 8.6%. The picrate had mp 176°. Found: N 16.6%. $C_{12}H_{16}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 16.8%.

1-Benzyl-2-(γ-aminopropyl)-3-methylindole (IX). This compound was obtained in 44% yield from α-benzyl-α-phenylhydrazine hydrochloride and 2-ethyl-Δ^1-pyrroline and had bp 220-225° (1 mm), Rf_1 0.83, and Rf_2 0.59. UV spectrum, λ_{max}, nm (log ε): 241 (4.18), 291 (3.62); 311 (3.58). IR spectrum: 1355, 1450, 1465, 1600 cm^{-1} (ring stretching vibrations), 3300 cm^{-1} (NH_2). PMR spectrum: NH_2 1.78 broad s; 2-α- and 2-γ-CH_2 2.62 two t; 2-β-CH_2 1.55 q; 1-N-CH_2 5.25 s. GLC: retention time 8.8 min. Found: C 81.4; H 7.9%. $C_{19}H_{22}N_2$. Calculated: C 82.0; H 8.0%. The picrate had mp 198-199°. Found: N 13.5%. $C_{19}H_{22}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 13.8%.

1-Benzyl-2-(δ-aminobutyl)-3-methylindole (X). This compound was obtained in 49% yield from α-benzyl-α-phenylhydrazine hydrochloride and 2-ethyl-Δ^1-piperideine and had bp 225-232° (1 mm), Rf_1 0.83 and Rf_2 0.5. UV spectrum, λ_{max}, nm (log ε): 231 (2.26); 246 (4.44); 292 (3.71). IR spectrum: 1355, 1450, 1490, and 1590 cm^{-1} (ring stretching vibrations), 3300 cm^{-1} (NH_2). GLC: retention time 9.4 min. Found: C 81.6; H 8.0%. $C_{20}H_{24}N_2$. Calculated: C 81.2; H 8.3%. The picrate had mp 199-200°. Found: N 13.6%. $C_{20}H_{24}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 13.4%.

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[*] With a G-800 chromatograph (Janaco) with a flow meter and a column packed with 10% polyethylene glycol (mol. wt. 150,000) + 1% KOH on porolit. The column was 2 m long and 3 mm in diameter, the temperature was 240°, and the hydrogen flow rate was 20 ml/min.