INDOLES

XXVIII.* METHOD FOR THE SYNTHESIS OF 7-AZATRYPTAMINES AND RELATED COMPOUNDS

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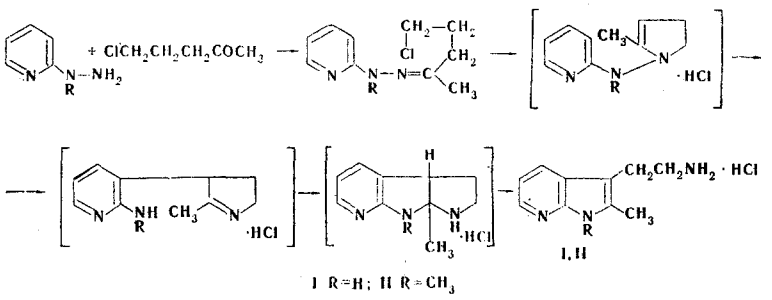
The synthesis of 2-methyl- and 1,2-dimethyl-7-azatryptamines and dinordeoxy-9-methyl-7-azaeseroline and its 8-methyl and 8-ethyl analogs was accomplished by the reaction of 2-pyridylhydrazine with γ-chloro carbonyl compounds. The spectral characteristics of the compounds obtained are presented.

The principle of aza analogy has recently been finding increasing acceptance among chemists engaged in the synthesis of physiologically active compounds. In this connection, many papers devoted to the investigation of the applicability of the Fischer reaction for the synthesis of azaindole systems [2] have been published. Of particular interest from our point of view are the investigations devoted to the synthesis of azatryptamines and their derivatives – the aza analogs of natural indole, alkaloid-like compounds.

The Fischer reaction, which proceeds readily and smoothly with various arylhydrazones, usually either does not give positive results [3,4] or proceeds under considerably more severe conditions [5] in the case of pyridyl- and quinolylhydrazones. The syntheses of tryptamines and especially azatryptamines are generally extremely laborious and give very low yields [6,7].

In 1967, one of us [8] observed that the reaction of diphenylhydrazine and γ-chlorobutyraldehyde in aqueous methanol leads to tryptamine hydrochloride in high yield. On the basis of this reaction, a large number of tryptamines having different substituents in both the benzene and pyrrole portions of the molecule were later synthesized [9-11].

We attempted to use this method to obtain the corresponding aza analogs of tryptamines using 2-pyridylhydrazines as the hydrazine components. In particular, we were able to isolate 2-methyl-7-azatryptamine (I) in good yield on heating a mixture of 2-pyridylhydrazine with γ-chloropropyl methyl ketone in aqueous methanol at 150°C.



I R=H; II R=CH$_3$

TABLE 1. UV Spectra of 7-Azaindoles and 7-Azaeserines

Compound	λ_{max}, nm	lg ε
I	226	4,29
	291	3,87
II	229	4,36
	293	4,08
III	242	3,97
	310	3,80
IV	250	4,14
	319	3,80
V	250	4,13
	316	3,88

Under similar conditions, we synthesized 1,2-dimethyl-7-azatryptamine (II) from N-methyl-N-(2-pyridyl)hydrazine. The structure of I was proved by means of UV, IR, and PMR spectroscopy. Two ab-

*See [1] for communication XXVII.

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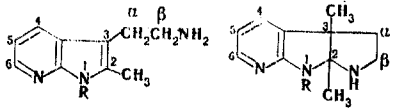
TABLE 2. Frequencies of the Primary Absorption Maxima (cm^{-1}) in the IR Spectra of 7-Azaindoles and 7-Azaeserines*

Compound I	Compound II	Compound III	Compound IV	Compound V	Proposed assignment
3420	—	—	3440	—	Free N—H
—	—	3240 s	—	3260 s	Bonded N—H
3020 s	3030 s	3040 c	3040 s	3040 s	ν_{CH} (aromatic)
2840—3000	2840—3000	2840—3000	2840—3000	2840—3000	ν_{CH_2}
1600	1600	1610	1610	1615	Aromatic absorption
1490	1490	1500	1495	1490	Aromatic absorption
1475	1465	1460	—	1460	Aromatic absorption
1390	1385	1383	1385	1380	δ_{CH_3}
1150	1180	1110	1130	1110	δ_{CH_3}
770	773	765	770	770	Three adjacent hydrogen atoms

*Strong absorption is indicated by s.

TABLE 3. PMR Spectra of 7-Azatryptamines and 7-Azaeserolines*



Substance	1-H	1-CH_3	1-CH_2CH_3		2-CH_3	3-CH_3
			CH_2	CH_3		
I	6,5 s	—	—	—	2,35 s	—
II	—	3,42 s	—	—	2,1 s	—
III	—	—	—	—	1,47 s	1,35 s
IV	—	2,75 s	—	—	1,27 s	1,27 s
V	—	—	3,3 q J=6,75	1,21 t J=6,75	1,28 s	1,28 s

Substance	4-H	5-H	6-H	α-CH_2	β-CH_2	NH_2
I	7,7 t $J_{4,5}$=7,5	6,87 d $J_{5,6}$=4,5	8,08 d $J_{4,6}$=1,5	2,78 t J=3,75	2,78 t J=3,75	1,7 s
II	7,42 d $J_{4,5}$=7,5	6,6 t $J_{5,6}$=4,5	7,91 d $J_{4,6}$=1,5	2,60 t J=3,75	2,60 t J=3,75	1,1 s
III	7,12 d $J_{4,5}$=7,5	6,45 t $J_{5,6}$=5,3	7,80 d	1,96 t	2,82 m	—
IV	6,8 d $J_{4,5}$=7,2	6,10 t $J_{5,6}$=5,3	7,55 d $J_{4,6}$=1,5	1,88 m	2,78 m	—
V	6,9 d $J_{4,5}$=7,5	6,2 t $J_{5,6}$=4,5	7,7 d $J_{4,6}$=1,5	1,91 m	2,75m	—

*The numbering of the carbon atoms in I-V is arbitrary for convenience in comparison of the chemical shifts of related protons. Abbreviations: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet. The chemical shifts are presented in parts per million, and the spin—spin splitting constants are presented in Hertz units.

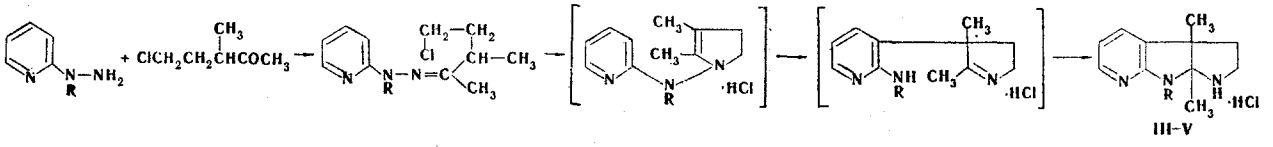
sorption bands at 230 and 290 nm are present in the UV spectrum of I. We observed the same bands in the spectrum of the model compound 2,3-dimethyl-7-azaindole, which we also synthesized. The IR spectrum of I contains intense absorption bands at 3100-3600 cm^{-1}, which are related to the stretching vibrations of associated NH and NH_2 groups. Three absorption bands at 1615, 1590, and 1490 cm^{-1}, which correspond to the analogous bands in the IR spectra of indoles and are probably related to the stretching vibrations of the ring [12], are present at 1400-1700 cm^{-1}.

The PMR spectrum also confirms the structure of I. A singlet of three protons at 2.35 ppm, which corresponds to a methyl group attached to a double bond, is present in the spectrum. The methylene groups in the α and β positions should appear in the spectrum as two triplets. However, one triplet at 2.78 ppm (J = 3.75 Hz), the intensity of which corresponds to four protons, is present in the spectrum. The

superimposition of two triplets of the aminoethyl residue occurs because the chemical shifts of the α- and β-methylene groups are identical. This phenomenon is also observed in the PMR spectrum of 2-methyltryptamine [13]. A doublet of the proton in the 4 position (7.7 ppm, J = 7.5 Hz), a 5-H quartet (6.85 ppm, J = 7.5 Hz), and a 6-H doublet (8.08 ppm) are observed in the aromatic proton region. In addition, the spectrum contains two broad signals at 1.70 and 6.50 ppm, which we assigned to the protons of the amine and imine groups, respectively.

It has previously been demonstrated that if γ-halo ketones that are substituted in the α position are used in the reaction to synthesize tryptamines, the products are eserine derivatives [14].

We carried out the reaction of 2-pyridylhydrazine and its N-methyl and N-ethyl derivatives with γ-chloro-α-methylpropyl methyl ketone and found that dinordeoxy-9-methyl-7-azaeseroline (III) and its methyl (IV) and ethyl (V) analogs are formed smoothly in this case.



III R=H; IV R=CH_3; V R=C_2H_5

Two absorption bands, which lie in the longer-wave region than the corresponding bands of 2-aminopyridine, are present in the UV spectra of III-V (Table 1). The IR spectra (Table 2) contain bands at 3300 cm^{-1}, which correspond to the stretching vibrations of the NH groups, and bands at 1615, 1590, and 1440 cm^{-1}, which pertain to the stretching vibrations of the pyridine ring.

The data on the PMR spectra of all of the synthesized compounds are presented in Table 3.

EXPERIMENTAL

The IR spectra of CCl_4 solutions and potassium bromide pellets were recorded with a Jasco-JRS spectrometer with a sodium chloride prism. The UV spectra of alcohol solutions were recorded with a Hitachi EPS-3T spectrometer. The PMR spectra of CCl_4 solutions were recorded with JNM-4H-100, H-60, and T-60 spectrometers with hexamethyldisiloxane as the internal standard.

Gas-liquid chromatography (GLC) was carried out with a Yanagimoto G-800 chromatograph. The carrier gas was hydrogen (flow rate 80 ml/min), and the column temperature was 200°. The stationary phase was 10% polyethylene glycol 3000 on Porolite with application of 1% potassium hydroxide.

Thin-layer chromatography (TLC) was carried out with Silufol UV-254 in methanol.

2-Methyl-7-azatryptamine (I). A 12.3-g (0.1 mole) sample of freshly distilled γ-chloropropyl methyl ketone was added to a solution of 10.8 g (0.1 mole) of freshly distilled 2-pyridylhydrazine [bp 100° (2 mm)] [15] in 200 ml of 80% ethanol, and the mixture was heated in an autoclave at 160° for 6 h. The ethanol was removed in a rotary evaporator, the residual 2-methyl-7-azatryptamine hydrochloride was dissolved in 200 ml of 0.1 N hydrochloric acid, and the neutral impurities were extracted with 50 ml of benzene. The aqueous solution was cooled and made alkaline with solid potassium hydroxide. The resulting oil was extracted three times with 50-ml portions of ether. The combined ether extracts were dried with potassium carbonate, the ether was removed by distillation, and the residue was vacuum-distilled under nitrogen to give 13.2 g of a product with bp 180-183° (1 mm), a retention time of 31.2 min, and R_f 0.64. Found: C 68.6; H 7.4%. $C_{10}H_{13}N_3$. Calculated: C 68.6; H 7.4%. The picrate had mp 182° (dec.). Found: N 20.8%. $C_{10}H_{13}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 20.8%.

1,2-Dimethyl-7-azatryptamine (II). This compound was obtained in 65% yield by the method described above from N-methyl-N-(2-pyridyl)hydrazine [16] and had bp 170-175° (1.5 mm), a retention time of 2.8 min, and R_f 0.70. Found: C 69.8; H 8.1%. $C_{11}H_{15}N_3$. Calculated: C 69.8; H 7.9%. The picrate had mp 300° (dec.). Found: N 19.9%. $C_{11}H_{15}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 20.0%.

Dinordeoxy-9-methyl-7-azaeseroline (III). A mixture of 10.8 g (0.1 mole) of freshly distilled 2-pyridylhydrazine [15] and 13.6 g (0.1 mole) of γ-chloro-α-methylpropyl methyl ketone in 200 ml of 80% ethanol was refluxed on a water bath for 6 h. The mixture was evaporated to dryness in a rotary evaporator, and the residue was dissolved in 200 ml of 0.1 N hydrochloric acid and extracted three times with 30-ml portions of benzene. The benzene extracts were discarded, and the aqueous layer was cooled and

made alkaline with solid potassium hydroxide. The resulting crystals were removed by filtration and recrystallized from petroleum ether to give 12.4 g (70%) of III with mp 132-133°, a retention time of 8.7 min, and R_f 0.81. Found: C 69.6; H 7.9%. $C_{11}H_{15}N_3$. Calculated: C 69.8; H 7.9%. The picrate had mp 165°. Found: N 19.8%. $C_{11}H_{15}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 20.0%.

Dinordeoxy-8,9-dimethyl-7-azaeseroline (IV). This compound was obtained in 70% yield by the method presented for III from N-methyl-N-(2-pyridyl)hydrazine and had bp 130-135° (0.5 mm). The product crystallized on standing to give a material with mp 68-69°, a retention time of 5.2 min, and R_f 0.60. Found: C 70.6; H 8.5%. $C_{12}H_{17}N_3$. Calculated: C 70.9; H 8.3%. The picrate had mp 153-154° (dec.). Found: N 19.6%. $C_{12}H_{17}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 19.4%.

Dinordeoxy-9-methyl-8-ethyl-7-azaeseroline (V). This compound was obtained in 60% yield from N-ethyl-N-(2-pyridyl)hydrazine by the method used to obtain III and had bp 140-145° (1.5 mm), a retention time of 6.1 min, and R_f 0.63. Found: C 72.1; H 8.9%. $C_{13}H_{19}N_3$. Calculated: C 71.9; H 8.8%. The picrate had mp 152°. Found: N 18.6%. $C_{13}H_{19}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 18.8%.

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