INDOLES

XVIII.* NEW ROUTE FOR THE SYNTHESIS OF 2-UNSUBSTITUTED HOMOTRYPTAMINES

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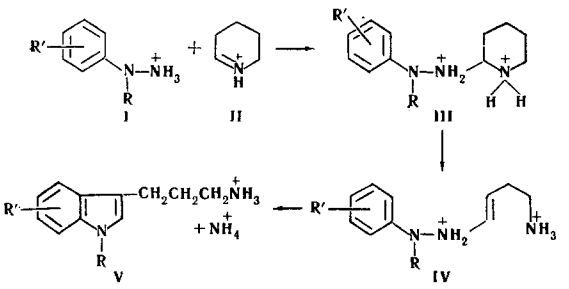
A new one-step synthesis of homotryptamines which are not substituted in the 2 position has been found by refluxing solutions of salts of various substituted arylhydrazines and Δ^1-piperideine salts.

It is well known that the biological activity of tryptamines and homotryptamines drops sharply when the 2 position is substituted. The synthesis of homotryptamines with an unsubstituted 2 position is therefore of particular interest.

As was shown in [1], the reaction between arylhydrazine salts and 2-substituted pyrroline salts by refluxing the components in dimethylformamide leads to tryptamines which have substituents in the 2 position. In order to synthesize homotryptamines with a free 2 position, the corresponding enamine also should not have a substituent in this position. However, cyclic enamines of this type are extremely reactive, and, as a result, exist only as trimers of the aldehyde-ammonia type [2]. As shown in the case of α-tripiperideine, the trimer decomposes in acid solutions to form three molecules of the monomer salt [3, 4], which was also used as the enamine component in our reaction. Arylhydrazine salts (R = H, CH_3, C_6H_5, $C_6H_5CH_2$; R' = H, CH_3) were used as the hydrazine component in the reaction. The formation of the homotryptamine proceeds according to the scheme



The arylhydrazine salt (I) initially adds to the active C = N double bond of the enamine salt (II). Addition product III then isomerizes to the enehydrazine (IV), which then forms the homotryptamine hydrochloride via the well-known scheme for the Fischer reaction.

N-Acetyl-Δ^2-piperideine was also used as the enamine component; the homotryptamine formed according to the scheme had an acylated amino group. N-Substituted phenylhydrazines give homotryptamines in higher yields (Table 1).

When the synthesis of N-benzylhomotryptamine was carried out with alcohol in place of dimethylformamide as the solvent, the yield of homotryptamine increased from 36 to 52% and the reaction mixture underwent virtually no resinification. When this reaction was carried out in a strongly acid medium (alcohol saturated with hydrogen chloride to pH 1), pronounced resinification occurred and the yield dropped to 20%.

*See [6] for communication XVII.

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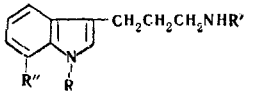
TABLE 1



Compound	R′	R″	R	bp (mm)	mp (°C)	UV spectra (ethanol) λmax nm	UV spectra (ethanol) lg ε	R_f paper*	R_f Al_2O_3†	IR Spectra (ring valence vibrations), cm^{-1}	Empirical formula	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
I	H	H	H	167 (1—2)		220 275 289	3,46 2,93 2,85	0,81		ν_{NH_2} 3400 (1455, 1500, 1545, 1595)	$C_{11}H_{14}N_2$	75,6	8,4	75,8	8,1	18
II	H	—CH(CH3)—CH2—CH2—		170—172 (1—2)		225 282 299	4,35 3,62 3,61	0,87		ν_{NH_2} 3300 (1460, 1495, 1545, 1615)	$C_{15}H_{20}N_2$	78,7	8,6	78,9	8,8	26
III	H	H	CH_3	215 (3)		225 289 321	4,58 3,82 3,08	0,83		ν_{NH_2} 3400 (1475, 1490, 1575, 1610)	$C_{12}H_{16}N_2$	76,2	8,9	76,6	8,6	33
IV	H	H	C_6H_5	185—186 (1)		218 258 291	4,41 4,20 4,08	0,83		ν_{NH_2} 3400 (1460, 1500, 1590)	$C_{17}H_{18}N_2$	81,2	7,4	81,6	7,3	23
V	H	H	$C_6H_5CH_2$	170 (1—2)	41	226 245 283 331	4,2 3,95 3,96 3,0	0,84		ν_{NH_2} 3400 (1460, 1470, 1505, 1600)	$C_{18}H_{20}N_2$	81,5	7,6	81,8	7,6	52
VI	$COCH_3$	H	CH_3	180—183 (1—2)		226 285 287	4,82 3,65 3,7		0,53	$\nu_{C=O}$ 1670, ν_{NH} 3300 (1480, 1505, 1560, 1610)	$C_{14}H_{18}N_2O$	72,4	7,7	73,0	7,8	39
VII	$COCH_3$	H	$C_6H_5CH_2$	185—186 (1—2)	46	225 282 289	4,63 3,83 3,85	0,81	0,53	ν_{NH} 3300, $\nu_{C=O}$ 1670 (1380, 1480, 1560)	$C_{20}H_{22}N_2O$	78,3	7,5	78,4	7,2	48
VIII	$COCH_3$	CH_3	H	220—225 (3—4)		234 270 279 332	4,2 3,41 2,79 3,32		0,50	$\nu_{C=O}$ 1700, ν_{NH} 3300 (1460, 1500, 1600)	$C_{14}H_{18}N_2O$	72,5	7,7	73,0	7,8	10

*"Fast" chromatographic paper from the Leningrad Volodarskii Factory, n-butanol-pyridine-water system (1:1:1).
†Activity II Al_2O_3, benzene-ethanol (9:1).

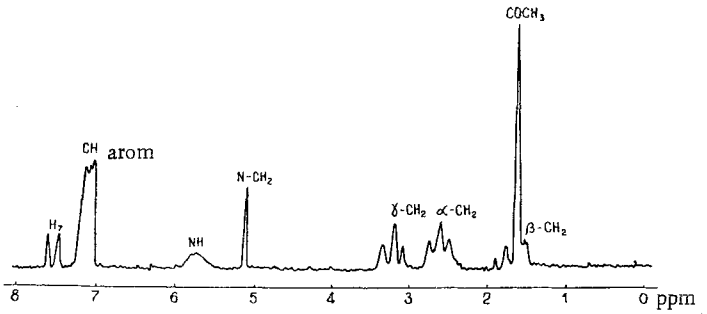


Fig. 1. PMR spectrum of acetylated 1-benzyl-3-(γ-aminopropyl)-indole.

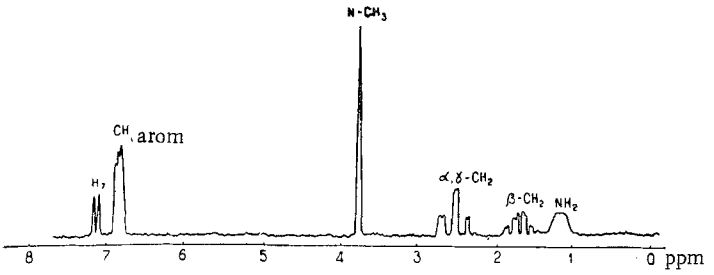


Fig. 2. PMR spectrum of 1-methylhomotryptamine.

Substitution in the ortho position of the phenyl ring of the hydrazine lowered the yield of homotryptamine to 10%, which is generally characteristic in the Fischer synthesis [5].

The PMR spectra of the homotryptamines confirm the structure of the compounds obtained. The protons of the α- and γ-methylene groups are manifested as two superimposed triplets at 2.5-2.7 ppm. When the amino group is acetylated, the signal from the protons of the γ-methylene group is shifted to weak field, and two separate triplets with chemical shifts of 2.9-3.2 and 2.6-2.7 ppm (J = 7 Hz), respectively, are observed. The signals from the protons of the β-CH_2 group are poorly resolved and shifted to strong field (1.8-1.9 ppm). In homotryptamines with an acylated amino group the signals from the protons of the β-CH_2 group are overlapped with the signals from the protons of the $COCH_3$ group (1.77-1.8 ppm). The diffuse signals from the protons of the NH_2 group lie at the strongest fields (1.3-1.5 ppm), while the protons from the methyl group attached to the ring nitrogen atom are manifested as a singlet at 3.5-3.6 ppm. The proton signal from the NH amide group is shifted to weak field and is manifested as a broad singlet at 5.5-5.8 ppm. The protons from the CH_2 group in N-benzyl derivatives of homotryptamine are manifested as a singlet at 5-5.1 ppm. The $H_{2,4,5,6}$ and H_7 aromatic protons appear at weak field (6.8-7.2 ppm and 7.1-7.2 ppm, respectively).

EXPERIMENTAL

General Method for Obtaining Homotryptamines I-V. A mixture of 0.05 mole of the salt of the substituted phenylhydrazine and 80 ml of solvent (dimethylformamide or ethanol) was heated until a homogeneous medium was obtained, and a solution of 0.016 mole of α-tripiperideine [2] in 20 ml of the same solvent

TABLE 2. Picrates of the Homotryptamines

Picrates of compounds	mp °C	Empirical formula	Found, %			Calculated, %		
			C	H	N	C	H	N
I	101	$C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$			17,6			17,4
II	162	$C_{15}H_{20}N_2 \cdot C_6H_3N_3O_7$			15,7			15,3
III	171	$C_{12}H_{16}N_2 \cdot C_6H_3N_3O_7$			17,0			16,8
V	176	$C_{18}H_{20}N_2 \cdot C_6H_3N_3O_7$	58,4	4,8		58,4	4,7	
VI	109	$C_{14}H_{18}N_2O \cdot C_6H_3N_3O_7$	52,4	4,6		52,2	4,6	

was added to it. The solvent was previously saturated (weight increase) with hydrogen chloride gas (0.05 mole). The mixture was heated on a boiling-water bath for 1 h and refluxed for 4-6 h. The precipitate of NH_4Cl that formed on cooling was filtered and washed thoroughly with benzene. The solvent was removed by vacuum distillation, 100 ml of water was added to the residue, and the neutral impurities were extracted with ether. The aqueous layer was made alkaline with solid sodium hydroxide, the homotryptamine was extracted with benzene, and the residue after removal of the solvent was vacuum-distilled under nitrogen.

General Method for Obtaining Homotryptamines with an Acylated Amino Group (VI-VIII). A mixture of 0.05 mole of the salt of the substituted arylhydrazine in 80 ml of dimethylformamide was heated, a solution of 0.05 mole of N-acetyl-Δ^2-piperideine [2] in 20 ml of dimethylformamide was added to it, and the resulting mixture was refluxed for 5 h. After cooling, the precipitate of NH_4Cl was suction-filtered and thoroughly washed with absolute benzene. The solvent was removed by vacuum distillation, 100 ml of water was added to the residue, and the mixture was extracted with benzene. The residue after removal of the solvent by distillation was vacuum-distilled under an inert gas. Additional purification was effected by column chromatography with automatic collection of samples (activity II Al_2O_3). The substances were introduced as benzene solutions and eluted with benzene-ethanol (9:1). The constants of the homotryptamines and their picrates are presented in Tables 1 and 2. The picrates were obtained from absolute ether solution and recrystallized from aqueous methanol.

The UV spectra were obtained with a "Hitachi" EPS-3T double-beam spectrophotometer, the IR spectra were obtained with a "Jasco" IR-S spectrometer, and the PMR spectra of 10% solutions of the compounds in deuterochloroform with tetramethylsilane as the internal standard were obtained with a JNM-C-60 H spectrometer.

LITERATURE CITED

1. I. I. Grandberg, N. M. Przheval'skii, and T. A. Ivanova, USSR Author's Certificate No. 248,689 (1969); Byull. Izobr., No. 24 (1969).
2. C. Schopf and H. Arm, Ann., 559, 1 (1948).
3. C. Schopf, H. Arm, and H. Koop, Ann., 712, 168 (1968).
4. I. I. Grandberg, S. B. Nikitina, and N. G. Yaryshev, Izv. Timiryazeva Sel'skokhozyaist. Akad., 2, 196 (1970).
5. B. Robinson, Chem. Rev., 63, 373 (1963).
6. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 51 (1971).