INDOLES

XXXVI.* METHOD FOR THE SYNTHESIS OF 2-UNSUBSTITUTED TRYPTAMINES

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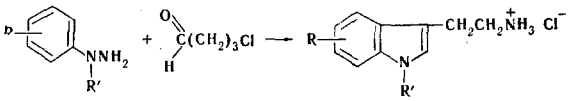
A number of tryptamines were obtained by the reaction of arylhydrazines with γ-chlorobutyraldehyde.

Continuing our investigation of the reaction of arylhydrazines with γ-halo carbonyl compounds [2,3], we have obtained a number of indolylalkylamines with substituents in the phenyl portion and 1-alkyl(or alkyl)-1,7-di- and -1,7-trimethylenetryptamines by refluxing equimolar amounts of differently substituted arylhydrazines and γ-chlorobutyraldehyde in aqueous alcohol solutions. The reaction proceeds via the scheme proved by one of us in [4, 5].

The yields of the tryptamines (Table 1) are quite high, particularly when α-substituted phenylhydrazines are used. The simplicity of the experimental method, the accessibility of the starting reagents, and the good yields make it possible to synthesize various previously hard-to-obtain β-indolylethylamines, a major class of biogenic amines.

Typical indole absorption at 220 and 280-290 nm is observed in the UV spectra of the indolylalkylamines (Table 2) [16, 17].



The IR spectra (Table 2) contain intense absorption bands at 3200-3400 cm^{-1}, related to the NH stretching vibrations, and bands at 1400-1700 cm^{-1}, related to the ring stretching vibrations [18]. The benzene ring CH deformation vibrations characteristic for substituted indoles determine the type of ring substitution.

The PMR spectra also confirm the structures of the tryptamines (Table 3) and are in agreement with the literature data [19, 20]. Signals of 3-α-CH_2 and 3-β-CH_2 groups, which correspond in intensity to four protons, appear in the 2.65-2.93 ppm region. It should be noted that the form of the signal of these groups for each concrete structure depends on the ratio of the spin-spin coupling constant and the chemical shifts of the protons of these groups (an A_2B_2 system). The aromatic ring protons of the tryptamines give signals at 6.54-7.60 ppm. An examination of the spectra of compounds with CH_3 groups in the 5 and 7 positions (VII and VIII) makes it possible to assign the signals of all of the protons in the 4, 5, 6, and 7 positions of the aromatic ring, although the complete interpretation of the ABCD system is difficult. The protons of the NH_2 group in the spectra of $CDCl_3$ solutions of the tryptamines give a broad singlet at 1.34-2.37 ppm. The signal of the proton of the NH group of the indole ring lies at 8.7-9 ppm and appears as a broad singlet.

EXPERIMENTAL

γ-Chlorobutyraldehyde. This compound, with bp 52-53° (16 mm) and n_D^{20} 1.4481, was obtained in 58% yield by Rosenmund reduction of γ-chlorobutyryl chloride in tetralin at 130-140° via the method in [21].

*See [1] for communication XXXV.

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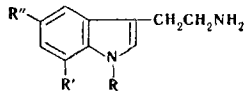
TABLE 1



Comp.	R	R′	R″	mp, °C*	bp, °C (mm)	Empirical formula	Found, %		Calc., %		Yield, %	Picrate				Acid tartrate, mp, °C (from alcohol)
							C	H	C	H		mp, °C (from alcohol)	empirical formula	N, % found	N, % calc.	
I	H	H	H	113—114[6]	185—187 (0,5)	$C_{10}H_{12}N_2$	75,3	7,6	75,0	7,5	71	247—248[6]	$C_{10}H_{12}N_2 \cdot C_6H_3N_3O_7$	18,2	18,0	182—183
II	CH_3	H	H	—	135—136[7] (2) n_D^{20} 1,6021	$C_{11}H_{14}N_2$	75,5	8,2	75,8	8,1	81	179—180[7]	$C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$	17,4	17,4	180—181
III	i-C_3H_7	H	H	138—140 (2)	138—140 (2) n_D^{20} 1,5775	$C_{13}H_{18}N_2$	77,2	9,0	77,2	9,0	87	146—148	$C_{13}H_{18}N_2 \cdot C_6H_3N_3O_7$	16,3	16,3	175—177
IV	C_6H_5	H	H	—	198—199 (2)	$C_{16}H_{16}N_2$	81,2	6,9	81,3	6,8	56	152—154	$C_{16}H_{16}N_2 \cdot C_6H_3N_3O_7$	15,0	15,1	215—217
V	$C_6H_5CH_2$	H	H	93—94[8]	157—161[8] (0,1)	$C_{17}H_{18}N_2$	81,3	7,3	81,6	7,3	75†	150—152[8]	$C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$	14,5	14,6	188—190
VI	2-(2-pyridyl)-ether	H	H	—	205—210 (1)	$C_{17}H_{19}N_3$	77,1	7,3	77,1	7,2	39	222—224	$C_{17}H_{19}N_3 \cdot 2C_6H_3N_3O_7$	17,7	17,5	115—117
VII	H	H	CH_3	95—96[9]	150—155 (0,1)	$C_{11}H_{14}N_2$	75,6	8,0	75,8	8,1	48	241—242[10]	$C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$	17,2	17,4	140—141
VIII	H	CH_3	H	132—133[11]	161—166 (0,2)	$C_{11}H_{14}N_2$	75,7	8,3	75,8	8,1	33	232—233[12]	$C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$	17,5	17,4	165—167
IX	H	H	OCH_3	118—119[13]	165—170 (0,08)	$C_{11}H_{14}N_2O$	69,4	7,7	69,5	7,4	45	216—217[13]	$C_{11}H_{14}N_2O \cdot C_6H_3N_3O_7$	16,4	16,7	166—167
X	H	OCH_3	H	134—135[14]	190—195 (1)	$C_{11}H_{14}N_2O$	69,8	7,5	69,5	7,4	24	237—238	$C_{11}H_{14}N_2O \cdot C_6H_3N_3O_7$	16,9	16,7	173—174
XI	H	H	Br	—	200—205 (1)	$C_{10}H_{11}BrN_2$	50,3	4,8	50,2	4,6	80†	239—240,5	$C_{10}H_{11}BrN_2 \cdot C_6H_3N_3O_7$	14,8	15,0	164—165
XII	H	Br	H	93—94	210—215 (3)	$C_{10}H_{11}BrN_2$	50,4	4,6	50,2	4,6	67†	227—229	$C_{10}H_{11}BrN_2 \cdot C_6H_3N_3O_7$	15,1	15,0	170—171
XIII	CH_2CH_2		H	—	167—170 (2)	$C_{12}H_{14}N_2$	77,2	7,7	77,4	7,6	43	183—185	$C_{12}H_{14}N_2 \cdot C_6H_3N_3O_7$	16,9	16,9	135—137
XIV	$CH_2CH_2CH_2$		H	33,5—34	168—170 (2)	$C_{13}H_{16}N_2$	78,0	8,1	78,0	8,1	74	174—175	$C_{13}H_{16}N_2 \cdot C_6H_3N_3O_7$	16,3	16,3	188—189
XV	$CH(CH_3)CH_2CH_2$		H	36—37	168—170 (1—2)	$C_{14}H_{18}N_2$	78,6	8,6	78,5	8,5	92	183—184	$C_{14}H_{18}N_2 \cdot C_6H_3N_3O_7$	15,8	15,8	200—201
XVI	$C_6H_5CH_2$	H	OCH_3	97—99[15]	195—200 (1)	$C_{18}H_{20}N_2O$	77,0	7,4	77,4	7,2	70†	167—169[15]	$C_{18}H_{20}N_2O \cdot C_6H_3N_3O_7$	13,6	13,8	165—167

*The melting points for V, VII-X, XII, and XVI are those obtained after sublimation.

† This is the yield of the hydrochloride.

TABLE 2. UV and IR Spectra of Tryptamines

Comp.	UV spectra,* in 95% ethanol		IR spectra,† cm^{-1}		
	λ_{max} nm	lg ε	ν_{NH}	ν ring	δ_{CH}
1	2	3	4	5	6
I	221	4,63			
	274	*3,77*	3400	1610	740 four adjacent hydrogen atoms
	281	3,81	3320	1590	
	289	3,74	3240	1500	
II	225	4,56		1610	740 four adjacent hydrogen atoms
	279	*3,72*	3360	1585	
	287	3,75	3280	1550	
				1490	
III	225	4,58	3290	1600	740 four adjacent hydrogen atoms
	279	*3,69*	3220	1575	
	288	3,74		1550	
	297	3,66			
IV	217	4,32	3360	1600	740 four adjacent hydrogen atoms
	258	4,20	3280	1555	
	297	3,95		1500	
V	220	4,63	3280	1600	740 four adjacent hydrogen atoms
	278	*3,76*	3220	1580	
	287	3,79		1555	
	295	3,72		1490	
VI	222	4,91	3360	1590	750 four adjacent hydrogen atoms
	267	4,04	3320	1570	
	285	3,98		1500	
	298	*3,91*			
VII	223	4,48	3380	1595	885 one isolated hydrogen atom
	277	*3,69*	3280	1490	
	284	3,67	3240		870 two adjacent hydrogen atoms
	295	*3,52*			
VIII	221	4,48	3280	1615	
	274	*3,79*	3240	1585	780 three adjacent
	279	3,71		1490	745 hydrogen atoms
	287	*3,61*			
IX	223	4,41	3320	1620	860 one isolated hydrogen atom
	276	3,84	3260	1590	
	281	*3,83*		1490	820 two adjacent hydrogen atoms
	283	3,78			
X	219	4,70	3350	1615	790 three adjacent
	268	3,84	3295	1585	745 hydrogen atoms
	277	*3,81*		1500	
	289	3,71			
XI	226	4,53	3370	1590	890 one isolated hydrogen atom
	280	*3,85*	3300	1490	
	286	3,83			820 two adjacent hydrogen atoms
	297	3,67			
XII	222	4,36	3350	1610	790 three adjacent
	277	*3,66*	3290	1590	740 hydrogen atoms
	284	3,68		1560	
	293	3,63			
XIII	227	4,27	3320	1600	750 three adjacent hydrogen atoms
	285	*3,60*	3210	1500	
	295	3,64			
	304	*3,57*			
XIV	224	4,66	3320	1610	780 three adjacent
	279	*3,84*	3210	1585	750 hydrogen atoms
	290	3,89			
	298	*3,84*			
XV	224	4,57	3320	1610	780 three adjacent
	279	*3,77*	3240	1510	750 hydrogen atoms
	288	3,81			
	297	3,75			
XVI	225	4,43	3380	1615	900 one isolated hydrogen atom
	274	*3,79*	3310	1580	
	280	3,83		1490	825 two adjacent hydrogen atoms
	303	3,68			

*The spectra were recorded with an EPS-3T spectrophotometer (Hitachi). The values corresponding to inflections are presented in italics.

† The spectra of I-V and XIII-XV were recorded with an IR-S spectrophotometer (Jasco) with an NaCl prism; the remaining spectra were obtained with a UR-20 spectrophotometer; the spectra of I, VII-X, XII, and XVI were obtained from KBr pellets, while the spectra of II-VI, XI-XV were obtained from thin films.

TABLE 3. PMR Spectra of Tryptamines*

Comp.	δ, ppm (J, Hz)									Solvent
	2-H	3-α, β-CH_2	NH_2	NH	4-H	5-H	6-H	7-H	substituent protons	
1	2	3	4	5	6	7	8	9	10	11
I	6,94 s	2,95 m	1,34 bs	8,78 bs	7,61 q ($J_{4,5}$=9) ($J_{4,6}$=1,5)	7,08 — 7,39 m			—	$CDCl_3$
II	6,66 s	2,80 m	0,98 s	—	7,35 q ($J_{4,5}$=7,5) ($J_{4,6}$=1,5)	6,97 — 7,15 m			3,61 s	CCl_4
III	6,80 s	2,80 m	1,45 s	—	7,37 q ($J_{4,5}$=7) ($J_{4,6}$=2)	6,81 — 7,25 m			4,35 quin (CH) 1,42 d (7) (CH_3)	CCl_4
IV	6,91—7,60	2,84 m	0,98 s	—	6,91 — 7,60 m				—	CCl_4
V	6,81 s	2,87 m	2,27 bs	—	6,85 — 7,55 m				5,15 s	$CDCl_3$
VI	6,43 s	2,68 m	1,05 s	—	6,55 — 7,43 m				4,38 t (1=α=CH_2) 3,10 t (7) (1=β=CH_2)	CCl_4
VII	6,91 s	2,79 m	—	—	7,24 s	—	6,82 d (9)	7,13 d (9)	2,32 s	CD_3OD
VIII	6,95 s	2,76 m	—	—	7,22 q ($J_{4,5}$=7) ($J_{4,6}$=2)	6,84 t (7)	6,82 q ($J_{6,5}$=7) ($J_{6,4}$=2)	—	2,37 s	CD_3OD
X	6,89 s	2,75 m	—	—	7,05 q ($J_{4,5}$=9) ($J_{4,6}$=1,5)	6,54 t (7)	6,86 q ($J_{6,5}$=9) ($J_{6,4}$=1,5)	—	3,78 s	CD_3OD
XI	6,95 s	2,85 m	—	—	7,65 s	—	7,15 —	7,20 m	—	CD_3OD
XII	6,95 s	2,65 m	1,95 bs	—	7,50 q ($J_{4,5}$=7,5) ($J_{4,6}$=1,5)	7,05 t (7,5)	6,70 q ($J_{6,5}$=7,5) ($J_{6,4}$=1,5)	—	—	$CDCl_3$
XVI	6,75—7,30 m	2,93 m	1,80 bs	—		6,75 —	7,30		(1-CH_2) 5,15 s (OCH_3) 3,87 s	$CDCl_3$

*The spectra of I, VII, and X were recorded with a JNM-4H-100 spectrometer, while the spectra of II-VI, XI, XII, and XIV-XVI were recorded with a JNM-4H-60 spectrometer. Solutions (10%) in the solvents indicated in the table were used, and the internal standard was hexamethyldisiloxane. The abbreviations used here and elsewhere are as follows: s is singlet, bs is broad singlet, d is doublet, t is triplet, q is quartet, quin is quintet, and m is multiplet.

Arylhydrazines. Commercial phenyl-, α-methylphenyl-, α-benzylphenyl-, α,α-diphenyl-, p-bromophenyl, o-bromophenyl-, p-tolyl-, and o-tolylhydrazines were used with additional purification by distillation or recrystallization. p-Methoxyphenylhydrazine (mp 64-65°, 52% yield) and o-methoxyphenylhydrazine [bp 105-107° (1 mm), mp 43°, 70% yield] were obtained from the appropriate anisidines by reduction of their diazonium salts with stannous chloride in hydrochloric acid [22]. α-Isopropylphenylhydrazine was obtained by reduction of the corresponding nitroso derivative with $LiAlH_4$ in absolute ether by inverse addition [bp 98-102° (3 mm), n_D^{20} 1.5539 [23], 91% yield]. The following compounds were similarly obtained: 1-amino-1,2,3,4-tetrahydroquinoline [24], with bp 141-143° (10 mm) and mp 54-55°, in 74% yield; 1-amino-1,2,3,4-tetrahydroquinaldine, with bp 115-116° (2 mm) and n_D^{20} 1.5863 [24], in 86% yield; 1-amino-2,3-dihydroindole, with bp 109-110° (11 mm) and n_D^{20} 1.5917 [24], in 82% yield; α-benzyl-α-(p-methoxyphenyl)-hydrazine hydrochloride, with mp 139.5-140° (see [2]), in 87% yield.

General Method for the Preparation of Tryptamines. A solution of 0.05 mole of γ-chlorobutyraldehyde in 20 ml of methanol was added to a refluxing solution of 0.05 mole of arylhydrazine in 50 ml of 90% methanol, and the reaction mixture was refluxed for 8-10 h (the reaction was monitored by chromatography on Silufol). The solvent was removed with a rotary evaporator, and the residue was dissolved in 100 ml of 0.1 N hydrochloric acid, and the neutral materials were extracted twice with ether. The solution was then filtered through 1-2 g of activated charcoal, cooled, and made strongly alkaline. The resulting oil was extracted with benzene (three times with 50-ml portions), and the extract was dried with alkali and vacuum distilled. The yields and physical constants of the synthesized tryptamines are presented in Table 1. The

TABLE 4. Chromatographic Characteristics of the Tryptamines

Compound	R_f		GLC,‡ stationary phase			
			SE-30		polyethylene glycol	
	paper*	silufol†	t°_R, min	α	t°_R, min	α
I	0,72	0,53	1,3	1,0	4,4	1,0
II	0,75	0,53	1,0	0,8	1,8	0,4
III	0,83	0,67	1,3	1,0	1,6	0,4
IV	0,86	0,64	4,4	3,4	9,0	2,0
V	0,82	0,59	4,8	3,7	12,9	2,9
VI	0,66	0,63	1,9	1,5	2,9	0,7
VII	0,74	0,56	1,8	1,4	5,6	1,3
VIII	0,76	0,51	1,4	1,1	5,0	1,1
IX	0,66	0,50	2,6	2,0	10,5	2,4
X	0,69	0,46	2,0	1,5	5,7	1,3
XI	0,82	0,54	—	—	—	—
XII	0,84	0,59	—	—	—	—
XIII	0,77	0,51	—	—	—	—
XIV	0,79	0,54	2,8	2,1	4,6	1,05
XV	0,79	0,58	2,5	1,9	4,3	0,97
XVI	0,85	0,73	5,8	4,5	28	6,4

*"Fast" paper from the Volodarsk Plant with an n-butanol–acetic acid–water (4:1:5) system with development with the Ehrlich reagent.
†Silufol UV-254 with an isopropyl alcohol–25% ammonium hydroxide (90:15) system with development with the Ehrlich reagent.
‡ The gas-chromatographic characteristics were obtained with a G-800 chromatograph (Janaco) with hydrogen as the carrier gas and a 2-m-long column with an inner diameter of 4 mm. The following two phases were used: the weakly polar phase was SE-30 silicone applied (in a 5% amount) on acid-washed Chezasorb AW-HMDC with particles 0.250-0.360 mm in diameter; the polar phase was 10% polyethylene glycol (mol. wt. 15,000) on Porolite (particles 0.250-0.360 mm in diameter) containing 1% KOH. In both cases, the thermostatting temperature of the column was 235°, and the optimum carrier-gas flow rate was selected as 120 ml/min in the first case, and 150 ml/min in the second. The retention times (t^0_R) were reckoned from the signal of air, and the relative retention (α) was calculated with respect to unsubstituted tryptamine.

picrates were obtained in absolute ether with a molar amount of picric acid and were recrystallized from the minimum amount of alcohol (Table 1). The acid tartrates were obtained in the minimum amount of absolute ethanol with a molar amount of tartaric acid and were recrystallized from absolute ethanol–absolute ether (Table 1). The individuality of the tryptamines was confirmed by means of TLC and GLC (Table 4).

1,7-Trimethylene-3-(β-aminoethyl)indole[10-(β-aminoethyl)-9-lilolidene] (XIV). PMR spectrum*: NH_2 (1.74 s), 7-CH_3 (3.97 t, J = 5 Hz), 6-CH_2 (2.08 q, J = 6 Hz), 5-CH_2; 10 α,β-CH_2 (2.82 m), 9-H (6.75 s), aromatic ring protons (1-H 7.34 d, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 1.5 Hz; 2-H 6.85 t, J = 7.5 Hz; 3-H 6.80 d, J = 7.5 Hz).

7-Methyl-10-(β-aminoethyl)-9-lilolidene (XV). PMR spectrum: NH_2 (0.84 s), 7-CH_3 (1.35 d, J = 7 Hz), 6-CH_2 (1.93 t, J = 7 Hz), 5-CH_2, 10-α,β-CH_2 (3.05 m), 7-H (4.02 m), 9-H (6.80 s), aromatic ring protons (1-H 7.13 d, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 1.5 Hz; 2-H 6.83 t, J = 7.5 Hz; 3-H 6.85 d, J = 7.5 Hz).

LITERATURE CITED

1. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, Khim. Geterotsikl. Soedin., 37 (1973).
2. I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, Dokl. Akad. Nauk SSSR, 176, 583 (1967).
3. I. I. Grandberg, N. I. Afonina, and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1038 (1968).
4. I. I. Grandberg, T. I. Zuyanova, N. M. Przheval'skii, and V. I. Minkin, Khim. Geterotsikl. Soedin., 750 (1970).
5. I. I. Grandberg and N. M. Przheval'skii, Izv. Mosk. Sel'skokhoz. Akad. im. Timiryazeva, 192 (1972).
6. T. Majima and T. Hoshino, Ber., 58, 2042 (1925).
7. K. Potts and J. Saxton, J. Chem. Soc., 2641 (1954).

*The PMR spectra were obtained from 10% solutions in CCl_4 with a JNM-4H-60 spectrometer.

8. A. Kalir and S. Szara, J. Med. Chem., 9, 793 (1966).
9. Z. Pelchovicz and E. Bergmann, J. Chem. Soc., 4699 (1960).
10. J. Gaddum, K. Hameed, D. Hatway, and F. Stephens, Quart. J. Exptl. Physiol., 40, 491 (1955); Chem. Abstr., 50, 1759 (1956).
11. K. Eiter and A. Nerzal, Monatsh., 81, 404 (1950).
12. R. Abramovich, J. Chem. Soc., 4593 (1956).
13. E. Späth and E. Lederer, Ber., 63, 2102 (1930).
14. L. De Bellis and M. Stein, Ann. Chim. (Roma), 51, 663 (1961).
15. N. N. Suvorov and V. S. Murashova, Med. Prom., 1, 6 (1961).
16. A. Jackson and A. Smith, J. Chem. Soc., 5510 (1964).
17. K. Eiter and O. Svierak, Monatsh., 83, 1453 (1952).
18. Y. Kanaoka, Y. Ban, T. Oishi, and O. Yonemitsu, Chem. Pharm. Bull. (Tokyo), 8, 294 (1960).
19. L. Cohen, J. Daly, H. King, and B. Witkop, J. Am. Chem. Soc., 82, 2184 (1960).
20. I. I. Grandberg, T. A. Ivanova, and T. I. Zuyanova, Izv. Moskovsk. Sel'skokhoz. Akad. im. Timiryazeva, 212 (1970).
21. R. Loffield, J. Am. Chem. Soc., 73, 1365 (1951).
22. K. Blaikee and W. Perkin, J. Chem. Soc., 313 (1924).
23. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 342 (1971).
24. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 52 (1971).