

INDOLES

II. New Pathway for the Synthesis of 1-Substituted Tryptamines*

I. I. Grandberg, N. I. Afonina, and T. I. Zuyanova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 6, pp. 1038-1040, 1968

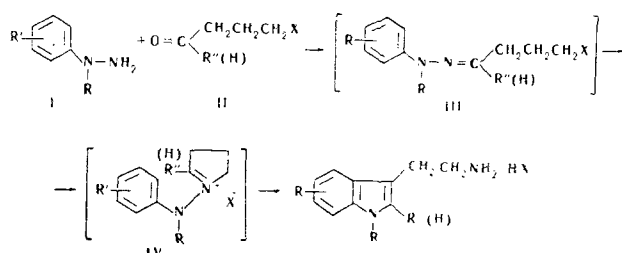
UDC 547.753.754.757.07

A new single stage method is described for the synthesis of 1-substituted tryptamines by boiling alcoholic solutions of various α -substituted phenylhydrazines and γ -halogen carbonyl compounds in neutral medium.

Tryptamine and its derivatives represent some of the most interesting biogenic amines from the practical point of view [1-3]. Syntheses of 1-substituted tryptamines are usually multistage processes and the yields are consequently small [4-6].

During the development of work concerning synthesis of substituted tryptamines [7], we also synthesized the 1-substituted tryptamines by an analogous scheme.

In our opinion, the essence of the reaction is that in boiling alcoholic solutions any α -substituted phenylhydrazine, I, reacts with γ -halogenated propyl ketone or γ -halogenated butyric aldehyde, II, with the formation of a hydrazone, III, and subsequent ring formation into IV, which then undergoes a Fisher dissociation rearrangement with the formation of the 1-substituted tryptamine (V):



where R = alkyl or aryl; R' = any substitute; R'' = H or any other substitute which does not alter the carbonyl nature of the group CO; X = Cl, Br, I, OSO_2 , C_6H_5 .

EXPERIMENTAL

α -Benzyl, α -methyl- and α -ethylphenylhydrazines were synthesized by well-known methods [8, 9].

γ -Chlorobutyric aldehyde. This compound was obtained by reducing the acid chloride of γ -chlorobutyric acid [10] in boiling benzene according to Rosemund with a yield of 56%. According to a previously described method [11], bp 52-53° C (16 mm), n_D^{20} 1.4481.

N-Benzyl-*p*-anisole. A mixture of 106 g (1 mole) of freshly-distilled benzaldehyde and 123 g (1 mole) of pure *p*-anisole in 300 ml toluene was heated to boiling and the toluene was simultaneously removed by distillation. After distillation of 250 ml of the distillate under the vacuum of a water jet pump the water was removed by distillation. The residue was dissolved in 800 ml isopropyl alcohol and 30 ml water and 45 g (0.86 mole) of KBH_4 were added, and the mixture was boiled under reflux with stirring for 10 hr. A 300 ml

volume of water was then added and the mixture was boiled for a further 2-hr period while the isopropyl alcohol (approximately 400 ml) was simultaneously removed by distillation. The residue was cooled to 50° C and the lower alkaline layer was removed by siphoning. The upper layer was allowed to crystallize for 5 hr and it was diluted with 500 ml water and cooled to 0° C over a 2-hr period. The precipitate was recrystallized from 85% isopropyl alcohol. A 207 g quantity (97.2%) of the substance was obtained with a mp of 50-51° C [12].

N-Nitroso-*N*-benzyl-*p*-anisole. A solution of 36.6 g (0.52 mole) of sodium nitrite in 100 ml water was slowly added dropwise to a solution of 107 g (0.5 mole) of *N*-benzyl-*p*-anisole in 250 ml acetic acid and 200 ml water at a temperature of 10° C during efficient mixing. The mixture was stirred for a further 15-min period at 10° C. The reaction mass was diluted with 400 ml water. The separated crystals were filtered by suction and dissolved in benzene. The benzene solution was carefully washed, dried under anhydrous calcium chloride, and evaporated under vacuum until crystallization commenced. The yield of the nitroso derivative was 107 g (88%), mp 73-74° C (benzene-petroleum ether).

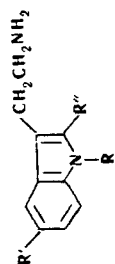
Hydrochloride of 1-benzyl-(1-*p*-methoxyphenyl)hydrazine. Over a 2-hr period an equimolar quantity (in relation to active hydrogen) of an ethereal solution of $LiAlH_4$ was added to a suspension of 48.4 g *N*-nitroso-*N*-benzyl-*p*-anisole in 500 ml absolute ether (distilled over lithium aluminium hydride) at a temperature from 0-5° C. The reaction mass was mixed for 2 hr at 20° C, carefully decomposed with 12 ml water, and heated for 1 hr with stirring, and then filtered by suction. The precipitate was carefully extracted with 800 ml ether with heating (thrice with 200 ml). The ethereal extracts were evaporated to a volume of 150 ml and after cooling to 0° C they were saturated with dry hydrogen chloride. The hydrochloride was filtered by suction, washed with ether, and dried under vacuum. Yield 46.4 g (87.5%), mp 139.5-140° C [5].

General Method for Preparation of 1-Substituted Tryptamines. A solution of 0.1 mole of the halogen carbonyl compound in 20 ml tertiary butyl alcohol was poured into a boiling solution of 0.1 mole of α -substituted phenylhydrazine in 260 ml methanol and 20 ml water. The reaction mass was heated to boiling for 20 hr continuously in a flask fitted with a reflux condenser and a stirrer. All solvent was then removed by distillation under the vacuum of a water-jet pump. The residue was dissolved in 150 ml hot 0.5% HCl and filtered through 1 g of activated carbon. The filtrate was evaporated under vacuum at 50° C to a volume of approximately 40 ml and made alkaline with 20 ml of a 40% solution of sodium hydroxide. The precipitated tryptamine was extracted with benzene, dried over alkali, and distilled under vacuum. The yields and constants of the tryptamines are presented in the table.

REFERENCES

1. G. Lewis, 5-Hydroxytryptamine, London, 1958.
2. G. A. Chernov and A. A. Lipats, Pat. fiziol. i eksper. ter., 4, 57, 1958.
3. D. Bulli, Studies on Antimetabolites [Russian translation], IL, Moscow, 1954.
4. A. N. Grinev, V. N. Ermakova, A. P. Terent'ev, DAN, 121, 862, 1958.
5. E. Show, J. Am. Chem. Soc., 77, 4319, 1955.

*For part I, see [7].



R	R'	R''	Bp, °C (pressure, mm)	Mp (sublimation), °C	Mp of picrate, °C	Empirical formula	Found, %		Calculated, %		pK _a in 50% ethanol	R _f *	Yield, %
							C	H	C	H			
CH ₃	H	CH ₃	162—164 (2)	—	185—186	C ₁₂ H ₁₆ N ₂	76.40	8.50	76.55	8.56	9.53	0.79	63.3**
C ₂ H ₅	H	CH ₃	186—187 (8)	n _D ²⁰ 1.5886 d ₄ ²⁰ 0.9226	131—132	C ₁₃ H ₁₈ N ₂	77.22	9.07	77.18	8.91	9.50	0.75	81
C ₆ H ₅ CH ₂	H	H	157—161 (0.1)	93—94 ⁶	145—147	C ₁₇ H ₁₈ N ₂					8.80	0.93	75.2
C ₆ H ₅ CH ₂	OCH ₃	H	—	97—99 ⁵	161—162	C ₁₈ H ₂₀ N ₂ O					8.97	0.91	70
C ₆ H ₅ CH ₂	H	CH ₃	170—172 (0.5)	54—55	188—189****	C ₁₈ H ₂₀ N ₂	58.22****	4.73	58.41	4.70	9.12	0.81	79
C ₆ H ₅ CH ₂	OCH ₃	CH ₃	—	57—58**** ⁵	182—184	C ₁₉ H ₂₂ N ₂ O					9.20	0.81	69

*Rapid paper of the Volodarskii factory; system of pyridine—water—butanol (1 : 1 : 1).

**1,2-Dimethyl tryptamine was obtained from the toluene sulfonyl derivative of acetopropyl alcohol [7].

***Hydrochloride, mp 230—231 °C.

****Found, %: C 58.22; H 4.73. Calculated for C₁₈H₂₀N₂ · C₆H₃N₃O₇ %: C 58.41; H 4.70.

6. N. N. Suvorov and V. S. Murashova, Med. prom. SSSR, 1, 6, 1961.
7. I. I. Grandberg and T. I. Zuyanova, KhGS [Chemistry of Heterocyclic Compounds], 4, 875, 1968.
8. N. N. Suvorov, Doctoral dissertation [in Russian], Moscow, p. 38, 1962.
9. L. Audrieth, and J. Weisiger, J. Org. Chem., 6, 417, 1941.
10. W. Reppe, Ann., 190, 596, 1955.
11. R. Loftfield, J. Am. Chem. Soc., 73, 1365, 1951.
12. E. Fröhlich, and E. Wedekind, Ber., 40, 1010, 1907.

19 August 1966

Timiryazev Agricultural
Academy, Moscow