TABLE 3. UV Spectra of 2- and 3-Formyl-4,5-benzindoles

2-Formyl-4,5-benzindole		3-Formyl-4,5 benzindole	
λ, nm	ε	λ, nm	ε
210	28 000	190	41 000
		216	47 000
236	44 000	249	17 000
231 sh	37 000		
260	10 000	273	30 000
286	16 000		
323	18 000	310	7 000
343	18 200	320	6 000
362	16 800		

2- and 3-Formyl-4,5-benzindoles (II, I). A mixture of these compounds was obtained in 95-98% yield via the Vilsmeier reaction from 4,5-benzindole [2]. The mixture was separated with a column packed with Chemapol silica gel (40/100 μm) by elution with chloroform. The yield of isomer I, with R_f 0.16 [benzene–acetone (4:1)] and mp 189-190°C (mp 185-176°C [2]), was 78-80%. The yield of isomer II, with R_f 0.44 [benzene–acetone (4:1)] and mp 252-253°C, was 6-8%. Found: C 79.6; H 4.8; N 7.9%. $C_{13}H_9NO$. Calculated: C 80.0; H 4.6; N 7.2%.

LITERATURE CITED

1. G. S. Grekova, V. P. Gorbunova, L. B. Shagalov, T. A. Babushkina, A. M. Vasil'ev, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 10, 1380 (1980).
2. L. B. Shagalov, T. A. Tkachenko, V. N. Eraksina, and N. N. Suvorov, Tr. Mosk. Khim.-tekhnol. Inst. im. Mendeleeva, 74, 61 (1973).

BENZINDOLES.

24.* SYNTHESIS AND SOME PROPERTIES OF 5,6-BENZOTRYPTAMINE HYDROCHLORIDE

G. M. Ostapchuk, E. I. Voronina,
T. M. Ivanova, T. A. Babushkina,
L. B. Shagalov, and N. N. Suvorov

UDC 547.759.3.07:543.422

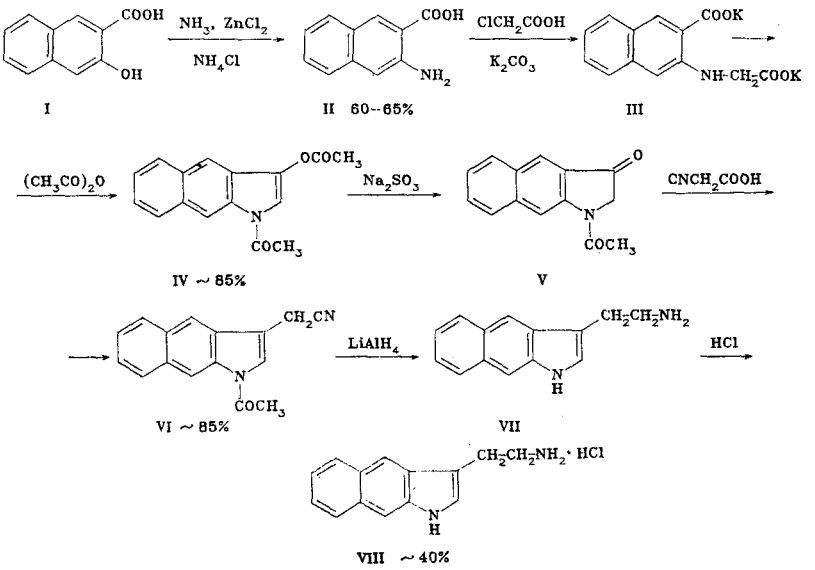
An improved method for the synthesis of 5,6-benzotryptamine hydrochloride from 3-hydroxy-2-naphthoic acid was developed; this method makes it possible to obtain the final product and a number of intermediates in high yields. The PMR spectra and the peculiarities of conjugation in the linear benzindole molecule are discussed.

Indolylalkylamines have many-sided biological activity [2-4]. Least study in this case of compounds has been devoted to the physiological action of benzotryptamines [2]; in particular, the literature does not contain any information regarding the properties and activity of 5,6-benzindole derivatives, which is explained by the difficulty involved in the synthesis of these compounds [5]. At the same time, the linear compact 5,6-benzotryptamine molecule, in which the degree of delocalization of the π-electron cloud should be higher than in angular analogs, may prove to be extremely promising from the point of view of its biological activity.

We have developed an improved method for the synthesis of 5,6-benzotryptamine via the following scheme [5]:

*See [1] for communication 23.

Institute of Biophysics, Ministry of Public Health of the USSR, Moscow 123182. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 346-348, March, 1984. Original article submitted June 29, 1983.



In the step involving the preparation of IV the use of purification by means of activated charcoal and column chromatography makes it possible to obtain N,O-diacetyl-5,6-benzindole in up to 85% yield. In the preparation of VI replacement of xylene by benzene led to less resinification of the reaction mass and increases the yield of the nitrile to up to 85%. 5,6-Benzotryptamine hydrochlorides was obtained at −20°C in dry methylene chloride at controllable pH 3-4. All of this makes it possible to obtain 5,6-benzotryptamine in up to 40% yield and to produce it in amounts sufficient for biological testing.

The signal of the NH proton (11) in the PMR spectrum of 5,6-benzotryptamine differs little from the corresponding signals in the spectra of 6,7- and 4,5-benzindoles. The signals of the aromatic protons constitute an AAXX system with centers at 8.12 and 7.22 ppm. The signals of the 4-H and 7-H protons are in the form of singlets at 8.12 and 7.85 ppm; the doublet at 7.52 ppm with spin–spin coupling constant (SSCC) J = 2.4 Hz was assigned to the 2-H proton. The broad signals with centers at 2.80 and 8.15 ppm, respectively, were assigned to the protons of the ethylene group and the NH_3^+ group.

The electronic absorption spectrum of the linear benzotryptamine provides evidence that more favorable conditions for conjugation are realized in this molecule than in the case of the angular analogs: The near absorption band of 5,6-benzotryptamine is shifted 30-40 nm to the long-wave side as compared with the 4,5- and 6,7-benzo isomers (Table 1).

The following fact also constitutes evidence for considerably greater conjugation in the VIII molecule: the 5,6-benzo isomer, like the 6,7- and 4,5-benzo isomers, has intense fluorescence that is overlapped with the absorption band in the region of the 0–0 transition [6]. This fluorescence substantially hinders obtaining the Raman spectra of benzindoles, and the Raman spectra cannot be observed for the 4,5- and 6,7-benzo isomers even in the case of excitation in the long-wave section of the spectrum (λ = 514 nm). However, a Raman band at 1570 cm^{-1} is observed on the fluorescence background for 5,6-benzotryptamine in the case of excitation of the Raman spectrum at λ = 514 nm, possibly in connection with the great closeness of the absorption bands and their high intensities. This line undoubtedly belongs to vibrations of the aromatic skeleton and can subsequently be used for analytical purposes and to form a judgment regarding the state of the system of conjugated bonds in 5,6-benzotryptamine derivatives.

TABLE 1. Parameters of the UV Spectra of Benzotryptamine Hydrochlorides

Isomer	λ	ε	λ	ε	λ	ε	λ	ε	λ	ε	λ	ε	λ	ε
4,5	209	23 000	227	36 000	250	31 000	305	7900	310 sh	7600	318	7400	332	3500
6,7	212	35 000			261	60 000	280sh	9000			320	2000	336	500
5,6			221	19 000	247	80 000			332	4500	349	5500	363	5200

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were obtained with a Varian H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of KBr pellets and solutions in $CHCl_3$ were recorded with a Perkin–Elmer 180 spectrometer; the accuracy in the measurement of the frequencies was ±1 cm^{-1}. The Raman spectra of KBr pellets were obtained with a Spex Ramalog 6 spectrometer with excitation by the line of an argon laser at 514 nm. The UV spectra of solutions in C_2H_5OH were recorded with a Shimadzu MPL 50 spectrophotometer.

N-Acetyl-5,6-benzindol-3-ylacetonitrile (VI). An 0.5-g (6 mmole) sample of freshly distilled cyanoacetic acid and a solution of 0.67 g (3 mmole) of indoxyl V in 15 ml of benzene were added successively to a previously heated solution of 0.1 g (1.3 mmole) of ammonium acetate in 3.0 ml [3.15 g (3.5 mmole)] of phenol in a reaction flask equipped with a Dean–Stark trap, and the reaction mixture was refluxed for 8 h, during which the course of the reaction was followed by means of azeotropic removal of the water by distillation and from disappearance of starting V on a thin layer chromatogram [elution with benzene–acetone (4:1)]. After azeotropic distillation was complete, the benzene and phenol were removed from the mixture by steam distillation. The solid brown residue was dissolved in chloroform and purified by chromatography with a column packed with silica gel (40/100 μm, Czechoslovakian SSR) at a ratio of 1:200. Elution with chloroform gave nitrile VI, with mp 170-171.5°C (mp 171°C [5]), in 75-85% yield. IR spectrum: 1687 ($N-COCH_3$) and 2248 cm^{-1} ($C\equiv N$).

5,6-Benzotryptamine Hydrochloride (VIII). A solution of 1 g (0.004 mole) of nitrile VI in 42 ml of absolute THF was added dropwise to a refluxing solution of 2 g (0.053 mole) of $LiAlH_4$ in 33.5 ml of absolute THF, after which the mixture was refluxed for 20 min and stirred at room temperature for 1.5-2 h until the starting nitrile vanished according to TLC [elution with isopropyl alcohol–ammonia–chloroform (4:1:8)]. The mixture was then cooled to −5°C, and the excess $LiAlH_4$ was decomposed with 2 ml of water, 2 ml of a 15% solution of NaOH, and 1 ml of water. After 30 min, the precipitate was removed by filtration and wahsed with absolute THF. The filtrate was evaporated to dryness in vacuo with the addition of absolute ether to the residue. The dry residue was dissolved in 15 ml of dry methylene chloride, and the solution was filtered to remove mechanical impurities. The resulting solution of 5,6-benzotryptamine was cooled to −20°C, and the 5,6-benzotryptamine was precipitated in the form of the hydrochloride by the dropwise addition of a 5% solution of HCl in absolute ethanol to pH 4. The precipitate was removed by filtration and washed with dry methylene chloride to give salt VIII, with mp 275-278°C (dec.), in 30-40% yield. IR spectrum: 3430 (NH); 2500-3200 br (NH_3^+); 1563; 1600 (aromatic C=C); 858 cm^{-1} (δNH). Found: C 68.2; H 6.2; Cl 14.3; N 11.2%. $C_{14}H_{15}ClN_2$. Calculated: C 68.2; H 6.1; Cl 14.4; N 11.4%.

IR spectrum of V: 1672 ($NCOCH_3$) and 1723 cm^{-1} (CO). IR spectrum of IV: 1695 ($NCOCH_3$) and 1761 cm^{-1} ($OCOCH_3$).

LITERATURE CITED

1. E. I. Voronina, T. M. Ostapchuk, T. M. Ivanova, T. A. Babushkina, L. B. Shagalov, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 3, 343 (1984).
2. P. G. Zherebchenko, Antiradiation Properties of Indolylalkylamines [in Russian], Atomiz-Atomizdat, Moscow (1971).
3. N. N. Suvorov and V. S. Shashkov, The Chemistry and Pharmacology of Agents for the Prophylaxis of Radiation Damage [in Russian], Moscow (1975). p. 108.
4. N. N. Suvarov, Zh. Vses. Khim. Ova., 9, 396 (1964).
5. S. I. Ambekar and S. Siddappa, J. Chem. Soc. (C), No. 4, 477 (1966).
6. L. G. Tret'yakova, N. N. Suvorov, T. K. Efimova, A. M. Vasil'ev, L. B. Shagalov, and T. A. Babushkina, Khim. Geterotsikl. Soedin., No. 8, 1057 (1978).