CROATICA CHEMICA ACTA CCACAA 46 (3) 217—224 (1974)

YU ISSN 0011—1643
CCA-838 547.75
Original Scientific Paper

Beta-hydroxytryptamines. I. Chemical Synthesis of 3-(2-Amino--1-hydroxyethyl)indole and 5-Hydroxy-3-(2-amino-1-Hydroxy--ethyl)indole

V. Plavšić S. Kveder, and S. Iskrić

Institute »Ruđer Bošković«, 41000 Zagreb, Croatia, Yugoslavia

Received May 29, 1974

From indole and 5-benzyloxyindole, respectively, the corresponding chloromethyl 3-indolyl ketones were prepared applying Grignard reaction with chloroacetyl chloride or Vilsmeier reaction with *N,N*-diethylchloroacetamide. By i. r. and n. m. r. spectroscopy it was proved that identical compounds were obtained in both reactions.

After the substitution of the halide with dibenzylamino group and the reduction of the carbonyl group to hydroxyl with lithium aluminum hydride, benzyl groups were removed by catalytic hydrogenation.

3-(2-Amino-1-hydroxyethyl)indole (beta-hydroxytryptamine) and 5-hydroxy-3-(2-amino-1-hydroxyethyl)indole (beta-hydroxyserotonin) were isolated in the form of crystalline creatinine sulphates. Solubility and satisfying stability in aqueous solutions make these salts suitable for biochemical and pharmacological investigations.

INTRODUCTION

In a preliminary communication[1] we announced the synthesis of beta-hydroxylated derivatives of tryptamines which might be of interest in the investigation of the role and interrelationship of arylalkyl biogenic amines in mammals.

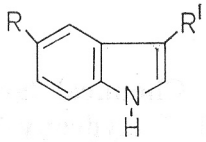
As to the synthesis of such compounds only beta-hydroxytryptamine has been synthesized[2–4], but always isolated as the picrate salt unsuitable for the investigations in biological systems. All the other compounds synthesized so far from this series were always substituted on at least one of the nitrogen atoms of the molecule[5–9].

In the present paper the details of the synthesis of beta-hydroxytryptamine and beta-hydroxyserotonin in the form of stable, water soluble creatinine sulphate salts will be given. The results of subsequent biochemical and pharmacological investigations will be presented elsewhere.

RESULTS AND DISCUSSION

3-(2-Amino-1-hydroxyethyl)indole (beta-hydroxytryptamine) and 5-hydroxy-3-(2-amino-1-hydroxyethyl)indole (beta-hydroxyserotonin) were prepared according to the general scheme presented previously[1]. The position of the side

chain in chloromethyl 3-indolyl ketone (Ia, Figure 1) was ascertained by i.r. and n.m.r. spectroscopy in order to solve the discrepancy in the literature regarding the position of substitution in the indole ring during the Grignard reaction.



Ia - IVa	R = H	Ia,b	R' = $COCH_2Cl$
Ib - IIIb	R = $PhCH_2O$	IIa,b	R' = $COCH_2N(CH_2Ph)_2$
IVb	R = OH	IIIa,b	R' = $CH(OH)CH_2N(CH_2Ph)_2$
		IVa,b	R' = $CH(OH)CH_2NH_2$

Fig. 1.

Namely, chloromethyl 3-indolyl ketone (Ia) prepared by Majima and Kotake[10] had a m. p. of 212—214 °C. Mingoia[11] obtained two products: the first, with m. p. 214 °C was identified as chloromethyl 3-indolyl ketone, while he believed the second (m. p. 230 °C) to be chloromethyl 2-indolyl ketone. Ames *et al.*[3] obtained by the same reaction two products: one with m. p. 229—230 °C, identified as chloromethyl 3-indolyl ketone and the other with m. p. 175—176 °C, identified as 1,3-di(chloroacetyl)indole. They suggested that the product of Majima and Kotake[10] and Mingoia[11] with m. p. 214 °C had been a mixture of these two compounds.

Repeating the synthesis of Majima and Kotake we obtained the product with m. p. 211—212 °C which, as it was shown by i.r. and n.m.r. spectra, was substituted only in the position 3 of the indole ring. A signal characteristic for the NH group appeared both in the i.r. and in the n.m.r. spectrum, indicating that there is no substitution in position 1 of the indole ring. The signal characteristic for H-2 proton of the indole ring appearing in n.m.r. spectrum indicated that this position is unsubstituted also[1].

The synthesis of chloromethyl 3-indolyl ketone by the Vilsmeier reaction, having a m. p. of 233—234 °C was also described in the literature[12,13]. Since the yield of Ia obtained by the Grignard reaction was rather poor, we also prepared it by the Vilsmeier reaction according to Preobrazhenskaya *et al.*[13]. Indeed, in this case the yield increased significantly and the product had a m. p. of 230—231 °C.

The products we obtained by both reactions, although with different melting points, had the same analyses and indentical i.r. and n.m.r. spectra in all details, thus indicating that they are identical compounds which in the next reaction step gave the same product.

By both reactions we also prepared the hitherto undescribed chloromethyl 3-(5-benzyloxy)indolyl ketone (Ib). The product of the Grignard reaction had a m. p. of 193—194 °C and that of the Vilsmeier reaction had a m. p. of 225—

226 °C. The position of the side chain and the identity of the products were again confirmed by i.r. and n.m.r. spectroscopy.

The reaction of Ia with ammonia gave aminomethyl 3-indolyl ketone[11]. Since our attempts to reduce this compound failed even with lithium aluminum hydride, an indirect route leading to the desired beta-hydroxytryptamine had to be applied.

The reduction of 3-acylindoles and related compounds represents a complex problem[14]. If the imino group of the pyrrole moiety is substituted, the reduction of the carbonyl group can be achieved without difficulties only to the stage of the alcohol[15,16]. However, with the derivatives that are unsubstituted on the pyrrole nitrogen, the degree of the reduction will depend on the reducing agent[3,17], reaction conditions[18], as well as on the steric situation in the molecule, *i. e.* on the substituent in the neighbourhood of the carbonyl[9] or the possibility for hydrogen bonding[15].

We substituted the halide in chloromethyl 3-indolyl ketones (Ia and Ib) with the dibenzylamino groups and obtained dibenzylaminomethyl 3-indolyl ketones (IIa and IIb). This enabled us to reduce the carbonyls with lithium aluminum hydride to the hydroxyl groups (IIIa and IIIb). We believe that the steric hindrance caused by the bulky dibenzylamino groups prevented the reduction to proceed beyond the stage of the alcohol.

Debenzylation of IIIa and IIIb was performed by catalytic hydrogenation which proceeded faster with palladium on charcoal than with palladium on barium sulphate. However, due to significant adsorption of indole compounds on the charcoal, the addition of the calculated stoichiometrical amount of creatinine hydrogensulphate led to an excess of sulphuric acid and to a marked decompositon of the final product. Therefore aqueous solutions obtained after hydrogenation were titrated with a solution of creatinine hydrogensulphate to a pH of 5.5—6.0. In this way crystalline beta-hydroxytryptamine (IVa) and beta-hydroxyserotonin (IVb) deposited in the form of white hygroscopic crystals.

However, the products still contained traces of impurities which could be removed only after repeated precipitation with acetone from water. Since indoles with the hydroxyl group in position 1 of the side chain are prone to dimerization to the corresponding diindolylmethanes[15,19,20], we believe that IVa and IVb also underwent partial dimerization during isolation and preparation of creatinine sulphates. This is further supported by the fact that on acidification of an aqueous solution the spots belonging to IVa and IVb, respectively, on thin-layer chromatography disappeared since they formed a new spot ascribed to the dimer.

When stored under anhydrous conditions at +4 °C the pure crystalline beta-hydroxylated tryptamines did not decompose even after a year. In aqueous solutions they are stable within several days permitting biochemical and pharmacological investigations.

The fluorescence spectra of these compounds differ to some extent from those of the beta-nonhydroxylated tryptamines (Figure 2), so that it might be possible to detect them in biological material by careful selection of the wavelengths of activation and fluorescence.

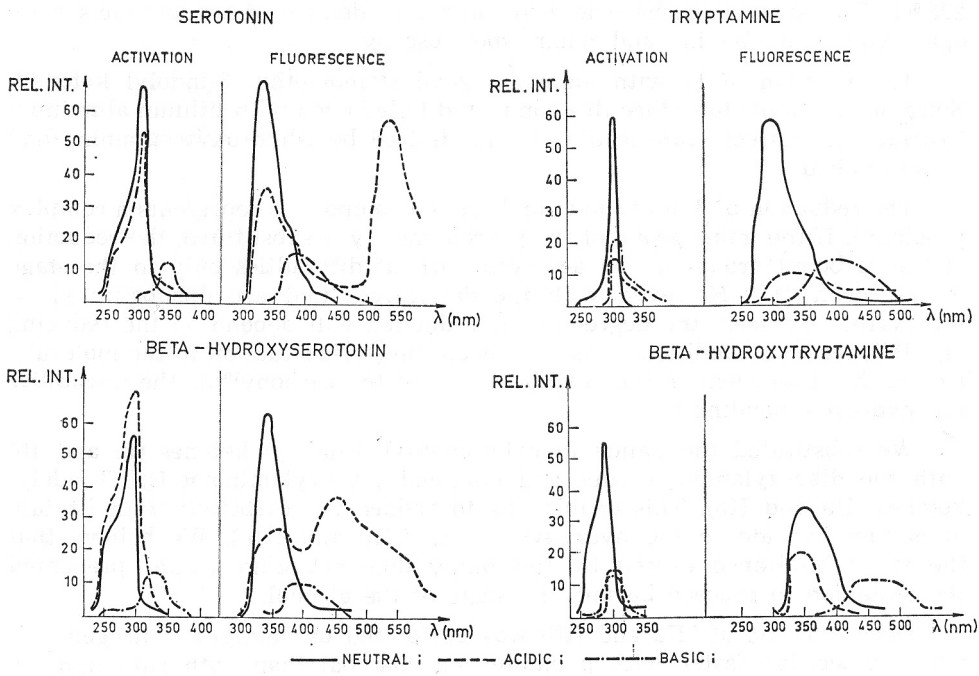


Fig. 2. Fluorescence spectra of serotonin, tryptamine, beta-hydroxyserotonin and beta-hydroxytryptamine

EXPERIMENTAL

Melting points are determined with a Culatti apparatus and are uncorrected. Thin-layer chromatography was carried out on microscope slides with silica gel G (E. Merck) using solvent systems: chloroform : ether (4 : 1) (A) and water : methanol (4 : 1) (B).

Solutions were dried with anhydrous sodium sulphate. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer 124 UV spectrofotometer and refer to aqueous solutions. The n.m.r. spectra were taken on a Varian A60-A instrument with tetramethylsilane as internal standard. Fluorescence spectra were obtained on a Farrand MK-1 spectrophotofluorometer.

Chloromethyl 3-indolyl ketone (Ia)

(A) By the Grignard reaction. — Ia was prepared according to Majima and Kotake[10], m. p. 211—212 °C (m. p. lit.[10] 212—214 °C), yield: 30%. I. r. spectrum (KBr): 3300 (NH), 1650 (CO), 1600, 1525, 1500 (C=C, indole ring), 735 and 750 (CH, o-subst. benzene) cm^{-1}. N.m.r. spectrum (methyl sulphoxide-d_6): τ-2(broad singlet, exchangeable with D_2O, 1H, NH), 1.5 (doublet, $J_{1,2} = 3$ Hz, collapses to a singlet on deuteration, 1H, H-2 of indole), 1.8 and 1.9 (doublet of doublets, $J_{ortho} = 6$ Hz, $J_{meta} = 3$ Hz, 1H, H-4 of indole), 2.3—2.9 (multiplet, 3H, aromatic) and 5.2 (singlet, 2H, CH_2).

(B) By the Vilsmeier reaction. — Ia was prepared according to Preobrazhenskaya *et al.*[13], m. p. 230—231 °C (m. p. lit. 232—233 °C), yield: 70%. The product had identical i. r. and n.m.r. spectra as the one obtained by the Grignard reaction.

Chloromethyl 3-(5-benzyloxy)indolyl ketone (Ib)

(A) By the Grignard reaction. — 5-Benzyloxyindole (1.10 g, 5 mmol) dissolved in dry ether (10 ml) and dry benzene (15 ml) was added dropwise at 0 °C to the

Grignard reagent prepared from magnesium turnings (240 mg, 0.01 mol) and ethyl iodide (1.60 g, 10 mmol), in dry ether (40 ml). The mixture was refluxed for 75 min and chloroacetyl chloride (1.12 g, 10 mmol) in dry ether (4 ml) was added under vigorous stirring and cooling in an ice bath. This mixture was stirred for 30 min in an ice bath and then for 2.5 hrs. at room temperature. The complex was decomposed with 30% acetic acid (6.5 ml), stirred for 15 min and the separated brown crystals (89 mg) were filtered off. The organic layer of the mother-liquor was washed with water, a saturated sodium hydrogencarbonate solution, and again with water. After drying and cooling a second crop of crystals (48 mg) separated; total yield: 35.4%. After recrystallisation from ethanol the compound had a m. p. of 193—194 °C; R_f 0.45 (solvent A, developed with 2,4-dinitrophenylhydrazine). I. r. spectrum (KBr): 3250 (NH), 1650 (CO), 1530, 1490 (C=C, indole ring), 840, 805 (1,2,4--subst.benzene), 720 and 698 (monosubst. benzene) cm^{-1}. N.m.r. spectrum (methyl sulphoxide-d_6): τ — 2.1 (broad singlet, exchangeable with D_2O, 1H, NH), 1.6 (doublet, $J_{1,2}$ = 2.5 Hz, collapses to a singlet on deuteration, 1H, H-2 of indole), 2.2 (doublet, J_{meta} = 2.5 Hz, 1H, H-4 of indole), 2.4—2.7 (multiplet, 6H, aromatic), 3.0 and 3.1 (doublet of doublets, J_{ortho} = 9 Hz, J_{meta} = 2.5 Hz, 1H, H-6 of indole), 4.9 (singlet, 2H, Ph**C**$\mathbf{H_2}$O) and 5.2 (singlet, 2H, CO**C**$\mathbf{H_2}$Cl).

Anal. $C_{17}H_{14}ClNO$ (299.76) calc'd.: C 68.11; H 4.71; N 4.67%
found: C 68.36; H 4.86; N 4.45%

(B) By the Vilsmeier reaction. — Freshly distilled phosphoryl trichloride (1.08 ml, 19 mmol and *N,N*-diethylchloroacetamide (3.6 g, 23 mmol) were stirred at room temperature for 20 min. whereupon a suspension of 5-benzyloxyindole (1.86 g, 0.84 mmol) in *N,N*-diethylchloroacetamide (1.8 ml) was added and the mixture was stirred at 50—55 °C for 1 hr. Cold water was added, the mixture was left overnight at 0 °C and after decantation a few drops of warm methanol were added to the gummy residue. The formed crystals (1.13 g, 45.4%) were recrystallised from methanol-acetone (3 : 1) to give a product with m. p. 225—226 °C which had identical i.r. and n.m.r. spectra as that obtained by the Grignard reaction.

Anal. $C_{17}H_{14}ClNO$ (299.76) calc'd.: C 68.11; H 4.71; N 4.67%
found: C 68.35; H 4.87; N 4.72%

N,N-*Dibenzylaminomethyl 3-indolyl ketone (IIa)*

The solution of Ia (1.62 g, 87 mmol) and dibenzylamine (4.27 g, 21 mmol) in dry ethanol (50 ml) was refluxed for 14 hrs. After evaporation *in vacuo* the residue was extracted with ether (5 × 15 ml) and the ethereal extracts were evaporated to dryness. Dibenzylamine was removed with n-hexane leaving white crystals (2.41 g, 80.3%). They were recrystallized from ethanol, to give a product with m. p. 158—161 °C, R_f 0.66, (solvent A, developed with 1% potassium permanganate). I.r. spectrum (KBr): 3250 (NH), 1640 (CO), 1600, 1540 (C=C, indole ring), 775, 698 (CH, monosubst. benzene), 755 and 750 (o-disubst.benzene) cm^{-1}. N.m.r. spectrum (chloroform-*d*): τ 0.8 (broad singlet, exchangeable with D_2O, 1H, NH), 1.5 (multiplet, 1H, H-4 of indole), 2.1 (doublet, $J_{1,2}$ = 3 Hz, collapses to a singlet on deuteration, 1H, H-2 of indole), 2.5—2.8 (multiplet, 13H, aromatic), 6.2 (singlet, 4H, (Ph**C**$\mathbf{H_2}$)$_2$) and 6.3 (singlet, 2H, CO**C**$\mathbf{H_2}$N).

Anal. $C_{24}H_{22}N_2O$ (354.43) calc'd.: C 81.33; H 6.25; N 7.90%
found: C 81.59; H 5.94; N 8.24%

N,N-*Dibenzylaminomethyl 3-(5-benzyloxy)indolyl ketone (IIb)*

IIb was prepared from Ib (880 mg, 2.97 mmol) and dibenzylamine (1.45 g, 7.4 mmol) in the same way as IIa. The crystalline product (1.16 g, 85.2%) was recrystallised from petroleum ether (b.p. 100—120 °C) to give a product with m. p. 134—136 °C, R_f 0.67 (solvent A, developed with 1% potassium permanganate). I.r. spectrum (KBr): 3180 (NH), 1610 (CO), 1505, 1480 (C=C, indole ring), 840, 800 (CH, 1,2,4-subst. benzene), 750, 735, 700 and 695 (CH, monosubst. benzene) cm^{-1}. N.m.r. spectrum (chloroform-*d*): τ 1.2 (broad singlet, exchangeable with D_2O, 1H, NH), 2.0

(doublet, $J_{meta} = 2$ Hz, 1H, H-4 of indole), 2.2 (doublet, $J_{1,2} = 3$ Hz, collapses to a singlet on deuteration, 1H, H-2 of indole), 2.5—2.9 (multiplet, 16H, aromatic), 3.0 and 3.1 (doublet of doublets, $J_{ortho} = 9$ Hz, $J_{meta} = 2$ Hz, 1H, H-6 of indole), 4.9 (singlet, 2H, PhC**H**$_2$), 6.2 (singlet, 4H, (PhC**H**$_2$)$_2$) and 6.3 (singlet, 2H, COC**H**$_2$N).

Anal. $C_{31}H_{28}N_2O_2$ (460.55) calc'd.: C 80.84; H 6.13; N 6.08%
found: C 80.90; H 6.30; N 6.05%

3-(2-N,N-Dibenzylamino-1-hydroxyethyl)indole (IIIa)

To a stirred suspension of lithium aluminium hydride (80 mg) in dry ether (20 ml) cooled in an ice-water bath a solution of IIa (100 mg, 0.28 mmol) in dry ether (50 ml) was added, and stirring was continued for 1.5 hrs. with cooling. The complex and excess of lithium aluminium hydride were decomposed by addition of water (0.5 ml), the ethereal layer was separated, dried and evaporated. The product (95 mg, 95.9%) was recrystallized from ether/*n*-hexane and m. p. 114—116 °C was obtained, R_f 0.60 (solvent A, developed with Ehrlich's reagent). I.r. sprectrum (KBr): 3550 (OH), 3400 (NH), 1560, 1500 (C=C, indole ring), 775, 700 (CH, monosubst. benzene), 740 and 755 (CH, o-disubst. benzene) cm^{-1}. N.m.r. spectrum (chloroform-*d*): τ 2.0 (broad singlet, exchangeable with D_2O, 1H, NH), 2.5—3.0 (multiplet, 14H, aromatic), 3.1 (doublet, $J_{1,2} = 2.5$ Hz, 1H, H-2 of indole), 4.9 and 5.1 (doublet of doublets, $J = 10$ Hz, $J = 4$ Hz, 1H, CH), 6.1 and 6.6 (two doublets, $J = 13.5$ Hz each, 4H, (PhC**H**$_2$)$_2$), 7.1 and 7.2 (two doublets, $J = 10$ Hz, $J = 4$ Hz, 2H, C**H**$_2$N).

Anal. $C_{24}H_{24}N_2O$ (356.46) calc'd.: C 80.86; H 6.78; N 7.86%
found: C 81.12; H 6.90; N 7.92%

5-Benzyloxy-3-(2-N,N-dibenzylamino-1-hydroxyethyl)indole (IIIb)

IIb (100 mg, 0.21 mmol) was reduced with lithium aluminium hydride (80 mg) in the same way as IIa. The crystalline IIIb (83 mg, 85.5%) was recrystallised from ether/*n*-hexane and m. p. 98—100 °C was obtained, R_f 0.66 (solvent A, developed with Ehrlich's reagent). I.r. spectrum (KBr): 3550 (OH), 3400 (NH), 1600, 1560 (C=C, indole ring), 1060 (C—O, sec. alcohol), 800 (CH, 1,2,4-subst. benzene), 755, 740 and 700 (CH, monosubst. benzene) cm^{-1}. N.m.r. spectrum (chloroform-*d*): τ 2.0 (broad singlet, exchangeable with D_2O, 1H, NH), 2.5—3.3 (multiplet, 19H, aromatic), 4.9 and 5.0 (doublet of doublets, $J = 10$ Hz, $J = 4$ Hz, 1H, CH), 5.1 (singlet, 2H, PhC**H**$_2$O), 6.0 and 6.5 (two doublets, $J = 13.5$ Hz each, 4H, (PhC**H**$_2$)$_2$), 7.0 and 7.2 (two doublets, $J = 10$ Hz, $J = 4$ Hz, 2H, C**H**$_2$N).

Anal. $C_{31}H_{30}N_2O_2$ (462.59) calc'd.: C 80.49; H 6.54; N 6.05%
found: C 80.30; H 6.67; N 6.23%

3-(2-Amino-1-hydroxyethyl)indole (beta-hydroxytryptamine) creatinine sulphate (IVa)

IIIa (100 mg, 0.28 mmol) was dissolved in methanol (20 ml) and hydrogenated over 10% Pd/C (80 mg) at room temperature and atmospheric pressure for 5 hrs. The catalyst was centrifuged off and washed with metanol. The combined methanol solution and washings were evaporated *in vacuo*, the residue was dissolved in water (1 ml) and titrated with 1.2 *M* solution of creatinine hydrogensulphate to pH 5.5—6.0. After addition of acetone (15 ml) white crystals (32 mg) precipitated and by adding more acetone a second crop of crystals (24 mg) was obtained, total yield: 62.3%. On t. l. c. in solvent B the crystals revealed a main spot at R_f 0.43 and traces of an impurity at R_f 0.11. The whole material was dissolved in a minimal amount of water, precipitated with acetone and the product with m. p. (dec.) 205 °C was obtained, R_f 0.43 (solvent B, developed with Ehrlich's reagent or ninhydrin). I.r. spectrum (KBr): 3350 (OH), 3000 (NH), 1750 (CO, creatinine), 1625, 1550 (C=C, indole ring), 1080 (C—O, sec. alcohol) and 750 (CH, o-disubst. benzene) cm^{-1}. U. v. spectrum: $\lambda_{max}^{H_2O}$ 200, 212, 240, 265, 285 nm; log ε 5.43, 5.48 4.77, 4.69, 4.64.

Anal. $C_{14}H_{21}N_5O_6S$ (387.41) calc'd.: C 43.40; H 5.46; N 18.08%
found: C 43.29; H 5.67; N 18.14%

5-Hydroxy-3-(2-amino-1-hydroxyethyl)indole (beta-hydroxyserotonin) creatinine sulphate (IVb)

IIIb (100 mg, 0.21 mmol) was hydrogenated in the same way as IIIa. After removal of methanol the aqueous solution was titrated with 1.2 M solution of creatinine hydrogensulphate to pH 5.5—6.0. By gradual addition of acetone three successive crops of white crystals were obtained (total: 27 mg, 32.7%). On t.l.c. in solvent B the first two precipitates revealed a main spot at R_f 0.65 and traces of an impurity at R_f 0.18; the latter was not visible in the third crop. The material from the third crop was dissolved in a minimal amount of water and precipitated with acetone. White crystals were obtained with m.p. (dec.) 215°, R_f 0.65 (solvent B, developed with Ehrlich's reagent or ninhydrin). I.r. spectrum (KBr): 3450 (OH), 3100 (NH), 1720 (CO, creatinine), 1550 (C=C, indole ring), 1120 (C—O, sec. alcohol) and 805 (1,2,4-subst. benzene) cm^{-1}. U.v. spectrum: $\lambda_{max}^{H_2O}$ 200, 270, 295 nm; log ε 5.58, 4.84, 4.74.

Anal. $C_{14}H_{21}N_5O_7S$ (403.43) calc'd.: C 41.68; H 5.25; N 17.36%
found: C 41.67; H 5.61; N 17.23%

Acknowledgments. This investigation was supported by NIH PL-480 Research Agreement No. 02-015-1. The authors thank to Mr. A. Vukušić for his skillful technical assistance, to Dr. O. Hadžija for microanalyses and to Mrs. L. Tomić for n.m.r. spectra. We are indebted to Dr. D. Keglević for helpful discussions.

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SAŽETAK

Beta-hidroksitriptamini. I. Kemijska sinteza 3-(2-amino-1-hidroksietil)indola (β-hidroksitriptamina) i 5-hidroksi-3-(2-amino-1-hidroksietil)indola (β-hidroksiserotonina)

V. Plavšić, S. Kveder i S. Iskrić

Iz indola i 5-benziloksiindola priređeni su Grignardovom reakcijom s kloroacetilkloridom kao i Vilsmeierovom reakcijom s *N,N*-dietilkloracetamidom odgovarajući klormetil-3-indolilketoni. I.r. i n.m.r.-spektroskopijom dokazano je da se u obadvije reakcije dobivaju identični spojevi. Nakon zamjene halogena dibenzilamino-skupinom i redukcije karbonilne skupine litium-aluminium-hidridom, benzilne skupine uklonjene su katalitičkim hidriranjem.

3-(2-Amino-1-hidroksietil)indol (β-hidroksitriptamin) i 5-hidroksi-3-(2-amino-1-hidroksietil)indol (β-hidroksiserotonin) izolirani su u obliku kristaliničnih kreatinin-sulfata. Topljivost i zadovoljavajuća stabilnost u vodenim otopinama čine ove soli pogodnima za biokemijska i farmakološka istraživanja.

41000 ZAGREB
INSTITUT »RUĐER BOŠKOVIĆ«

Primljeno 29. svibnja 1974.