Synthesis of Tetrahydroisoquinolines Based on Homoveratrilamine and 3–Indolylacetic Acid

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Abstract

Indole–tetrahydroisoquinoline derivatives based on homoveratrilamine and 3-indolylacetic acid by the Bischler-Napieralski reaction have been obtained and their structures were confirmed by IR and NMR spectra.

Keywords: 3 - indolylacetic acid, homoveratrilamine, Bischler - Napieralski and Mannich reactions.

Introduction

Indole and isoquinoline alkaloids are the two large groups of alkaloids widespread in the plant kingdom with a wide ranging spectra of biological activities[1-3]. The synthesis of these groups of alkaloids and their derivatives has a significant impact on the development of organic chemistry and the manufacture of medicines[4]. In the present report the synthesis of the bimolecular compounds containing the fragments of tetrahydroisoquinoline and β - carboline, as well as indolylisoquinoline is provided.

Materials and Methods

Experimental section

IR spectra were recorded in KBr pellets on an FTIR System 2000 instrument (Perkin-Elmer). PMR spectra were recorded on a Unity-400+ spectrometer (400 MHz, $CDCl_3$, CD_3OD solvent, HMDS internal standard). The R_j-values were determined on LS 5/40 silica gel plates (Czechoslovakia) using $CHCl_3$:MeOH (system 1, 10:1; system 2, 4:1). Melting points of all synthesized compounds were determined on a Boetius microstage.

HPLC. Agilent 1100, Eclipse XDB-18, 3.5μm 3.0 × 150 mm (CH_3OH solvent, CH_3CN (V: V = 1:1), 210 nm, 0.250 ml / min)

N-(3,4-dimethoxyphenethyl)-2-(1H-indol-3-yl)acetamide (3), $C_{20}H_{22}N_2O_3$.

A mixture of homoveratrylamine (**1**, 3.04 g, 0.016 mol) and 2-(1H-indol-3-yl)acetic acid (3 g, 0.017 mol) in MeOH (5 mL) underwent spontaneous heating. The mixture was heated on an oil bath for 3 h at 178 °C. The course of the reaction was monitored by TLC. Then treated with $CHCl_3$ (100 mL), and washed with HC1 solution (3%), NaOH solution (2%), and H_20 until neutral. The $CHC1_3$ was evaporated. The residue was crystallized from Me_2CO or hexane. The resulting crystals were filtered off. The yield of **3** is 70% (4 g), mp 116-119 °C (Me_2CO), R_f 0.65 (system 1).

FT-IR (KBr): *v* 3387, 3332, 2936, 1655, 1592, 1514 см$^{-1}$;

^{1}H NMR (400 MHz, CDC1$_3$-*d*$_6$) δ: 2.55 (t, *J* 6.8 Hz, 2H, Hα), 3.35 (q, *J* 6.8 Hz, 2H, Hβ), 3.64 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.65 (1H, NH), 6.34 (dd, *J* 2 Hz, *J* 8 Hz, 1H, H-6), 6.47 (d, *J* 2 Hz, 1H, H-2), 6.51 (d, *J* 8 Hz, 1H, H-5), 6.96 (d, *J* 2.4 Hz, 1H, H-2'), 7.06 (t, *J* 7.8 Hz, 1H, H-6'), 7.16 (t, *J* 7.8 Hz, 1H, H-7'), 7.32 (d, *J* 8.2 Hz, 1H, H-8'), 7.42 (d, *J* 7.8 Hz, 1H, H-5'), 8,38 (1H, NH) ppm.

1-((1H-Indol-3-yl)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4), $C_{20}H_{22}N_2O_2$.

A mixture of amide **3** (1 g, 3 mmol), anhydrous benzene (30 mL), and $POCl_3$ (3 mL, 0.033 mol) was refluxed for 2 h. The course of the reaction was monitored by TLC. Benzene and $POCl_3$ were distilled off. The residue was dissolved in MeOH (40 mL). The resulting solution was cooled to 0-5 °C and treated in portions with $NaBH_4$ (3 g 0.08 mol). The MeOH was distilled off. The residue was dissolved in H_20 and extracted with $CHCl_3$. The $CHC1_3$ was removed. The solid was crystallized from Me_2CO. The yield is 70% (0.7 g), mp hydrochloride 219-221 °C (Me_2CO), R_f 0.32 (system 2).

FT-IR (KBr): *v* 3389, 3247, 2921, 2734, 1613, 1521, 1456 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD-*d*$_6$) δ: 1.14 (1H, NH), 3.02 (m, 2H, H-4), 3.25 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 3.53 (m, 2H, H-3), 3.76 (s, 3H, OCH_3), 4.48 (br.s, 1H, NH), 4.73 (t, *J* 7.5 Hz, 1H, H-1), 6.54 (s, 1H, H-8), 6.75 (s, 1H, H-5), 7.01 (t, *J* 8 Hz, 1H, H-6'), 7.10 (t, *J* 7.8 Hz, 1H, H-5'), 7.12 (s, 1H, H-2'), 7.34 (d, *J* 8 Hz, 1H, H-7'), 7,55 (d, *J* 7.8 Hz, 1H, H-4') ppm.

Preparation of Compound (5).

Method A. To the solution of isoquinoline 4 (0.2 g, 0.6 mmol) in methanol (10 mL) have been added formalin (32 % , 0.02 mL), molecular sieves (Sito molekularne typ 4A) and concentrated HCl until acidic reaction. The mixture was refluxed for 4 h. The reaction was monitored by TLC. The solvent was distilled off, the residue was dissolved in water and extracted with chloroform. The residue, after removal of the chloroform, was dissolved in acetone and HCl was added. Yield 5 is 67 % (0.14 g), m.p. hydrochloride 154-156 °C, Rf 0.65 (system 2)

Method B. A mixture of 0.4 g (1.2 mmol) of isoqunioline 4, 25 ml of methanol , 0.4 ml (32 %) of formalin was refluxed on a water bath for 4 h. The reaction was monitored by TLC. To the resulting solution at 0-5 °C. 2 g (0.05 mol) $NaBH_4$ was added by portion. Methanol was distilled off, the residue was dissolved in water and extracted with chloroform. The residue after removal of chloroform was crystallized from methanol. Yield 5 is 44 % (0.18 g) , m.p. 119-122 °C, Rf 0.6 (System 2).

FT-IR (KBr): *v* 3410, 3206, 2930, 2825 , 1609, 1514, 1462 cm^{-1}.

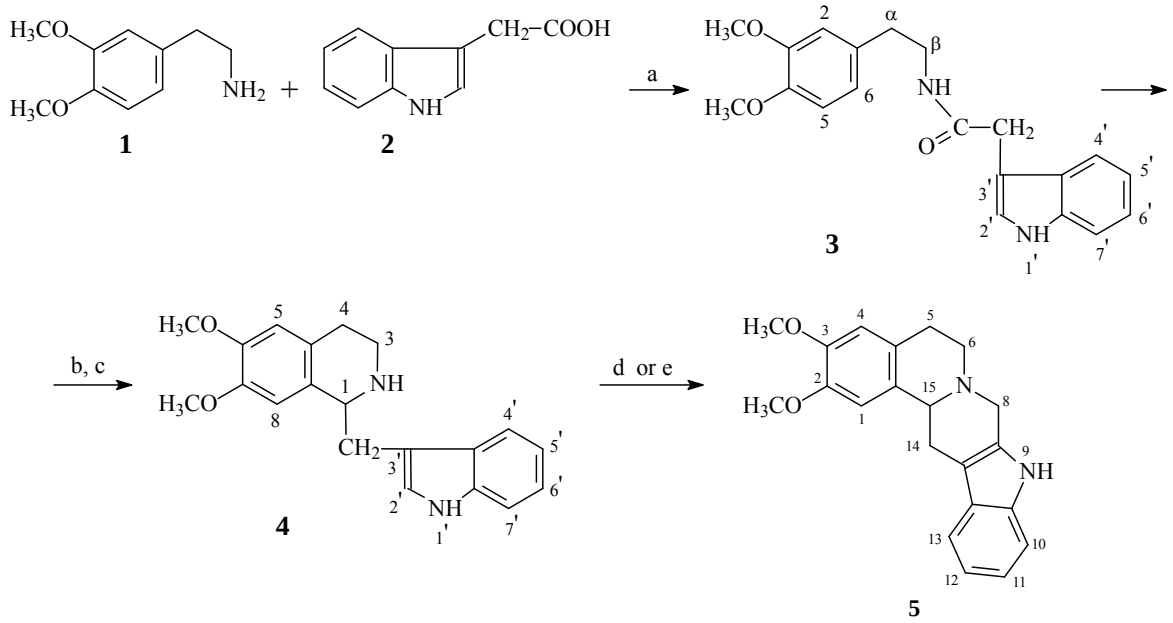
^{1}H NMR (400 MHz, $CDCl_3$-*d*$_6$) δ: 2.72 (m, 2H, H-14), 2.76 (m, 1H, H-5a), 3.14 (m, 1H, H-15), 3.18 (m, 1H, H-6a), 3.33 (dd, *J* 2.4, 5 Hz, 1H, H-5e), 3.75 (dd, *J* 3.6, 5.3 Hz, 1H, H-6e), 3.80 (d, *J* 14.7

Hz, 1H, H-8a), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.00 (d, *J* 14.7 Hz, 1H, H-8e), 6.63 (s, 1H, H-1), 6.83 (s, 1H, H-4), 7.10 (t, *J* 7 Hz, 1H, H-11*), 7.14 (t, *J* 7 Hz, 1H, H-12*), 7.30 (d, *J* 7.5 Hz, 1H-10*), 7.50 (d, *J* 7.5 Hz, 1H, H-13*), 7.92 (bs, 1H, NH) ppm.

Results and Discussion

On the first step, from homoveratrilamine (1) and 3- indolylacetic acid (2) in heating up to 178° C for 4 hours[5] the amide 3 was obtained with 70% yield. Cyclization of the amide 3 was performed by the Bischler - Napieralski reaction with $POCl_3$ in benzene solution for 2 hours. By the restoration of $NaBH_4$ 3,4-dihydroisoqunioline the target tetrahydroisoquinoline 4 was obtained.

The structures of 3-4 were proven based on NMR- spectroscopy. Thus ^1H NMR spectrum of the amide 3 has three aromatic proton signals attributed to the 1,3,4 - substituted β- phenylethylamine of aromatic ring, for example H-6 protons of doublet-doublet at δ 6.34 ppm, and the signals of H -2 and H -5 protons appear as a doublet δ 6.47, 6.51 ppm, the protons of indole aromatic ring appear at δ 6.96, 7.06, 7.16, 7.32 and 7.42 ppm. The cyclization of compound 3 gives isoquinoline 4, in PMR spectrum of which the signal H-1 at 4.73 ppm appears, in the form of triplet the signals of aromatic protons H -5 and H-8 of the isoquinoline fragment resonate in the form of two singlets at δ 6.54 - 6,75 ppm, indole at δ 7.01, 7.10, 7.12, 7.34 and 7.55 ppm.



a) CH_3OH, 178°; b) $POCl_3$, C_6H_6; c) $NaBH_4$, CH_3OH; d) HCOH, CH_3OH, HCl; e) HCOH, CH_3OH, $NaBH_4$

Scheme 1. General synthetic scheme: (3) synthesis of N-(3,4-dimethoxyphenethyl)-2-(1H-indol-3-yl)acetamide, (4) synthesis of 1-((1H-Indol-3-yl)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, and preparation of compound (5)

Condensation of 4 with formalin and concentrated HCl using dehydrating molecular sieves (4A) produces the product 5 with a yield of 67%. The methylation reaction of 4 by Craig did not give the expected result, and also led to the product 5 with 44% yield. The product 5 has been characterized by IR and NMR spectroscopy. Purity of the obtained compounds 3, 4 and 5 was confirmed by HPLC, the retention time of the compounds were 2.90, 3.93 and 3.12 min. respectively.

Conclusion

Synthesis methods have been developed for obtaining three new products based on amide and indolyl-tetrahydroisoqunoline.

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