Synthesis of Tetrahydroisoquinolines Based on Homoveratrilamine and Isotropic Acid

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Abstract

By the reaction of homoveratrilamine and chloride of isotropic acid, N^1,N^4-bis(3,4-dimethoxyphenethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene-1,4-dicarbox-amide and 1,1'- (1-phenyl-1, 2,3,4-tetrahydronaphthalene -1,4-diyl) bis (6,7-dimethoxy -1,2,3,4-tetrahydroisoquinoline) have been prepared. The structure of compounds were confirmed by IR and NMR spectra

Keywords: bellodonine, isotropic acid, chloride isotropic acid, homoveratrilamine.

Introduction

It is known that tropane alkaloids of *Solanaceae* family have a high physiological activity, and some of them are used in medicine as pharmaceuticals. For example, atropine, hyoscyamine, scopolamine are the major alkaloids of *Solanaceae* plants. Dimeric tropane bases isolated from different species of this family (*Datura stramonium, D. inoxia, Physochlaina alaica etc.*) in small amounts, show interesting pharmacological properties. Therefore, a series of derivatives of α- β- belladonnin and α- and β-skopodonnin presenting practical interest was synthesized [1-3].

Formation of dimeric tropane alkaloids in a plant occurs by the dimerization of acids. Thus, in the case of formation of alkaloids of the group of belladonnine and skopodonnine occurs dimerization of tropic acid, which under certain conditions (under the influence of light) turns into isotropic acid [4,5].

Despite the variety of resulting structures, are not found in nature, compounds containing fragments of isotropic acid and isoquinoline. The biological activity of isoquinoline alkaloids stimulates the synthesis of various bis-isoquinoline compounds, as evidenced by numerous studies [6-10].

Materials and Methods

General Conditions

^{1}H-NMR spectra were recorded in $CDCl_3$ + CD_3OD on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisilane (HMDS) was used as internal standard, chemical shifts δ of ^{1}H were recorded in ppm.

IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer). The reaction process was monitored by TLC on LS 5/40 silica gel plates (Czech. SSR) using $CHCl_3$:MeOH (system 1, 8:1; system 2, 6:1; system 3, 4:1) solvent system and developed plates were visualized under UV lamp, and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 or with the dried $CaCl_2$.

Synthesis

Isotropic acid (1), $C_{18}H_{16}O_4$

A mixture of 1 g bellodonine and 20 mL of 10% KOH (2 g KOH + 18 ml MeOH) was refluxed for 3 hours. Methanol was distilled off, the residue was dissolved in 20 mL of water and washed once with benzene. After acidification with hydrochloric acid up to pH = 3 acid **1** was extracted with chloroform. Chloroform was distilled off. The residue was crystallized from benzene.

Yield 82% (0.45 g), R_f 0.70 (system 3), amorphous (benzene).

FT-IR (KBr): *ν* 3423, 3065, 2959, 2621, 1698, 1598, 1494 см$^{-1}$.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.81 (dddd, *J* 2.3, 6.4, 8.9, 13.4 Hz, 0.5H, H-3a); 1.95-2.09 (m, 1.5H, H-3a,e); 2.17 (dt, *J* 2.7, 13.3 Hz, H-2a); 2.55 (ddd, *J* 2.2, 7.4, 13.5 Hz, 0.5H, H-2e); 2.79 (ddd, *J* 2.2, 7.4, 13 Hz, 0.5H, H-2e); 3.81 (dt, *J* 2.9, 9.3, 16 Hz, 1H, H-1); 6.92 (d, *J* 7.2 Hz, 1H, H-Ar); 7.04-7.24 (m, 8H, H-Ar).

N^1,N^4-bis(3,4-dimethoxyphenethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene-1,4-dicarbox-amide (4), $C_{38}H_{42}N_2O_6$.

To a mixture of 0.68 g homoveratrilamine, 10 mL of toluene and 0.4 mL of TEA was added dropwise a solution of 0.31 g chloride of isotropic acid in 5 ml of toluene over 1 hour. The reaction mixture was kept at room temperature for 3 hours. The reaction was monitored by TLC. The solvent was distilled off. The residue was dissolved in chloroform and 2% solution of NaOH, then with water until neutral medium. The residue after removal of the chloroform gave 4 as oil. Yield 89.6% (0.52 g), R_f 0.5 (System 1).

FT-IR: *ν* 3417, 3312, 3015, 2936, 2836, 1645, 1592, 1515, 1464 см$^{-1}$.

^{1}H NMR (400 MHz, $CDC1_3$) δ: 1.66 (dddd, *J* 2.1, 6.5, 10.7, 13.2 Hz, 1H, H-3a); 1.97 (m, 1H, H-3e); 2.05 (ddd, *J* 2.2, 7.4, 13.5 Hz, 1H, H-2a); 2.61-2.75 (m, 4H, H-α',α''); 2.79 (ddd, *J* 2.5, 10.7, 13.5 Hz, 1H, H-2e); 3.34-3.58 (m, 4H, H-β',β''); 3.60 (t, *J* 6 Hz, 1H, H-4); 3.74 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 5.78 (t, *J* 5.8 Hz, 1H, NH); 5.90 (t, *J* 5.6 Hz, 1H, NH); 6.53 (dd, *J* 2, 8.2 Hz, 1H, H-6'); 6.57 (d, *J* 2 Hz, 1H, H-2'); 6.61 (dd, *J* 1.9, 8.0 Hz, 1H, H-6"); 6.63 (d, *J* 1.9, Hz, 1H,

H-2"); 6.67 (d, *J* 8.2 Hz, 1H, H-5'); 6.69 (d, *J* 8 Hz, 1H, H-5"); 6.81 (dd, *J* 1.6, 7.7 Hz, 1H, H-5); 6.87 (dd, *J* 2.4, 6.1 Hz, 2H, H-10,14); 6.99 (dd, *J* 1.6, 7.7 Hz, 1H, H-8); 7.06 (td, *J* 1.6, 7.6 Hz, 1H, H-6); 7.12 (td, *J* 1.6, 7.6 Hz, 1H, H-7); 7.13-7.17 (m, 3H, H-11,12,13).

1,1'-(1-Phenyl-1,2,3,4-tetrahydronaphthalene-1,4-diyl)bis(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline) (5), $C_{38}H_{42}N_2O_4$.

A mixture of 0.48 g of diamide 4 and 2 mL of $POCl_3$ was heated in a water bath for 6 hours under reflux. The reaction was monitored by TLC. The reaction mixture was poured into ice and basified with 25% NH_4OH solution up to pH = 9 and extracted with chloroform, the residue after distillation of $CHCl_3$ was dissolved in 30 mL of methanol. To this solution at 0 – 5 ° C was added portion wise 2 g $NaBH_4$. Methanol was distilled off, the residue was dissolved in water and extracted with chloroform. The residue after removal of chloroform is 0.44 g.

0.25 g of the reaction mixture was divided by a silica gel column (10 g) were collected 25 fractions.

R_f 0.6 (System 2).

FT-IR: *ν* 3350, 3014, 2933, 2846, 1605, 1513, 1463 $см^{-1}$.

^{1}H NMR (400 MHz, $CDC1_3$) δ: 1.38 (ddd, *J* 1.9, 4.6, 13.3 Hz, 1H, H-2e); 1.78 (dt, *J 2.1,* 13.6 Hz, 1H, H-2a); 1.94 (dd, *J* 5.3, 15.8, 1H, H-4'a); 2.29 (dd, *J 2.3, 4.4,* 15.4 Hz, 1H, H-4"e); 2.58 (m, 2H, H-4', 4"); 2.62 (m, 1H, H-3a); 3.18 (m, 1H, H-3',3"); 3.22 (s, 3H, OCH_3); 3.29 (m, 2H, H- 3',3"); 3.36 (1H, kv, *J* 5.9, 13.8, H-3e); 3.50 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.86 (s, 1H, h-1"); 3.89 (ddd, *J* 2.3, 5.2, 14.7 Hz, 1H, H-1'); 4.06 (ddd, *J* 2.2, 5.4, 15.0 Hz, 1H, H-4); 6.42 (s, 1H, H-8'); 6.49 (s, 1H, H-5'); 6.50 (s, 1H, H-8"); 6.58 (s, 1H, H-5"); 6.95-7.02 (4H, m, H-Ar); 7.17-7.32 (5H, m, H-Ar).

Result and Discussion

Continuing systematic studies on the synthesis of bis-tetrahidroisoquinolines on the Bischler-Napieralski reaction, we carried out the reaction using diamides derived from chloride of isotropic acid **(3)**.

The mixture of α- and β- isotropic acid **(2)** was synthesized from bellodannine by alkaline hydrolysis under heating for 3 hours.

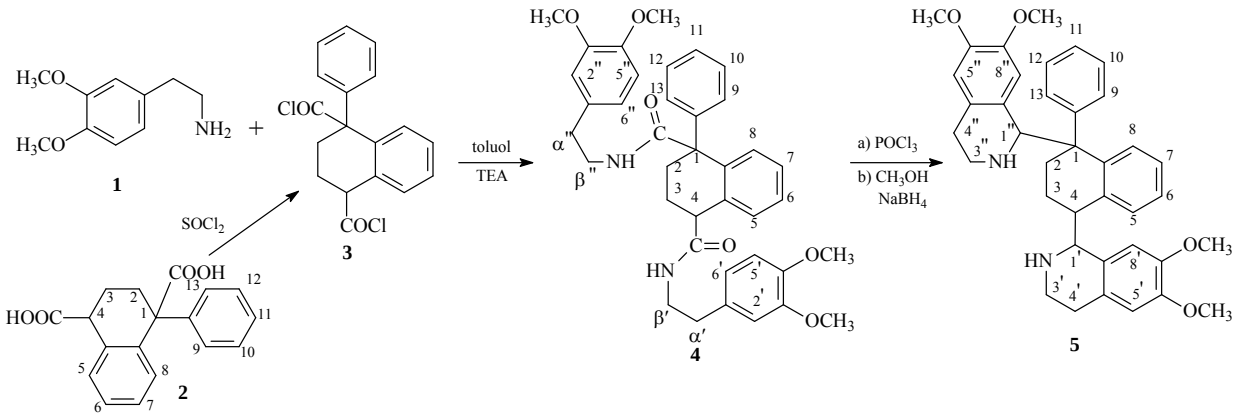
The chloride of isotropic acid (3) was obtained under the influence of tionjlchloride to **2** at room temperature.

Diamide **4** is formed with a yield of 89.6% at room temperature under stirring homoveratrilamine **(1)** with a chloride of isotropic acid **(3)** for 3 hours.

The structure of diamide **4** has been proved by IR, NMR-spectra. The IR spectrum has strong absorption bands at 1645 cm^{-1}, 2836-2936 cm^{-1}, 3115 – 3417 cm^{-1} corresponding to valent vibration of CO, Ar–CH,

OH and NH-groups. NMR-spectrum of **4** is characterized by the presence of the methylene protons H-α and H-β in the form of a triple and a quintet at 2.70 ppm and 3.38, 3.42 and 3.53 ppm. Protons of methoxyl groups resonate as a singlet at 3.74, 3.77, 3.78 and 3.79 ppm.; there are three signals of aromatic protons typical for 1,3,4-substituted β-phenylethylamine (H-6 protons give a doublet doublet at δ 6.53, 6.62 ppm, and the signals of H-2 and H-5 protons appear as doublets at 6.57, 6.60 and 6.67 ppm, 6.69 ppm) and signals of isotropic parts of the molecule as a triplet at δ 3.60 ppm (CH), and the signals from aromatic protons appear at δ 6.80, 6.87, 6.99, 7.06, 7.11 and 7.15 ppm.

Subsequent cyclization of diamides **4** was, carried out by the Bischler-Napieralski reaction with $POCl_3$ for 6 hours. By recovering $NaBH_4$ 3,4-dihydroisoquinoline was obtained target bis-tetrahydroisoquinoline **5** of scheme:



The structure of base **5** was installed on the basis of analysis data of PMR spectra. In spectrum **5** appears the signals of H – 1 'as a doublet of doublets at 3.89 ppm and H – 1" in the form of a singlet at 3.86 ppm; signals from the aromatic protons H – 5', 5" and H – 8', 8" as singlets at δ 6.50, 6.58 and 6.42, 6.49 ppm, indicating the formation of tetrahydroisoquinoline fragments in the molecule of bis-compound **5**.

Conclusion

Synthesis methods have been developed for obtaining two new products based on diamide and bis-tetrahydroisoqunoline. The structure of compounds were confirmed by IR and NMR spectra

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