

New Synthesis of Polymethyleneamine Alkaloid Haplamidine and Its Homologues

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Abstract

A new approach to the synthesis of the natural alkaloid haplamidine and its homologues is developed. The possibility of selective removal of eth phthalyl protection by means of hydrazinolysis in the presence of benzoyl group is demonstrated.

INTRODUCTION

The chemical composition of all the living organisms (from bacteria to mammals) is known to contain aliphatic amines putrescine, cadaverine, spermidine and spermine [1]. These biogenic amines play important part in the regulation of cell division.

In addition, the above-listed compounds serve as the structural basis for natural and semi-synthetic biologically active compounds of various pharmacological groups [2].

According to the data of A. N. Blagoveshchensky [3], alkaloid haplamidine **I**, isolated for the first time from *Haplophyllum Latifolium*, possesses antihelmintic properties, causes sedative action on the central nervous system, is used to treat the diseases of gastrointestinal and respiratory diseases of mammal animals and humans.

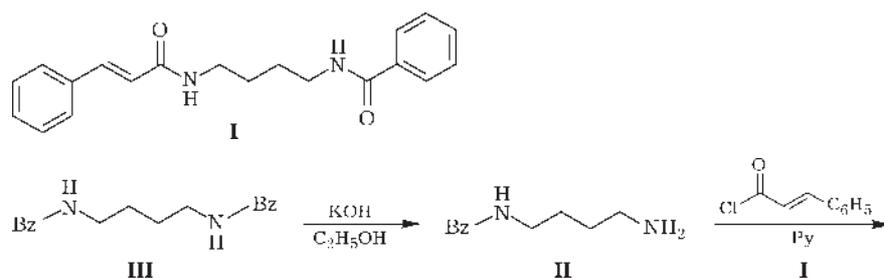
Its content in the plant material is negligibly small (0.001 %), so its synthesis is urgent.

The synthesis of alkaloid haplamidine **I** (Scheme 1) involving partial hydrolysis of *N,N'*-dibenzoyl-1,4-butylenediamine **III** and subsequent acylation of monobenzoyl derivative **II** with cinnamoyl chloride [3] was described.

However, the difficulty connected with the isolation of amide from hydrolysis products and rather low yield (*ca.* 4 %) hinder the use of this scheme to obtain haplamidine and its substituted derivatives.

EXPERIMENTAL

Reaction progress was monitored by means of TLC on the Silufol UV-254 plates (Czechia) in the benzene/ethanol system at a ratio equal



Scheme 1.

to 3 : 1 (5 : 1) under standard conditions. Melting points of the synthesized compounds were measured with the device of capillary type PTP(M) (Khimlabpribor Enterprise, Russia) and were not corrected. IR spectra were recorded with Perkin-Elmer 684 spectrometer in KBr tablets; UV spectra were recorded with Flash EA 1112 analyser. The ^1H and ^{13}C NMR spectra were recorded with AM-400 spectrometer (Bruker), for solutions in DMSO. The signal of the solvent (2.50 and 39.5 ppm for ^1H and ^{13}C NMR spectrum, respectively, was used as a reference.

Synthesis of haplamidine

N-monobenzoylputrescine in the amount of 5.76 g (0.03 mol) and 40 mL of pyridine were placed into a four-necked round-bottomed flask 250 ml in volume, equipped with a mechanical mixer, reflux cooler, thermometer and a dropping funnel. The mixer was turned on, and the solution was cooled to 0–5 °C, then the solution of 6.4 g (0.04 mol) of cinnamoyl chloride in 40 mL of pyridine was slowly added drop by drop under intense mixing. To complete the reaction, the mixture was kept under mixing for 1 h and then poured into a mixture of ice and hydrochloric acid. The precipitated crystals were separated by filtering, squeezed and washed with three portions (20 mL each) of acetone.

Thus we obtained 8.11 g (84 %) of haplamidine **I** as white crystals with $T_{\text{melt}} = 138\text{--}140$ °C.

The absorption bands expressed in the IR spectrum appear at 3318, 1634, (NH–CO) and 1578, 1534, 765, 716 cm^{-1} (monosubstituted benzene ring), UV spectrum (ethanol): λ_{max} 216, 222, 272 nm.

^1H NMR spectrum, δ , ppm: 1.57 (q, 2H, H – 4.5); 3.22 (d, $J = 5$ Hz, 2H, H – 6); 3.30 (t, 2H, H – 3); 3.35 (d, 2H, H_2O); 6.64 (s, 1H, H – 9); 7.43 (m, 1H, CH–O, H'_{p} , H'_{m} , H'_{m} , H'_{p}); 7.84 (d, $J = 3$ Hz, 1H, H'_{o}); 8.07 (s, 1H, H – 7); 8.24 (s, 1H, H – 2).

^{13}C NMR spectrum, δ , ppm: 26.6 (s, C – 4.5); 38.4 (s, C – 6); 38.8 (s, C – 3); 122.35 (s, C – 9); 127.03 (s, C_{m}); 127.34 (s, C'_{m}); 128.09 (s, C_{o}); 128.79 (s, C'_{o}); 129.21 (s, C_{p}); 130.85 (s, C'_{p}); 134.67 (s, C'_{i}); 134.93 (s, C_{i}); 138.31 (s, C – 10); 164.81 (s, C – 8); 166.11 (s, C – 1).

The data of elemental analysis correspond to the gross formula $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$. Calculated, %:

C 74.51, H 6.88, N 8.69, O 9.92. Found, %: C 73.35, H 6.76, N 8.57, O 11.73.

Synthesis of homohaplamidine

Monobenzoylcadaverine in the amount of 4 g (0.02 mol) and 10 mL of pyridine were placed into a four-necked round-bottomed flask 250 ml in volume, equipped with a mechanical mixer, reflux cooler, thermometer and a dropping funnel. The mixer was turned on, and the solution was cooled to 0–5 °C, then the solution of 4.14 g (0.02 mol) of chloranhydride of cinnamic acid in 50 mL of pyridine was slowly added drop by drop under intense mixing. To complete the reaction, the mixture was kept under mixing for 1 h and then poured into a mixture of ice and hydrochloric acid. The precipitated heavy oil was washed with water and mixed with ether. The precipitate was separated by filtering and dried.

Thus we obtained 5.85 g (87 %) of homohaplamidine **IX** in the form of pink-coloured crystals with $T_{\text{melt}} = 86\text{--}91$ °C.

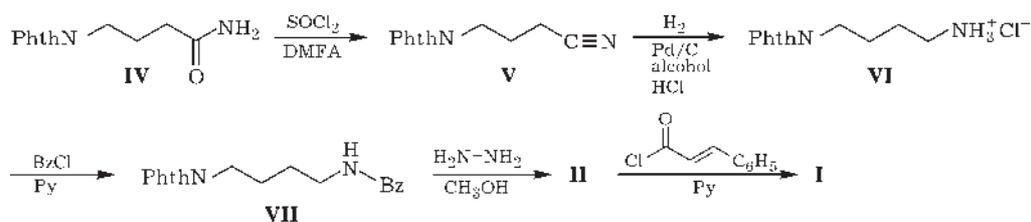
After recrystallization from aqueous ethanol, a beige-coloured product with $T_{\text{m}} = 149\text{--}151$ °C as obtained.

The absorption bands expressed in the IR spectrum appear at 3302, 1639 (NH–CO) and 1578, 1539, 765, 726 cm^{-1} (monosubstituted benzene ring), UV spectrum (ethanol): λ_{max} 216, 222, 272 nm.

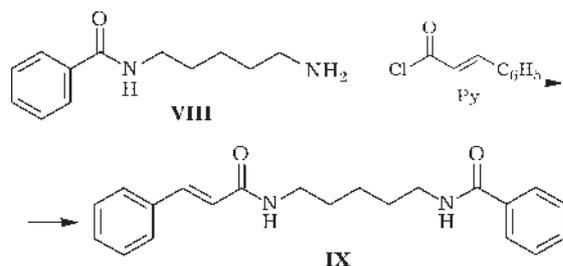
^1H NMR spectrum, δ , ppm: 1.35 (d, $J = 8$ Hz, 2H, H – 5); 1.54 (q, 2H, H – 4.5); 3.19 (t, 2H, H – 7); 3.27 (q, 2H, H – 3); 3.33 (d, H_2O); 6.63 (s, 1H, H – 10); 7.42 (d, $J = 16$ Hz, CH–O, H'_{p} , H'_{m} , H'_{m} , H'_{p}); 7.55 (d, $J = 4$ Hz, 1H, H_{o}); 7.84 (d, $J = 4.5$ Hz, 1H, H'_{o}); 8.06 (s, 1H, H – 8); 8.39 (s, 1H, H – 2).

^{13}C NMR spectrum, δ , ppm: 23.8 (s, C – 5); 28.8 (d, $J = 20$ Hz, C – 10); 38.5 (s, C – 7); 39 (s, C – 3); 122.4 (s, C – 10); 126.21 (s, C_{m}); 127.2 (s, C'_{m}); 128 (s, C_{o}); 128.8 (s, C'_{o}); 129.2 (s, C_{p}); 130.8 (s, C'_{p}); 134.7 (s, C_{i}); 134.9 (s, C'_{i}); 138.2 (s, C – 11); 164.8 (s, C – 9); 166.1 (s, C – 1); 126.9 (s, C'_{o}); 130.85 (s, C'_{p}); 138.31 (s, C – 10); 164.81 (s, C – 8); 166.11 (s, C – 1).

The data of elemental analysis correspond to the gross formula $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$. Calculated, %: C 74.97, H 7.19, N 8.33, O 9.51. Found, %: C 73.10, H 6.83, N 8.06, O 10.31.



Scheme 2.



Scheme 3.

RESULTS AND DISCUSSION

In the method of haplamidine **I** synthesis proposed by us (Scheme 2), the initial compound is ω -phthalimidobutyric acid [4] from which the amide of ω -phthalimidobutyric acid **IV** was obtained.

ω -Phthalimidobutyronitrile **V** was obtained by dehydration of amide **IV** with a mixture of thionyl chloride and DMFA at 0 °C for 7 h (yield 75–77 %). Calculated, %: C 67.28, H 4.71, N 13.08. Found, %: C 67.74, H 4.83, N 13.06.

Hydrogenation of nitrile was performed in ethanol under atmospheric pressure and temperature 25–27 °C in the presence of hydrochloric acid. The catalyst was Pd/C (5 %). Monophthaloylputrescine **VI** was isolated in the form of hydrochloride (yield 54–56 %). Calculated, %: C 56.59, H 5.94, N 11.00. Found, %: C 56.82, H 6.12, N 11.32.

Benzoylation of hydrochloride **VI** was carried out in pyridine. Diamide **VIII** was obtained in the form of white crystals with $T_m = 118$ –119 °C

(yield 85–87 %). Calculated, %: C 70.79, H 5.63, N 8.69. Found, %: C 70.69, H 5.61, N 8.68.

N-monobenzoylputrescine **II** was obtained by boiling diamide **VIII** in methanol with hydrazine at a ratio of 2 : 3 (see Scheme 2) with the quantitative yield. Its structure was confirmed with physicochemical methods; it was established that the reaction possesses high selectivity and does not affect benzoyl group.

Homohaplamidine **IX** was synthesized from monobenzoylcadaverine **VIII** [5] by acylation with cinnamoyl chloride (Scheme 3).

CONCLUSION

Thus, a new method to synthesize the natural alkaloid haplamidine was developed; the nearest homologue of this compound was obtained from benzoylcadaverine. The physicochemical investigations fully confirmed the structure of the synthesized compounds.

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