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TO THE QUESTION OF SYNTHESIS AND STANDARDIZATION OF PHARMACOLOGICALLY ACTIVE PYRIDINE AND PYRROLE DERIVATIVES

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Abstract. The pilot studies on derivative synthesis based on pyrrolo-pyridine and pyrrolo-pyrrole groups possessing pharmacological activity have been conducted. Domino reactions principle has been used during the studies. The possibility of physico-chemical methods appliance has been studied in order to standardize the obtained chemical compounds. Synthesized benzyl ether 5-tert-butyl-1-benzyl-2,4-dioxohexahydro-1H-pyrrolo[3,2]pyridine-3a,5-(6H)-dicarboxylate and benzyl ether 5-tert-butyl-2,4-dioxo-1-phenethylhexahydro-1H-pyrrolo[3,2c]-3a,5(6H)-dicarboxylate were isolated by column chromatography (adsorbent - silica gel). The purity of products were monitored by TLC (thin layer chromatography) during the purification steps, eluent cyclohexane:acetone=3:2, sorbent on Silufol silica gel plates.

Keywords: pyrrolopyridines, synthesis, pyrrolo-pyrroles, analysis, pharmacologically active compounds.

К ВОПРОСУ О СИНТЕЗЕ И СТАНДАРТИЗАЦИИ БИОЛОГИЧЕСКИ АКТИВНЫХ ПРОИЗВОДНЫХ ПИРИДИНА И ПИРРОЛА

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Резюме. Проведены предварительные поисковые исследования в области синтеза производных из группы пирролопиридинов, обладающих биологической активностью. Предложен механизм реакции с использованием принципа домино-реакций. Структура полученных соединений установлена физико-химическими методами. Синтезированные бензиловый эфир 5-трет-бутил-1-бензил-2,4-диоксогексагидро-1Н-пирроло[3,2]пиридин-3а,5-(6Н)-дикарбоксилата и бензиловый эфир 5-трет-бутил-2,4-диоксо-1-фенэтилгексагидро-1Н-пирроло[3,2с]-3а,5(6Н)-дикарбоксилата выделены методом колоночной хроматографии (адсорбент – силикагель), чистота продуктов на этапах очистки контролировались методом тонкослойной хроматографии [ТСХ, элюент – циклогексан : ацетон (3:2), сорбент на пластинках Silufol – силикагель].

Ключевые слова: пирролопиридины, синтез, домино-реакции, анализ, биологически активные соединения.

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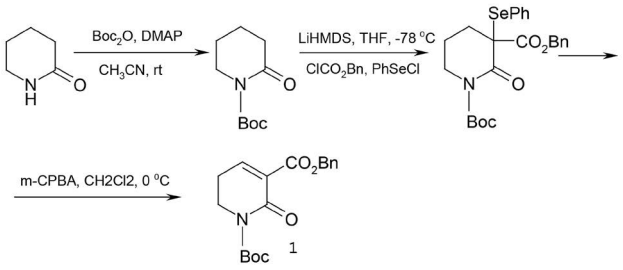
INTRODUCTION

The most important goal of modern pharmaceutical science is the search for new biologically active compounds. Currently, both screening of synthesized compounds and targeted synthesis of compounds remain up-to-date in drug discovery. In modern organic synthesis, domino reactions are more and more successful on the way to rationalization of reactions and obtaining target products, which allows deriving new compounds in one step, avoiding isolation of unstable intermediates, and, finally, making work more cost-effective.

According to the literature data [1, 2], it is known about the biological activity of a number of diketo-derivatives of pyrrolopyridines, which have high analgesic and antiviral activity, as well as, are promising in the treatment of hyperproliferative diseases.

Due to that, it was appropriate to carry out studies including the synthesis of individual bicyclic derivatives of the structure using Michael acceptors.

The initial Michael acceptors were synthesized according to the scheme [3]:

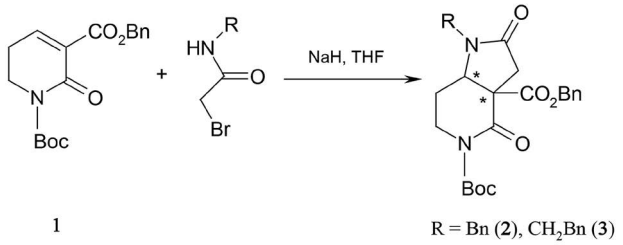


MATERIALS AND METHODS

The obtained benzyl ester of 1-tert-butoxycarbonyl-2-carbonyl-piperidine-3-ene-3-carboxylic acid (**1**), Michael acceptor, was introduced into a domino reaction with N-benzyl-α-bromoacetamide in the presence of sodium hydride (Acros Organics, Belgium, ref. number 189860050, CAS number 7646-69-7, expiration date 05/15/2018), reaction was carried out in tetrahydrofuran solution (99.9%, extra pure, anhydrous, stable with BHT, Acros Organics, Belgium, ref. number 181500025, CAS number 109-99-9, expiration date 04/08/2017). As a result, 3a-benzyl ester of 5-tert-butyl-1-benzyl-2,4-dioxohexahydro-1H-pyrrolo-lo[3,2]pyridine-3a,5-(6H)-dicarboxylate (**2**) and 5-tert-butyl-2,4-dioxo-1-phenethylhexahydro-1H-pyrrolo[3,2c]-3a,5(6H)-dicarboxylate 3a-benzyl ester (**3**) as a single diastereomer were isolated by column chromatography, as evidenced by their ^{1}H-NMR spectra. The structure of the intermediates was established on the basis of the ^{1}H- and 13C-NMR spectroscopy data.

RESULTS AND DISCUSSION

The domino reaction for the synthesis of octahydro-1H-pyrrole[3,2-c]pyridine derivatives was carried out according to the scheme:

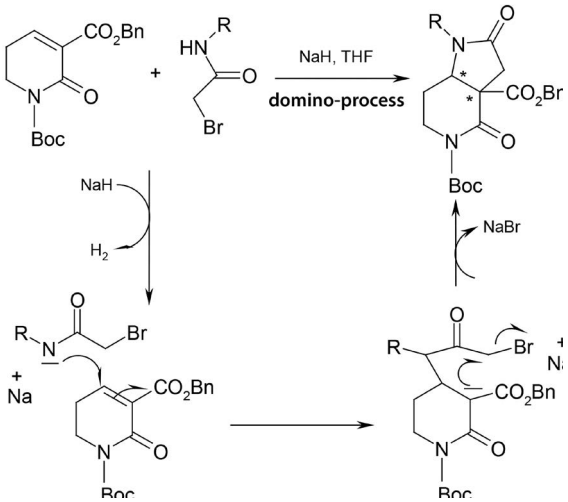


1

R = Bn (**2**), CH_2Bn (**3**)

The yields of bicyclic bislactam products were 25% (**2**) and 33% (**3**), respectively.

The following scheme can be proposed as a domino reaction mechanism:



The progress of the reaction and the purity of the obtained compounds were controlled by preparative thin-layer chromatography on Silufol UV-254 plates using the ascending chromatography in mobile phase cyclohexane:acetone (3:2).

The NMR data of the compounds recorded in CDCl3 confirm anticipated structures of the derived compounds. Signals were found in 1H spectra areas for 3a-benzyl ester of 5-tert-butyl-1-benzyl-2,4-dioxohexahydro-1H-pyrrolo[3,2]pyridine -3a,5-(6H)-dicarboxylate (**2**), ppm: 1.79 (CH_3), 1.81 (CH_2 multiplet), 2.26 CH_2 m, 3.04-3.10 (CH_2 d), 3.37-3.48 CH_2 d , 5.00-5.25 (C_6H_5 m), 6.93 (OCH_2 t), 7.25-7.35 (C_6H_5); ^{13}C spectra show signals in the following areas, ppm: 26.94; 27.92; 37.93; 39.14; 41.08; 56.10; 59.02; 68.28; 77.08; 77.28; 77.51; 84.11; 125.96; 127.02; 128.55; 128.67; 134.75; 137.72; 151.65; 167.38; 169.39; 170.78. The signals in the ^{1}H-NMR spectra of 3a-benzyl ester of 5-tert-butyl-2,4-dioxo-1-phenethylhexahydro-1H-pyrrolo[3,2c]-3a,5(6H)-dicarboxylate, respectively, were found in areas, ppm: 1.70 (CH_3), 1.71-1.76 (CH_3 m), 2.15-2.20 (CH_3 m) 3.75-3.79 and 3.80-3.83 (CH_2 m), 4.90 -4.95 and 5.08-5.19 (CH_2 d and q, respectively), 7.21-7.28 (C_6H_5 m).

CONCLUSION

The mechanism of domino reactions with the formation of new pyrrolopyridines has been studied and proposed. The results allow expanding the number of agents that enter into similar reactions using Michael acceptors, which, in turn, opens up prospectives for the synthesis of the range of biologically active substances.

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