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Interaction of *d*-treo-2-methylamino-1-phenyl-1-propanol with 4-morpholylbenzaldehyde in the conditions of convectional heating and microwave activation

The synthesis of 1,3-oxazolidine was made by condensation reaction of *d*-treo-2-methylamino-1-phenyl-1-propanol with 4-(N-morpholyl)-benzaldehyde under the conditions of convectional and microwave activation. The structure of 1,3-oxazolidine has been proved by IR- and ^{1}H NMR-spectroscopies. Physico-chemical constants of the oxazolidine obtained by both methods were identical. 4-(N-morpholyl)-benzaldehyde, 4-(4-((*4R,5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)phenyl)morpholine obtained very promising in terms of learning conformational features of the structure and biological properties. The structure of the new heterocyclic compounds — 4-(N-morpholyl)-benzaldehyde, 4-(4-((*4R,5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)-phenyl)morpholine is proved by data IR and NMR 1H spectroscopy, as well as a comparative study of the influence of convection and microwave heating on the yield and character formation of the final product has been made.

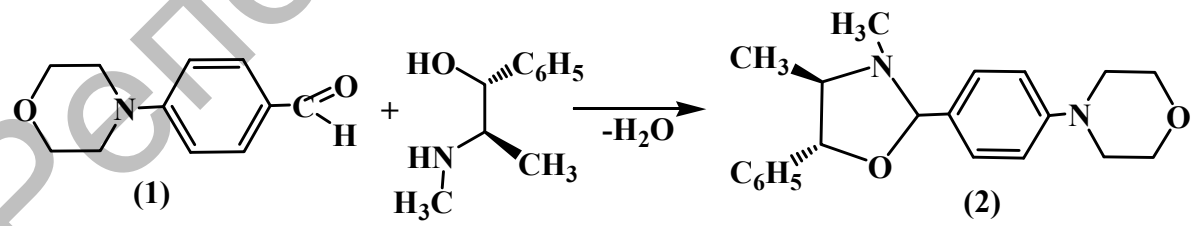
Key words: 1,3-oxazolidines, *d*-treo-2methylamino-1-phenyl-1-propanol, alkaloid of d-pseudoethedrine, β-aminoalcohols, 4-morpholinephenylic, tetramethylsilane, 4-(4-((*4R,5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)phenyl)morpholine, spin-spin interaction.

Introduction

High interest to 1,3-oxazolidines is caused by the fact that these compounds posses unique properties which allow to use them for different practical purposes in medicine and industry, and they are of great scientific interest as the products of enantioselective synthesis of planar-chiral compounds [1–3]. The absolute configurations of chiral centers of 1,3-oxazolidine compounds obtained on the basis of *d*- and *l*-ephedrines have been previously determined by us [4]. Availability of these compounds stimulates intensive development of the synthesis methods as well as the expansion of a number of new oxazolidine representatives.

Results and discussion

We have studied the interaction of *d*-treo-2-methylamino-1-phenyl-1-propanol (the alkaloid of *d*-pseudoethedrine) (1) with 4-morpholylbenzaldehyde in absolute benzene medium which leads to the formation of oxazolidine (2) according to the following scheme:



The reaction mixture was boiled for 2 hours in the flask equipped with Dean-Stark trap. The yield of the product (2) was 72 %. With the aim of increasing the yield of a targeted product (2) and comparative study of the process of formation of the final product the interaction of 4-morpholylbenzaldehyde (1) with *d*-treo-2-methylamino-1-phenyl-1-propanol was carried out under the conditions of microwave activation. As a result of investigations of the influence of microwave field on reaction medium it was found that during irradiation of the ethanol solution of reaction mixture during 15–20 min with pauses at 500 Wt the process goes likewise stereoselectively (according to the results of TLC) with the formation of individual epimer (2) with the yield of 99.5 %. Physicochemical constants of oxazolidine (2) obtained by both methods were identical. The results of TLC have shown that the only one product is formed as a result of the reaction.

Different configurations of chiral centers in the molecules of *d*- and *l*-ephedrines should lead to different conformations of oxazolidine cycle (2). According to data given by different researchers [5–8], the interaction of β-aminoalcohols with different aldehydes usually proceeds stereoselectively either with the formation of *S*-stereoisomer or *R*-epimer.

Stereoselectiveness of the process depends on the nature of reagents and solvents.

The structure of the compound (2) has been investigated on the basis of the results of IR- and ^{1}H NMR-spectroscopy (DMSO-d_6, 500 MHz). In the IR-spectra of the compound (2) there is no absorption band of hydroxyl and carbonyl groups of the initial reagents.

It was established from the ^{1}H NMR-spectra of oxazolidine (2) that in the weak field area along with the signals of protons of phenyl cycle with 7.30–7.42 ppm there are two duplets which are typical to ortho- and meta-protons of 4-morpholinephenylic fragment with 6.95 and 7.35 ppm correspondingly (figure). The signal of secondary methyl group as a duplet (J_{HH} 5,8 Hz) resonates at 1.12 ppm, and the signal of N-methyl group is situated at 2.39–2.45 ppm as a singlet. The methine proton which is vinyl to hydroxyl-group resonates at 2.39–2.45 ppm as a complex multiplet. The signal of methine proton of CH-O group is seen in the 4.63 ppm and splits into duplet J=4.6 Hz because of the spin-spin interaction with neighboring proton. The methine proton in the position C2 of oxazolidine cycle resonates in the range of 4.83 ppm as a singlet. The signals of protons of NCH_2- and OCH_2 groups of morpholine fragment are seen as two triplets in the range of 3.13 and 3.74 ppm correspondingly. The ratio of integral intensiveness of the signals corresponds to the structure (2).

On the basis of spectroscopic study of the structure of obtained oxazolidine (2) and literature [5–8], it can be claimed that when *d*-treo-2-methylamino-1-phenyl-1-propanol (alkaloid of *d*-pseudoethedrine) interacts with 4-morpholyl-benzaldehyde the oxazolidine (2) of *S*-configuration of C2 atom of oxazolidine cycle (1) is formed. It can most likely be the result of thermodynamic control of cyclization process, i.e. under conditions studied 2*R*-stereoisomers are sterically less favorable.

The conclusion

So, on the basis of *d*-treo-2-methylamino-1-phenyl-1-propanol (alkaloid of *d*-pseudoephedrine) a novel heterocyclic compound — 4-(4-((*4R,5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)phenyl)morpholine (2) was obtained. It is quite promising substance for investigation of conformational features of the structure as well as its biological properties. The structure of the compound is proved by data obtained by IR- and ^{1}H NMR-spectroscopy. Also comparative study of the influence of convectional and microwave heating on the yield and character of formation of the final product was carried out.

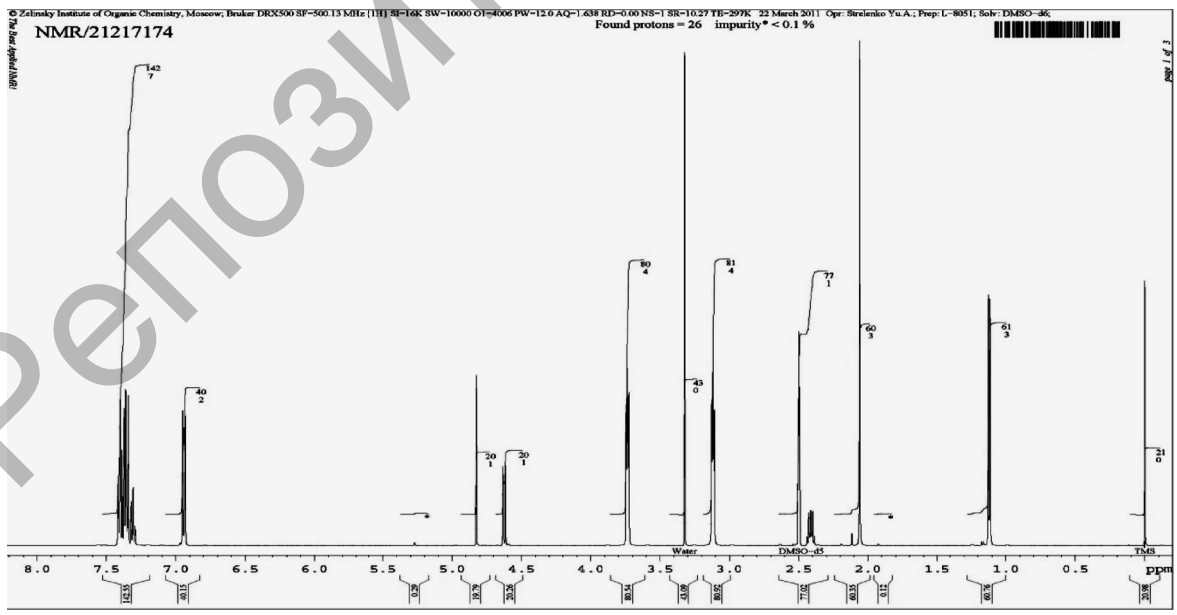


Figure. ^{1}H NMR-spectra of 4-(4-((*4R, 5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)phenyl)morpholine (2)

Experimental part

^{1}H NMR-spectra were recorded on spectrometer Bruker DRX500 with the frequency of 500 MHz in DMSO-d_6 of relativity internal standard of tetramethylsilane. IR-spectra were made by Fourier transform spectrometer «AVATAR-320» in a pill with KBr. Mass-spectrum was made on FINNIGAN MAT.INCOS 50 by direct introduction of the substance with the ionization energy of 70 eV. Melting temperature was determined on «Boetius». TLC analysis was made on «Sorbfil» plates, manifestation by iodine vapors.

4-(4-((*4R,5R*)-3,4-dimethyl-5-phenyloxazolidine-2-yl)phenyl)morpholine (2) in the classical conditions. The mixture of 0.68 g (0.004 moles) of *d*-treo-2-methylamino-1-phenyl-1-propanol and 0.78 g (0.004 moles) of 4-morpholyl-benzaldehyde in 30 ml of absolute benzene had been boiling for 2 hours with azeotropic distillation which is formed during the reaction of water. After finishing the reaction the solvent had been evaporated and the residue was passed through the column with aluminium oxide Al_2O_3, where the eluent is benzene.

After evaporation of the solvent the residue was crystallized and 0.97 g of the product (2) was obtained with melting point at 133–134 ºC.

The synthesis (2) under the condition of microwave radiation. 0.68 g (0.004 moles) of *d*-treo-2-methylamino-1-phenyl-1-propanol and 0.78 g (0.004 moles) of 4-morpholyl-benzaldehyde in 30 ml of absolute toluene were put into 100 ml volume cone flask and 1–2 drops of formic acid were added. The reaction mixture was subjected to microwave radiation within 15–20 minutes at 500 Wt. The resulting precipitate was filtered, washed with toluene and dried at room temperature. The compound was recrystallized from the mixture of benzene – 2-propanol (2:1). 1.29 g (96 %) of the product with melting point at 133–134 ºC was obtained. ^{1}H NMR δ, ppm: 1.12 d (3H, CH_3-C, J_{HH} 7.2 Hz), 2.06 s (3H, CH_3-N), 2.42 m (1H, CH-N), 3.12 t (2H, $\underline{CH_2}CH_2$), 3.74 t (2H, $CH_2\underline{CH_2}$), 4.63 d (1H, CH-O, J_{HH} 7.4 Hz), 4.82 s (1H, CH-Ar), 6.94 d (1H, CH_{ar}, J_{HH} 7.6 Hz), 7.38 d (1H, CH_{ar}), 7.28–7.42 m (5H, C_6H_5). Found, %: C 74.59; H 7.80; N 8. 34. $C_{21}H_{26}N_2O_2$. Calculated, %: C 74.52; H 7.74; N 8.28.

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Конвекционды жылыту мен микротолқынды активация шарттарында *d*-трео-2-метиламино-1-фенил-1-пропанолының 4-морфолилбензальдегидімен өзара әсерлесуі

Мақалада *d*-трео-2-метиламино-1-фенил-1-пропанол мен 4-морфолилбензальдегидті конвекционды қыздыру және микротолқынды белсендендіру жағдайында әрекеттестіру арқылы алынған 1,3-оксазолидинді синтездеудің шамалары көрсетілген. Екі әдіспен алынған оксазолидиннің физика-химиялық тұрақтылары ұқсас болып шықты. Алынған 4-(4-((*4R,5R*)-3,4-диметил-5-фенилоксазолидин-2-ил)-фенил)морфолин құрылымының конформационды ерекшеліктері және де биологиялық қасиеттері болашағы зор болып табылады. Сонымен қатар шығым мен ақырғы өнімнің түзілу сипатына конвекционды және микротолқынды қыздырудың әсері салыстырмалы түрде зерттелді. 4-(4-((*4R,5R*)-3,4-диметил-5-фенилоксазолидин-2-ил)фенил)морфолин жаңа гетероциклдық қоспасының құрылымы ИҚ- мен ЯМР ^{1}Н-спектроскопия жолымен дәлелденді.

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Взаимодействие *d*-трео-2-метиламино-1-фенил-1-пропанола с 4-морфолилбензальдегидом в условиях конвекционного нагрева и микроволновой активации

В статье приведены данные по синтезу 1,3-оксазолидина взаимодействием *d*-трео-2-метиламино-1-фенил-1-пропанола с 4-морфолилбензальдегидом в условиях конвекционного нагрева и микроволновой активации. Показано, что физико-химические константы 1,3-оксазолидина, полученного обоими методами, оказались идентичными. Полученный 4-(4-((*4R,5R*)-3,4-диметил-5-фенилоксазолидин-2-ил)фенил)морфолин является весьма перспективным в плане изучения как конформационных особенностей строения, так и биологических свойств. Проведено сравнительное изучение влияния конвекционного и микроволнового нагревов на выход и характер образования конечного продукта. Строение 4-(4-((*4R,5R*)-3,4-диметил-5-фенилоксазолидин-2-ил)фенил)морфолина доказано данными ИК- и ЯМР ^{1}Н-спектроскопии.