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SYNTHESIS OF 2-MORPHOLINOETHANOL AND ITS DERIVATIVES

Annotation. Analysis of literature data in recent years indicates that morpholine and its derivatives are of considerable interest as potential bioactive compounds. This paper presents data on methods of analysis and synthesis of new morpholine derivatives which are of interest for further research. As a result of alkylation reaction of morpholine with ethylene chlorohydrin were synthesized 2-morpholinoethanol (II) with a fairly high yield (92%). During the reaction of 2-morpholinoethanol (II) with epichlorohydrin in the presence of boron trifluorideetherate,it was obtained 1-chloro-3-(2-morpholinoethoxy) propan-2-ol (III). Dehydrochlorination of compound (III) in an alkaline environment led to 4-(2-(oxirane-2-ylmethoxy)ethyl)morpholine (IV). As a result of the alkylation of the compound (IV) with pyperidine was synthesized 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (V). The structure of the synthesized compounds was confirmed by IR and NMR spectra and elemental analysis. The synthesized compounds areof interest for further study of the biological activity.

Key words: morpholine, piperidine, alkylation reaction, aminoalcohols, chlorohydrins, biological activity.

Morpholine derivatives have a broad spectrum of biological activity and are part of many drug substances [1].

The continued interest in the chemistry of morpholine, as well as its derivatives (alcohols, oxides, esters, hydrazides, thiosemicarbazides), is associated with the study of theoretical questions of organic chemistry: stereochemical regularities, relationship between the fine chemical structure and bioactivity, as well as the possibility of using morpholine derivatives as structural units for targeted synthesis of biologically active compounds.

The presence of various functional groups in the morpholine cycle allows to use morpholine as basic synthon in organic synthesis and to regard its derivatives as potential precursors of biologically active compounds. Having multiple electrophilic centers with different activity involves numerous options for interaction of such compounds with nucleophiles.

In development of our research on the synthesis of biologically active substances and practically useful materials, one of the areas of chemical modification of morpholine derivatives is working out a scheme of synthesis of new derivatives with fragments of morpholine, piperidine, diethanolamine, alcohols, ethers, oxides, esters, hydrazides and thiosemicarbazides.

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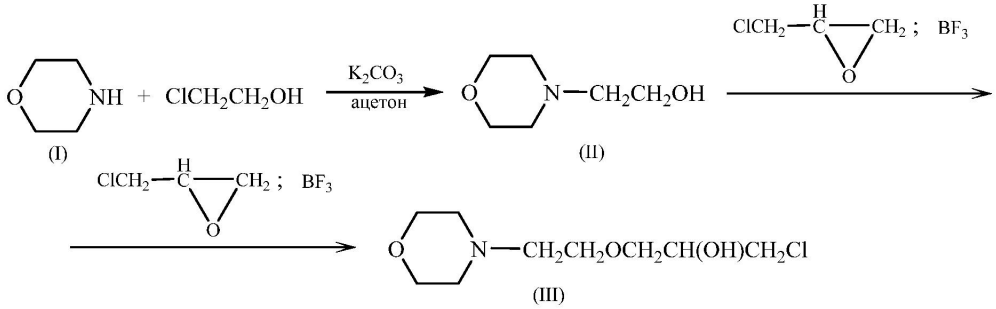


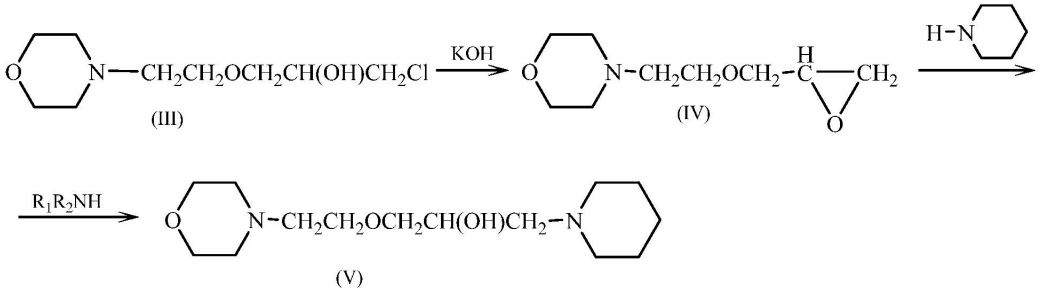
Since having a high reactivity of aminoalcohols [2], by alkylation of morpholine (I) ethylenechlorohydrine we have synthesized 2-morpholinoethanol (II). The output of this compound is very high (92%), which involves the use of this compound (II) as a synthon for further syntheses.

In the IR spectrum of 2-morpholinoethanol (II) it was revealed absorption bands at 3400-3450 cm^{-1} typical of HO-groups. The characteristic absorption band of C-O-C morpholine cycle manifested as intensive peak at 1110 cm^{-1}.

In the PMR spectrum of the compound (II) morpholine ring protons resonate as triplets at 2.35 and 3.65 ppm. Protons atC_2 and C_6 carbon atoms are shown at 2.35 ppm as fourprotonic triplet, and the protons at C_3 and C_5 carbon atoms, due to the influence of oxygen atoms, are displaced in the area of weaker fields and prescribed at 3.65 ppm. Protons of N-CH_2 and -CH_2 -O fragments resonate as triplets at 2.50 and 3.45 ppm. Protons of OH-group appear as a one proton singlet at 3.75 ppm area.

It was established that the compound (II) is reacted with epichlorohydrin in the presence of boron trifluorideetherate to form 1-chloro-3-(2-morpholinoethoxy) propan-2-ol (III).

In the IR spectrum of 1-chloro-3-(2-morpholinoethoxy)propan-2-ol (III) it is stored in the absorption band of 3400-3450 cm^{-1} typical for the OH bond. Absorption bands are observed at 1720 cm^{-1} characteristic for an ether linkage, and the absorption band of 1122 cm^{-1} refers to the stretching vibrations of morpholin cycle of C-O-C group.



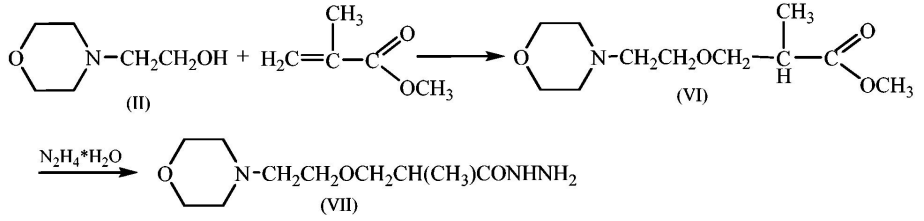
It is known that chlorohydrins are dehydrochlorinated under alkaline conditions to form oxides. Thus, while stirring and cooling (8-10°C) of 1-chloro-3-(2-morpholinoethoxy)propan-2-ol (III) with powdered potassium hydroxide ite was synthesized 4-(2-(oxirane-2-ylmethoxy)ethyl)morpholine (IV).

In the IR spectrum of compound (IV) it is remained the absorption bands in the area 1710-1720 cm^{-1}, characteristic for ether linkage and also there are absorption bands at 950, 1180 and 3060 cm^{-1}, corresponding to the epoxy group. The characteristic absorption band of C-O-C morpholine cycle is also stored in the 1110 cm^{-1}. The bands characteristic of the HO-group are not observed.

The reaction of epoxy compounds with amines is important as one of the most convenient methods for synthesis of vicinal amino alcohols, used as building blocks in the construction of the natural molecules and biologically active organic compounds [3-5]. Among the various medications there are vicinal amino alcohols and their derivatives with the hydroxyl group and the nitrogen atom, exhibiting various activity [6]. Consequently, the synthesis of new derivatives of vicinal aminoalcohols is relevant, due to the prospect of research in this series of new biologically active substances.

In terms of the known, high bioactivity of amines of heterocyclic series, we conducted the alkylation of 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (IV) with piperidine. The reaction synthesized crystalline compound, namely 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (V).

In the IR spectrum of 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (V) it is not observed the absorption bands characteristic for the epoxy. Characteristic absorption band for C-O-C morpholine cycle in the area 1115 cm^{-1} is reserved. In the spectrum there are absorption bands in the area 1710-1720 cm^{-1} characteristic for the ether linkage and bands appear in the area 3400-3450 cm^{-1} characteristic for the OH bond.



Methyl 2-methyl-3-(2-morpholinoethoxy)propanoate (VI) was synthesized by reacting 2-morpholinoethanol (II) with methyl methacrylate in anhydrous acetone in the presence of potassium carbonate at a temperature 55-60°C.

In the IR spectrum of the compound (VI) there is a characteristic absorption band of the stretching vibrations of C=O groups of ester in the area 1735 cm^{-1} and the absorption band of C-O-C group in the area 1245 cm^{-1}.

Further, we synthesized 2-methyl-3-(-morpholinoethoxy)propanohydrazide (VII) by reacting methyl 2-methyl-3-(2-morpholinoethoxy)propanoate (VI) with hydrazine hydrate in ethanol medium during 2 hours at 75-80°C.

In the IR spectrum of the compound (VII) there is a characteristic absorption band of the stretching vibrations of NH_2 group in the area 3310-3260 cm^{-1}, of NH group in the area 3180 cm^{-1}, and the absorption band of carbonyl C=O group in the area 1665 cm^{-1} remains.

In the PMR spectrum of 2-methyl-3-(-morpholinoethoxy)propanohydrazide (VII) all protons correspond to expected values of chemical shifts. Methylene protons of morpholino fragment resonate at 2.2 and 3.5 ppm and 2.5-3.6 ppm (protons of >N-CH_2-, -CH_2-O, O-CH_2- fragments). Proton signals of hydrazide groups are located in the area 8.3 ppm for NH and 3.7 ppm for NH_2.

Experimental procedure

Control of reactions and purity of the synthesized compounds was performed by TLC on Silufol UV-254 plates (developed with iodine vapor). IR spectra of synthesized compounds were recorded by Specord 75 IR spectrometer as thin layer in KBr tablet, in vaseline oil, in chloroform solutions and carbon tetrachloride. PMR spectra were recorded by Bruker WM 250 and Bruker DRX 500 spectrometers operating at 250, 500 MHz, at 25°C. HMDS internal standard, CD3OD, DMSO-d_6 solvents, chemical shifts of protons are expressed in scale δ, ppm

Synthesis of 2-morpholinoethanol (II)

A mixture of 8.7 g (0.1 mole) of morpholine (I), 8.86 g (0.11 mol) of ethylenechlorohydrine, 21 g (0.15 mol) of potassium carbonate with stirring is heated in acetone (abs.) for 6-8 hours at temperature 55-60°C. The solution was cooled, the potassium bromide is separated, which is washed with anh. acetone. Acetone is distilled off, the residue is distilled to get 10.61 g (81%) of 2-morpholinoethanol (II) with b.p. 187°C / 2 mmHg, $n^{20}d$=1.4760.

Synthesis of 1-chloro-3-(2-morpholinoethoxy)propan-2-ol (III)

To 26.2 g (0.2 mol) of 2-morpholinoethanol (II), containing 0.2 ml of boron trifluorideetherate, with stirring and cooling (0-5°C) it was added 8 g (0.086 mol) of epichlorohydrin. The reaction mixture was stirred for 5 hours at 25°C. It was isolated by vacuum distillation 31.22g (70%) of 1-chloro-3-(2-morpholinoethoxy)propan-2-ol (III) with b.p. 174oC/4 mmHg, $n^{20}d$=1.4635.

Synthesis of 4-(2-((3-chlorooxirane-2-yl)methoxy)ethyl)morpholine (IV)

To 11.5 g (0.05 mol) of a solution of 1-chloro-3-(2-morpholinoethoxy)propan-2-ol (III) at 60 ml of ether under stirring and cooling (8-10°C) it was added 8.4 g (0.15 mol) of powdered potassium hydroxide. The reaction mass was stirred another 2 hours at 12-14°C. After the usual treatment, distillation of the

solvent and vacuum distillation it was isolated 7.51 g (68%) of 4-(2-((3-chlorooxirane-2-yl)methoxy)ethyl)morpholine (IV) with b.p. 180°C / 2 mmHg, n20d=1.4210.

Synthesis of 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (V)

To 6.63 g (0.03 mol) of solution of 4-(2-((3-chlorooxirane-2-yl)methoxy)ethyl)morpholine (IV) in 60 ml of absolute ethanol it was added with stirring 2.55 g (0.03 mol) of piperidine and 4.55 g of (0.03 mole) of potassium carbonate. The reaction mass was stirred for 6 hours at 70-80°C. After recrystallization, from ethyl alcohol it was obtained 5.71 g (70%) of 1-(2-morpholinoethoxy)-3-(piperidin-1-yl)propan-2-ol (V) with f.p. 120-122°C.

Synthesis of methyl 2-methyl-3-(2-morpholinoethoxy)propanoate (VI)

To the mixture of 13.1 g (0.1 m) of 2-morpholinoethanol (II) and 21 g (0.15 m) of calcined potassium carbonate in 200 ml of anh. acetone it was added 11.0 g (0.11 m) of freshly distilled methyl methacrylate. The reaction is conducted at a temperature 55-60°C during 8 hours. The solvent was evaporated and the residue was dispersed. It was obtained 18.48 g (83%) of methyl 2-methyl-3-(2-morpholinoethoxy)propanoate (VI) with b.p. 93°C / 5 mmHg, $n^{20}d$=1.4115.

Synthesis of 2-methyl-3-(-morpholinoethoxy)propanohydrazide (VII)

A mixture of 23.1 g (0.1m) of methyl 2-methyl-3-(2-morpholinoethoxy)propanoate (VI), 6 g (0.12 m) of hydrazine hydrate (100%) in ethanol is heated during 2 hours at temperature 75-80oC. After the reaction, ethanol was distilled off. The product is a viscous, oily substance, which was used for further synthesis without purification. It was obtained 20.10 g (87%) of 2-methyl-3-(-morpholinoethoxy)-propanohydrazide (VII).

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2-МОРФОЛИНОЭТАНОЛДЫҢ ЖӘНЕ ОНЫҢ ТУЫНДЫЛАРЫНЫҢ СИНТЕЗІ

Аннотация.Соңғы жылдардың әдебиеттерінен алынған мәліметтерді талдау арқылы морфолин мен оның туындылары жақсы биологиялық активтілік көрсететіні анықталды. Бұл жұмыста әрі қарайғы зерттеулерде маңызды болып табылатын жаңа морфолин туындыларын алудың әдістемелері келтірілген. Морфолиннің этиленхлоргидринмен алкилденуі нәтижесінде 2-морфолиноэтанолдың (II) жоғары шығыммен (92%) синтезі жүргізілді. 2-Морфолиноэтанолдың (II) эпихлоргидринмен үшфторлы бор эфираты қатысында әрекеттесуінен 1-хлоро-3-(2-морфолиноэтокси)пропан-2-ол (III) алынды. Қосылысты (III) сілтілік ортада дегидрохлорлаған кезде 4-(2-(оксиран-2-илметокси)этил)морфолин (IV) синтезделді. Осы қосылысты (IV) пиперидинмен алкилдеу нәтижесінде 1-(2-морфолиноэтокси)-3-(пиперидин-1-ил)пропан-2-ол (V) синтезделді. Синтезделген қосылыстардың құрылыстары ИК-, ПМР спектрлермен және элементтік анализ нәтижелерімен дәлелденді. Синтезделген қосылыстар әрі қарай биологиялық активтіліктерін зерттеуді қажет етеді.

Түйін сөздер: морфолин, пиперидин, алкилдеу реакциясы, аминоспирттер, хлоргидринер, биологиялық активтілік.

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СИНТЕЗ 2-МОРФОЛИНОЭТАНОЛА И ЕГО ПРОИЗВОДНЫХ

Аннотация. Анализ литературных данных за последние годы свидетельствует о том, что морфолин и его производные представляют значительный интерес в качестве потенциальных биологически активных соединений. В настоящей работе приведены данные о методах синтеза и анализа новых производных морфолина, которые представляют интерес для дальнейших исследований. В результате реакции алкилированияэтиленхлоргидриномморфолина осуществлен синтез 2-морфолиноэтанола (II) с довольно высоким выходом (92%). При взаимодействии 2-морфолиноэтанола (II) с эпихлоргидрином в присутствии эфирата трехфтористого бора 1-хлоро-3-(2-морфолиноэтокси)пропан-2-ола (III). Дегидрохлорирование соединения (III) в щелочной средепривело к 4-(2-(оксиран-2-илметокси)этил)морфолин (IV). А в результате алкилирования данного соединения (IV) пиперидином синтезирован 1-(2-морфолиноэтокси)-3-(пиперидин-1-ил)пропан-2-ол (V). Структура синтезированных соединений подтверждена данными ИК-, ПМР-спектров и данных элементного анализа. Синтезированные соединения представляют интерес для дальнейшего исследования биологической активности.

Ключевые слова: морфолин, пиперидин, реакция алкилирования, аминоспирты, хлоргидрины, биологическая активность.