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SYNTHESIS AND PROPERTIES OF *N*-(2-ETHOXYETHYL) PIPERIDINE DERIVATIVES OF ANABASINE

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The synthesis and pharmacological activity of ethers of 1-(2-ethoxyethyl)-4-[3-anabasin-1-yl-1-prop-1-ynyl]piperidin-4-ol were described.

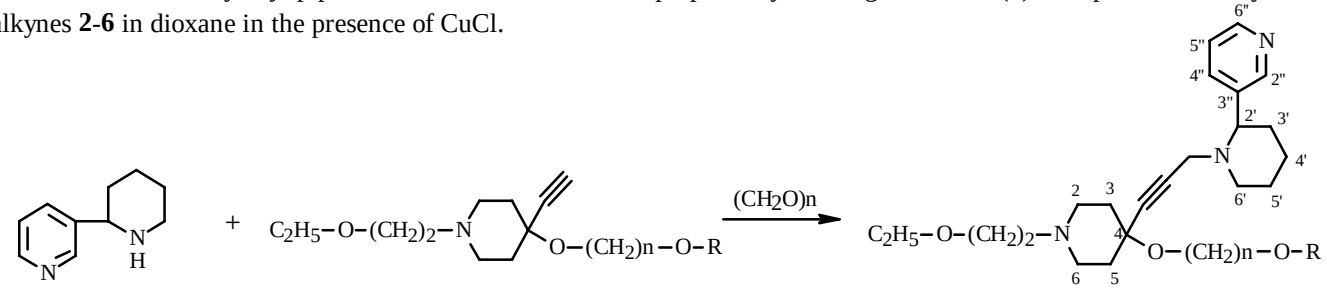
Key words: anabasine, Mannich reaction, ethers, propargylamines.

Combining different pharmacophores in a single molecule is interesting for studying their mutual effect on the biological activity of the resulting compounds. In this respect, anabasine, acetylenic alcohols, and propargylamines are important building blocks. Depending on the structure, anabasine derivatives exhibit various pharmacological activities [1-3]. At present the most promising lead compounds are found among piperidine derivatives that contain the common structural moiety *N*-ethoxyethylpiperidine, which indicates that the ethoxyethyl substituent plays a key role in producing the biological activity [4, 5].

We previously modified *N*-ethoxyethyl-4-ethynyl-4-hydroxypiperidine at the hydroxyl group by adding an additional alkoxy- or phenoxyalkyl substituent through a Williamson reaction [6]. Converting the hydroxyl to an ether in piperidine is known to produce compounds with high biological activity. Preparations synthesized from 4-aryloxypiperidines are used widely in medical therapy to treat depression and allergy [7-9]. Furthermore, compounds with anti-tuberculosis activity are found among ethers of 4-hydroxypiperidine [10]. Alkoxy- and phenoxyalkyl ethers of *N*-ethoxyethyl-4-ethynyl-4-hydroxypiperidine exhibited *in vitro* analgesic, spasmolytic, and other activities [6].

Herein we present results from a study of the structure—activity relationship of such molecules modified at the acetylene hydrogen to form propargylamines containing anabasine. Propargylamines are important synthetic intermediates for the synthesis of various nitrogenous compounds and components of many biologically active compounds [11, 12].

One of the most important and common methods for synthesizing propargylamines is the Mannich reaction. Anabasine derivatives of dialkoxyalkyl piperidine derivatives **7-11** were prepared by reacting anabasine (**1**) with paraformaldehyde and alkynes **2-6** in dioxane in the presence of CuCl.



1 **2 - 6** **7 - 11**

	2, 7	**3, 8**	**4, 9**	**5, 10**	**6, 11**
R	Me	Et	Ph	Ph	Ph
n	2	2	2	3	4

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TABLE 1. Spasmolytic Activity and Acute Toxicity of New Piperidine Derivatives (1 mg/mL Medium)*

Compound	Intestinal contraction after administration of new compound		LD_{50}, mg/kg
	acetylcholine, mm (M ± m)	$CaCl_2$ solution (10%), mm (M ± m)	
ICC-**12**	2.0±0.1	2.1±0.3	175.0±14.40
ICC-**13**	3.9±0.4	2.1±0.1	390.0±44.10
ICC-**14**	3.0±0.3	1.0±0.1	460.0±56.40
ICC-**15**	1.0±0.1	0.0±0.0	175.0±14.40
ICC-**16**	5.2±0.3	0.0±0.0	700.0
Drotaverine	0.0±0.0	0.0±0.0	66.0±12.10
Euphyllin	0.0±0.0	0.0±0.0	240.0±17.21
Acetylcholine	5.0		
$CaCl_2$		2.5	

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Intestinal contraction after administration of new compound, mm (M ± m), 0.

Propargylanabasines were prepared in high yield (85-93%). The structures of the new compounds were established using elemental analysis and IR and NMR spectroscopy. The IR spectra of the new compounds lacked an absorption band for the stretching vibrations of the acetylene hydrogen ≡C–H at 3230-3245 cm^{-1}, which was characteristic of starting compounds **2**-**6**. Absorption bands for stretching of the phenyl ring were observed at 1600, 1496, and 1472 cm^{-1} (C=C) and 3040 (ArH) for **9**-**11**. The ^{13}C NMR and PMR spectra were most informative for establishing the structures.

A doublet for H-2″ appeared at 8.56 ppm in the PMR of **7**-**11**. Next to it at 8.51 ppm, a doublet of doublets for H-6″ appeared. Proton H-4″ gave a doublet of triplets at 7.68 ppm; H-5″, a doublet of doublets at 7.25 ppm. The methine proton of anabasine at the bonding site to pyridine and piperidine (H-$2'_{ax}$) gave a doublet of doublets at 3.33 ppm. The equatorial proton in the 6′-position appeared as a broad doublet at 2.92 ppm. The resonance of axial proton H-6′ overlapped those of four ring protons and the triplet from two protons of the methylene that were located on the nitrogen of the *N*-ethoxyethylpiperidine. A multiplet for the two H-5′ protons, equatorial H-3′ and H-4′ protons, and ring protons H-3 and H-5 of the *N*-ethoxyethylpiperidine was found at 1.66-2.02 ppm. Axial proton H-3′ appeared as a quartet of doublets at 1.58 ppm; axial proton H-4′, a quartet of triplets at 1.35 ppm. Methylene protons of the ≡C–CH_2 group appeared as a doublet at 3.18 ppm.

The synthesized compounds were thick oils. Their solid complexes with β-cyclodextrin (β-CD) were prepared in order to conduct the pharmacological studies. β-CD is especially interesting as a drug carrier over other complexants because it is very stable and has a large cavity diameter. In addition, test animals show good tolerance to β-CD drug forms [13]. Complexation increases the stability of drugs by protecting them from hydrolysis, oxidation, dehydration, and evaporation; improving the molecular dispersion and solubility, including in water; making them biologically available and pharmacologically active while masking the odor and taste; transforming liquids into crystalline forms; and decreasing their toxicity.

Ethers of 1-(2-ethoxyethyl)-4-[3-anabasin-1-yl-1-prop-1-ynyl]piperidin-4-ol (**7**-**11**) and β-CD were used in equimolar amounts in order to prepare the inclusion complexes.

The inclusion complexes of the ethers (**12**-**16**) with β-CD (ICC-**12**-**16**) were tested for spasmolytic and antibacterial activities and acute toxicity.

We used white mongrel mice of both sexes (17-23 g). Spasmolytic activity was studied using spasm in isolated slices of mouse small intestine elicited by acetylcholine and $CaCl_2$ (Table 1). Pharmacological tests showed that the LD_{50} of these preparations fell in the range 175-700 mg/kg whereas the LD_{50} of drotaverine (no-shpa) was 66 mg/kg; of euphyllin (aminophyllin), 240.0 mg/kg. These results indicate that ICC-**12**-**16** are significantly less toxic than no-shpa although ICC **16** and ICC **15** are more toxic than euphyllin. The spasmolytic activity was highest for aromatic ethers **14**-**16**, with **15** and **16** completely suppressing spasm elicited by $CaCl_2$. Compound **15** was also active for the acetylcholine spasm model.

The studied preparations did not exhibit antibacterial activity and did not affect the growth of gram-positive (staphyllococcus) and gram-negative (*E. coli* and salmonella) microorganisms in meat-peptone bullion.

Thus, modification of anabasine produced new compounds that were several times less toxic than anabasine (LD_{50} 39.0 mg/kg) and exhibited spasmolytic activity. Ethers of 1-(2-ethoxyethyl)-4-[3-anabasin-1-yl-1-prop-1-ynyl]piperidin-4-ol

include a reactive center, the –C≡C– triple bond, that can be further modified and can improve or change the pharmacological activity of the molecule.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Al_2O_3 (activity II) with development by I_2 vapor. Column chromatography was carried out over Al_2O_3 (activity II) with elution by Et_2O:hexane (10:1). IR spectra of thin layers were recorded on a Nicolet 5700 FT-IR spectrometer. ^{13}C NMR and PMR spectra in $CDCl_3$ were recorded on a Mercury-300 (Varian) spectrometer with HMDS internal standard.

1-(2-Ethoxyethyl)-4-(2-methoxyethoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (7). A suspension of paraformaldehyde (0.1 g, 0.0034 mol) and anabasine (**1**, 0.47 g, 0.0029 mol) in dry dioxane (15 mL) was stirred, treated dropwise with 1-(2-ethoxyethyl)-4-(2-methoxyethoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (**2**, 0.6 g, 0.0024 mol) dissolved in dry dioxane (10 mL), treated with freshly prepared CuCl (0.02 g), stirred at 100°C until the starting material dissolved (~15 min), and cooled. The dioxane was evaporated. The dry solid was dissolved in a small amount of water, treated with HCl solution (15 mL, 1:1) until the pH was ~2, and washed with Et_2O (3×). The pH of the solution was adjusted to ~10 with NaOH solution. The product was extracted several times with hexane. The organic extract was dried over $MgSO_4$. The desiccant was filtered off. The filtrate was evaporated. The product was purified from side products by column chromatography (Al_2O_3, activity II, Et_2O:hexane, 10:1) to afford **7** (0.98 g, 97.1%) as an oil.

IR spectrum (KBr, ν, cm^{-1}): 1101 (C–O–C). ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 150.2 (C-2″), 148.9 (C-6″), 139.1 (C-3″), 135.0 (C-4″), 123.5 (C-5″), 86.6, 80.5 (C≡C), 72.2 (C-4, C-12), 68.6 (C-8), 66.5 (C-9), 63.1 (C-2′), 62.8 (C-11), 59.0 (C-13), 57.7 (C-7), 53.1 (C-6′), 50.6 (C-2, C-6), 44.4 (≡C–$\underline{C}H_2$), 36.9 (C-3, C-5), 35.9 (C-3′), 26.1 (C-5′), 24.9 (C-4′), 15.2 (C-10, C-14).

1-(2-Ethoxyethyl)-4-(2-ethoxyethoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (8) was prepared by the above method from **3** (0.4 g, 0.0015 mol), anabasine (0.29 g, 0.0018 mol), and paraformaldehyde (0.06 g, 0.0018 mol), yield 0.6 g (91.0%), oil.

IR spectrum (KBr, ν, cm^{-1}): 1101 (C–O–C). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.57 (1H, d, J = 1.3, H-2″), 8.51 (1H, dd, J = 3.8; 1.1, H-6″), 7.68 (1H, dt, J = 5.9; 1.4, H-4″), 7.25 (1H, dd, J = 5.7; 3.5, H-5″), 3.71 (2H, t, CH_2-11), 3.61 (2H, t, CH_2-12), 3.57 (2H, t, CH_2-8), 3.55 (2H, q, CH_2-13), 3.51 (2H, q, CH_2-9), 3.34 (1H, dd, J = 8.5; 2.3, H-2′$_{ax}$), 3.18 (2H, d, J = 9.3, ≡C–CH_2), 2.92 (1H, br.d, J = 8.6, H-6′$_{eq}$), 2.73 (2H, br, H-2,6$_{eq}$), 2.62 (3H, t, CH_2-7, H-6′$_{ax}$), 2.50 (2H, br, H-2,6$_{ax}$), 1.66-2.02 (8H, m, 4H-3,5, H-3′$_{eq}$, H-4′$_{eq}$, 2H-5′), 1.58 (1H, qd, J = 9.9; 3.0, H-3′$_{ax}$), 1.35 (1H, qt, J = 9.6; 3.1, H-4′$_{ax}$), 1.20 (6H, t, CH_3-10, CH_3-14).

^{13}C NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 149.5 (C-2″), 148.9 (C-6″), 139.1 (C-3″), 135.1 (C-4″), 123.6 (C-5″), 80.3, 86.6 (C≡C), 72.0 (C-4), 69.9 (C-12), 68.3 (C-8), 66.7 (C-13), 66.5 (C-9), 63.0 (C-2′), 62.8 (C-11), 57.7 (C-7), 53.1 (C-6′), 50.5 (C-2, C-6), 44.3 (≡C–$\underline{C}H_2$), 36.6 (C-3, C-5), 35.7 (C-3′), 26.0 (C-5′), 24.8 (C-4′), 15.2 (C-10, C-14).

1-(2-Ethoxyethyl)-4-(2-phenyoxyethoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (9) was prepared by the above method from **4** (0.5 g, 0.0016 mol), anabasine (0.26 g, 0.0016 mol), and paraformaldehyde (0.07 g, 0.0022 mol), yield 0.63 g (82.0%), oil.

IR spectrum (KBr, ν, cm^{-1}): 1104 (C–O–C), 1600, 1496 (C=C$_{ar}$), 3034 (C–H$_{ar}$). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.57 (1H, br.s, H-2″), 8.51 (1H, br.s, H-6″), 7.68 (1H, br.d, J = 4.9, H-4″), 7.26 (3H, br.d, 2H$_{ar}$, H-5″), 6.92 (3H, m, H$_{ar}$), 4.15 (2H, t, CH_2-12), 3.90 (2H, t, CH_2-11), 3.57 (2H, t, CH_2-8), 3.51 (2H, q, CH_2-9), 3.34 (1H, br.d, J = 8.1, H-2′$_{ax}$), 3.18 (2H, d, J = 8.1, ≡C–CH_2), 2.92 (1H, br.d, J = 8.0, H-6′$_{eq}$), 2.44-2.80 (7H, m, 4H-2,6, CH_2-7, H-6′$_{ax}$), 1.65-2.05 (8H, m, 4H-3,5, 2H-5′, H-3′$_{eq}$, H-4′$_{eq}$), 1.58 (1H, br.q, J = 9.3, H-3′$_{ax}$), 1.32 (1H, br.q, J = 9.3, H-4′$_{ax}$), 1.20 (3H, t, CH_3-10).

^{13}C NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 158.9 (C$_{ar}$ on O), 149.4 (C-2″), 148.8 (C-6″), 139.0 (C-3″), 135.0 (C-4″), 129.3 (C$_{ar}$-*m*), 123.6 (C-5″), 120.7 (C$_{ar}$-*p*), 114.6 (C$_{ar}$-*o*), 80.5, 86.6 (C≡C), 72.2 (C-4), 68.3 (C-8), 67.3 (C-12), 66.4 (C-9), 63.0 (C-2′), 62.0 (C-11), 57.7 (C-7), 53.0 (C-6′), 50.3 (C-2, C-6), 44.3 (≡C–$\underline{C}H_2$), 36.6 (C-3, C-5), 35.6 (C-3′), 25.9 (C-5′), 24.7 (C-4′), 15.1 (C-10).

1-(2-Ethoxyethyl)-4-(3-phenoxypropoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (10) was prepared by the above method from **5** (0.5 g, 0.0015 mol), anabasine (0.24 g, 0.0015 mol), and paraformaldehyde (0.06 g, 0.0021 mol), yield 0.6 g (78.7%), oil.

IR spectrum (KBr, ν, cm $^{-1}$): 1103 (C–O–C), 1497, 1600 (C=C_{ar}), 3063 (C–H_{ar}). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.56 (1H, br.s, H-2″), 8.50 (1H, br.d, J = 2.1, H-6″), 7.67 (1H, br.d, J = 7.5, H-4″), 7.23 (3H, m, 2H_{ar}, H-5″), 6.87 (3H, m, H_{ar}), 4.06 (2H, t, CH_2-13), 3.71 (2H, t, CH_2-11), 3.55 (2H, t, CH_2-8), 3.48 (2H, q, CH_2-9), 3.31 (1H, dd, J = 10.8; 2.4, H-2′$_{ax}$), 3.12 (2H, d, J = 6.2, ≡C–CH_2), 2.88 (1H, br.d, J = 11.5, H-6′$_{eq}$), 2.40-2.75 (7H, m, 4H-2,6, CH_2-7, H-6′$_{ax}$), 2.05 (2H, quin, CH_2-12), 1.66-2.00 (8H, m, 4H-3,5, 2H-5′, H-3′$_{eq}$, H-4′$_{eq}$), 1.56 (1H, qd, J = 11.5; 3.0, H-3′$_{ax}$), 1.32 (1H, qt, J = 12.4; 3.8, H-4′$_{ax}$), 1.20 (3H, t, CH_3-10).

^{13}C NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 159.1 (C_{ar} on O), 149.4 (C-2″), 148.8 (C-6″), 139.1 (C-3″), 135.0 (C-4″), 129.3 (C_{ar}-*m*), 123.6 (C-5″), 120.5 (C_{ar}-*p*), 114.4 (C_{ar}-*o*), 80.1, 86.7 (C≡C), 71.5 (C-4), 68.3 (C-8), 66.4 (C-9), 64.7 (C-13), 63.0 (C-2′), 59.5 (C-11), 57.7 (C-7), 53.0 (C-6′), 50.5 (C-2, C-6), 44.2 (≡C–$\underline{C}H_2$), 36.7 (C-3, C-5), 35.6 (C-3′), 30.0 (C-12), 25.9 (C-5′), 24.7 (C-4′), 15.1 (C-10).

1-(2-Ethoxyethyl)-4-(4-phenoxybutoxy)-4-(3-anabasin-1-ylprop-1-ynyl)piperidine (11) was prepared by the above method from **6** (0.5 g, 0.0014 mol), anabasine (0.28 g, 0.0017 mol), and paraformaldehyde (0.06 g, 0.002 mol), yield 0.70 g (93.1%), oil.

IR spectrum (KBr, ν, cm $^{-1}$): 1109 (C–O–C), 1600, 1498 (C=C_{ar}), 3060 (C–H_{ar}). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.55 (1H, br.s, H-2″), 8.50 (1H, dd, J = 4.7; 1.4, H-6″), 7.67 (1H, dm, J = 7.9, H-4″), 7.25 (3H, m, 2H_{ar}, H-5″), 6.89 (3H, m, H_{ar}), 3.98 (2H, t, CH_2-14), 3.60 (2H, t, CH_2-11), 3.56 (2H, t, CH_2-8), 3.50 (2H, q, CH_2-9), 3.33 (1H, dd, J = 11.2; 2.8, H-2′$_{ax}$), 3.17 (2H, d, J = 6.6, ≡C–CH_2), 2.90 (1H, br.d, J = 11.5, H-6′$_{eq}$), 2.44-2.78 (7H, m, 4H-2,6, CH_2-7, H-6′$_{ax}$), 1.66-2.02 (12H, m, 4H-3,5, CH_2-12, CH_2-13, 2H-5′, H-3′$_{eq}$, H-4′$_{eq}$), 1.57 (1H, qd, J = 12.4; 3.4, H-3′$_{ax}$), 1.34 (1H, qt, J = 12.5; 4.2, H-4′$_{ax}$), 1.20 (3H, t, CH_3-10).

^{13}C NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 159.1 (C_{ar} on O), 149.4 (C-2″), 148.8 (C-6″), 139.0 (C-3″), 135.0 (C-4″), 129.3 (C_{ar}-*m*), 123.6 (C-5″), 120.4 (C_{ar}-*p*), 114.4 (C_{ar}-*o*), 80.0, 87.0 (C≡C), 71.5 (C-4), 68.3 (C-8), 67.5 (C-14), 66.4 (C-9), 63.0 (C-2′), 62.6 (C-11), 57.7 (C-7), 53.0 (C-6′), 50.5 (C-2, C-6), 44.3 (≡C–$\underline{C}H_2$), 36.7 (C-3, C-5), 35.6 (C-3′), 26.6 (C-13), 26.3 (C-12), 25.9 (C-5′), 24.7 (C-4′), 15.1 (C-10).

General Method for Preparing Inclusion Complexes of Ethers of 1-(2-Ethoxyethyl)-4-[3-(anabasin-1-yl)-1-prop-1-ynyl]piperidin-4-ol with β-Cyclodextrin (12-16). Solutions of the ether (**7**-**11**, 0.15 g, 0.00038 mol) in ethanol (30 mL) and of β-CD (0.43 g, 0.00038 mol) in distilled water (90 mL) were mixed and placed in a drying chamber. Ethanol and water were evaporated at 50-55°C to afford inclusion complexes **12**-**16** (0.58 g).

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