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One-Pot Synthesis of N-Substituted Alkylaminocyclohexanols by the Addition of Electrophiles Formed *in situ* in the System H_2O_2 + HBr (HCl)

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Abstract—Highly selective one-pot synthesis of N-substituted aminocyclohexanols has been performed by hydroxyhalogenation of the corresponding cyclohexenes with electrophilic reagents formed in situ in the system H_2O_2 + HHlg (Hlg = Cl, Br), with subsequent substitution of halogen atoms with amines. Some products were tested as antimicrobial additives to motor oils and cooling lubricants and showed high antibacterial and antifungal activity.

Keywords: hydroxyhalogenation; electrophilic intermediates; aminocyclohexanols; alicyclic aminoalcohols

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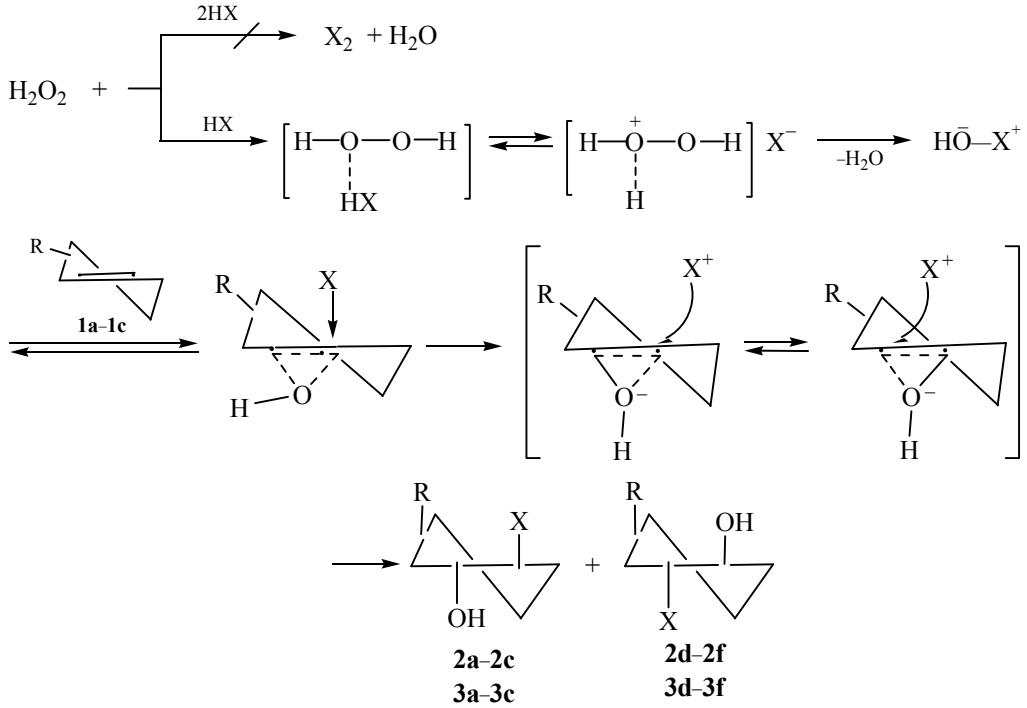
Acyclic aminoalcohols possess unique properties and are used as reagents in the synthesis of numerous analogs of complex natural and biologically active compounds [1–3]. Monocyclic aminoalcohols of cyclohexane series and their N- and O-substituted derivatives are fragments of some synthetic pharmaceuticals possessing sedative, antispasmodic, analgesic, and local anesthetic properties. Thus, a number of vicinal aminoalcohols containing a piperidine motif were used for preparation of widely used multifunctional drugs [4–6]. A general method for the synthesis of cyclic aminoalcohols of a given structure is the aminolysis of epoxide compounds with nitrogen-containing nucleophilic reagents [2]. In this case the synthesis of aminoalcohols is performed by successive epoxidation of cycloolefins with peroxoacids or organic hydroperoxides, isolation of the obtained epoxides, and their reaction with amines in acidic or basic media.

The present article describes the preparation of vicinal aminoalcohols by hydrohyhalogenation of cyclohexene derivatives with electrophilic reagents formed *in situ* in the system H_2O_2–HX (X = Cl, Br) with subsequent treatment of the formed products with primary or secondary amines without isolation from the reaction mixture.

Earlier, we have shown that HCl or HBr solutions of low concentration in the presence of H_2O_2 or NaOCl are effective hydroxyhalogenating reagents for vinyl- and allylacetylene, as well as mono- and bicyclic unsaturated compounds [7–9]. In particular, it was established that alkylcyclohexenes under mild conditions (30–50°C) selectively add electrophiles formed in the system H_2O_2 (or NaOCl)–HX (8–15% aqueous solution), as shown in Scheme 1.

It is known that the course of the oxirane ring opening is determined by conformational effects and the reaction proceeds predominantly in *trans*-diaxial manner. The regularities of electrophilic addition were investigated by the example of the model reaction of 4-methylcyclohexene or 1-(cyclohex-1-en-1-yl)ethan-1-one with a pre-prepared solution of HOX (X = Cl, Br) [7]. According to IR spectroscopy data [2], the addition of HOX to the double bond of cycloolefins occurs to the diaxial *trans* position. The addition of electrophilic halogen in this case is apparently controlled by the location of the substituent and by structural-conformational orientation, similar to the nucleophilic oxirane ring opening according to the Fürst-Plattner rule [2].

Scheme 1.



X= Cl (**2**), Br (**3**); R = 1-CH_3 (**a**, **d**), $COCH_3$ (**b**, **e**), $CH{=}CH_2$ (**c**, **f**).

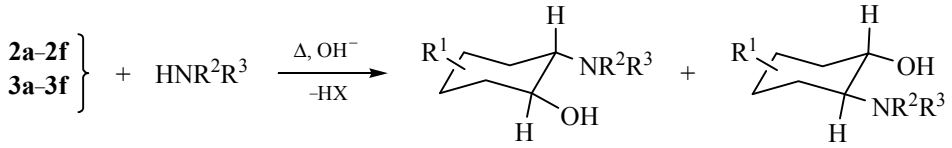
To optimize the reaction conditions, we have studied the dependence of the yield of compounds **2a–2c** and **3a–3c** on the temperature, concentration of aqueous solutions of hydrohalogenic acids, molar ratio of the components, and the rate of stirring of heterogeneous reaction mass. The formation of electrophilic intermediate occur in aqueous phase, while hydroxyhalogenation of cycloolefins, in organic phase or at the boundary between the phases. Without vigorous stirring the transition of electrophilic intermediate from aqueous to organic phase is hindered, which lowers the yield of the target products **2a–2c** and **3a–3c**. Therefore, all experiments were carried out at vigorous stirring.

In the system under investigation the formation of electrophilic intermediates is reversible, while their addition to the double bond of the substrate is irreversible. It is worth noting that no induced hydroxyhalogenation of cycloolefins occurs in the absence of H_2O_2 or NaOCl, since HX does not add to the double bond of the substrate in a dilute solution. The role of H_2O_2 in this reaction consists in intensification of formation of active electrophilic substrate, which then irreversibly adds to the double bond of the substrate until full consumption of the oxidant.

The obtained results show that for molar ratio substrate : HX : H_2O_2 (NaOCl) = 1 : 1–1.5 : 1–5 and the use of 8–15% solutions of hydrohalogenic acids the yields of products **2a–2c** and **3a–3c** are maximal reaching 69–80%. For HCl concentration less than 10% products **2a–2c** and **3a–3c** are not formed. Addition of 3–5 wt % of metal chloride $MeCl_n$ (Me = Na, K, Co; n = 1, 2) increases the yield of the target products by 8–12%. The yield of hydroxyhalides increases when the temperature rises to 30–50°C reaching 72–80.5% for hydroxychlorides and 64–75.4% for hydroxybromides. It is not recommended to increase the temperature above 50°C because of the increased rate of decomposition of the electrophilic intermediate with the formation of molecular chlorine or bromine, and accumulation in the products of the reaction, along with hydroxyhalogenides, of up to 25–35% of dichloro(dibromo)derivatives.

Substitution of halogen atoms by primary or secondary aminogroups in products **2a–2c** and **3a–3c** was performed without isolation from the reaction mixture to afford the corresponding alkylaminocyclohexanols **4a–4e**–**6a–6e** and their isomers **7a–7e**–**9a–9e** (Scheme 2).

Scheme 2.



4a–6e **7a–9e**

R^1 = 1-CH_3 (**4**, **7**), $COCH_3$ (**5**, **8**), $CH{=}CH_2$ (**6**, **9**); $R^2 = R^3 = C_2H_5$ (**a**), $R^2 + R^3 = CH_2CH_2OH$ (**b**), $(–CH_2–)_5$ (**c**), $(–CH_2CH_2–)_2O$ (**d**); R^2 = H, $R^3 = C_6H_5$ (**e**).

The main factors affecting the course of the reaction of hydroxychloro(bromo)derivatives and the yield of N-substituted cyclohexanols are the temperature of the reaction and pH of the medium. At 40–50°C after 3–5 h primary and secondary alkylamines readily enter the reaction of substitution with hydroxychloro(bromo) derivatives **2a–2f** and **3a–3f** with the formation of the corresponding N-substituted cyclohexanols **4a–4e**–**6a–6e** and **7a–7e**–**9a–9e**. The results of investigation of the effect of temperature and pH of the medium on the selectivity of reactions of 2-chloro-1-methylcyclohexan-1-ol **2a** and 1-(1-bromo-2-hydroxycyclohexyl) ethan-1-one **3b** with piperidine are summarized in Table 1. It is clearly seen that the reactions effectively proceed at 40–60°C and the pH of the medium of 9.8–10.2. It is recommended to carry out the reactions of amines with hydroxyhalogenides with excess of amine (1 : 1.5–2.5), which allows to reach a full conversion and simplifies the isolation of the target product.

The course of the reaction strongly depends on the basicity of the medium. At pH above 10.2 the rate of dehydrohalogenation of hydroxyhalides to the corresponding oxiranes increases but the yield of aminoalcohols strongly decreases due to lowering the rate of aminolysis of the latter under these conditions. High yields of aminoalcohols of 92.0–96.4% are reached at pH = 9.8–10.2, the temperature of 50–60°C, and the reaction time 5–6 h. Lowering the pH to 8.0–8.5 notably decreases the rate of condensation because amines form ammonium salts with the formed HBr or HCl.

The selectivity and the yield of aminoalcohols is higher in the reactions of amines with hydroxybromides than with hydroxychlorides.

We have examined the reaction of aminolysis of 3-ethenyl-7-oxabicyclo[4.1.$0^{1,3}$]heptane with piperidine in the temperature range 70–120°C with participation of $MgBr_2$. The highest yield of isomers 4- (**6c**) and 5-ethenyl-2-(piperidin-1-yl)cyclohexan-1-ol (**9c**) is reached at the temperature of 110–120°C and pH 5.5–6.3 (42.5–47.3%). IR and ^{1}H NMR spectra of the synthesized compound practically coincide with those of the product of condensation of 2-bromo-5-ethenylcyclohexan-1-ol **3c** with piperidine.

The oxirane ring opening proceeds regioselectively, by the Krasusky rule [2], with preferable formation of isomer **9c**, **6c** : **9c** = (32–35) : (65–68). In contrast to aminolysis of the aforementioned oxirane, the condensation of 2-bromo-4-ethenylcyclohexan-1-ol **3c**

Table 1. Selectivity and yield of aminoalcohol in the reaction of 2-chloro-2-methylcyclohexan-1-ol (**2a**) and 1-(1-bromo-2-hydroxycyclohexyl)ethan-1-one (**3b**) with piperidine[a]

Exp. no.	*T*, °C	pH	Reaction time, h	Selectivity, %	Yield, %
1	40	8.5	10.0	–	–
2	50	7.5	8.5	–	–
3	60	7.0	7.5	–	–
4	70	7.0	7.0	–	–
5	50	9.8	6.0	97.5/96.0	93.5/92.6
6	60	9.8	6.0	97.3/97.0	94.6/95.4
7	70	9.8	6.0	92/90.5	71.4/70.5
8	60	10.2	6.5	98.0/97.5	96.4/96.6

[a] Molar ratio 1 : (1.1–1.2), 0.05 mol/L (**2a**), 0.05 mol/L (**3b**), 50 mL of propan-2-ol, K_2CO_3

Table 2. Antimicrobial properties of the synthesized N-substituted cyclohexanols[a]

Comp. no.	Concentration, wt %	Diameter of inhibition zone, cm			
		Oil M-10		Azerol-5	
		bacteria mixture	fungi mixture	bacteria mixture	fungi mixture
6a	1.0	++	1.4–1.6	1.2–1.2	1.6–1.8
	0.5	++	1.3–1.5	++	1.4–1.6
	0.25	++	++	++	1.0–1.2
6b	1.0	0.7–0.9	1.4–1.2	2.0–2.2	++
	0.5	++	1.2–1.3	1.4–1.6	++
	0.25	++	++	1.2–1.2	++
6c	1.0	0.8–0.6	1.6–1.8	2.0–2.2	1.4–1.6
	0.5	0.6–0.6	++	1.8–2.0	1.2–1.4
	0.25	++	++	1.2–1.4	1.0–1.0
6d	1.0	1.0–0.8	2.0–2.0	2.2–2.4	++
	0.5	0.8–0.8	1.6–1.8	2.0–1.8	++
	0.25	++	1.2–1.4	1.4–1.6	++
6e	1.0	2.0–1.8	1.8–1.6	1.4–1.6	1.2–1.4
	0.5	1.3–1.7	1.1–1.3	1.2–1.4	1.0–1.2
	0.25	0.8–0.6	0.8–0.8	1.0–0.8	++

[a] ("+") full absence of the zone of inhibition of microorganisms growth.

with piperidine leads predominantly to another isomer. The ratio **6c** : **9c** = (84–87) : (13–16) practically corresponds to the isomeric ratio of the original halohydrine.

The synthesized N-alkylderivatives of alkylcyclohexanols were tested as antimicrobial additives to motor oils M8, M10 and emulsion cooling lubricant Azerol-5, which are not bioresistant. The obtained results show that some representatives of this class of compounds (**6a–6e**) in concentration of 1.0–0.25% demonstrate the activity and protecting properties (Table 2).

EXPERIMENTAL

IR spectra of the synthesized compounds were taken on a Fourier spectrometer Alpha in the range 400–4000 cm^{-1} from suspensions in mineral oil or KBr pellets. ^1H and ^{13}C NMR spectra were registered on a Bruker 300 spectrometer with working frequency 300.18 MHz (^1H) in $CDCl_3$, internal reference HMDS. Elemental analysis was performed on a TruSpes Micro Leco Corporation analyzer (USA). GC analysis was done on a Tsvet-100 chromatograph, detector: katharometer, column 2000×4 mm, 10% poly(ethylene glycol succinate) on Chromasorb W, gas-carrier helium, oven temperature 150°C.

1-Methylcyclohexene was obtained by dehydration of 2-methylcyclohexanol-1 at 220–250°C over γ-Al_2O_3 and careful rectification of the product. 1-Cyclohexenylethanone was prepared by acylation of cyclohexene with acetyl chloride [7], 4-vinylcyclohexene, by dimerization of buta-1,3-diene by the known procedure [10]. Commercially available amines (Alfa Aesar) were used. Hydroxychloro(bromo)alkylcyclohexanes were obtained by the earlier elaborated procedure [7–9].

From the GC analysis, the products of the reaction of hydroxyhalogenation of cyclohexene derivatives and of aminolysis of chloro(bromo)hydroxyhalogenides are the corresponding mixtures of two isomers **2a–2c**, **2d–2f** and **3a–3c**, **3d–3f**, **4a–6e** and **7a–9e**. The isomeric composition was determined by GC analysis.

2-Chloro-1(2)-methylcyclohexan-1-ol (2a, 2d) was obtained from 9.6 g (0.1 mol) of 1-methylcyclohex-1-ene **(1a)**. Yield 11 g (74.1%), the ratio of isomers **2a** : **2d** = 84 : 16, bp 110–112°C (10 mmHg). IR spectrum, ν, cm^{-1}: 3486 (OH), 2950 (CH_2), 2870 (CH_3), 1460 (CH_2), 1115 (OH), 780, 760 (CCl). ^1H NMR spectrum, δ, ppm: 1.41–1.78 m (8H, H^{3-6}), 1.65 s (3H, CH_3, **2a**), 1.27 s (3H, CH_3, **2d**), 4.46 t (1H, HCCl, J = 7.2 Hz, **2a**), 3.46 t (1H, HCOH, J = 7.1 Hz, **2d**), 3.62 br.s (1H, $HOCCH_3$, **2a**), 3.55 br.s (1H, HCOH, **2d**). ^{13}C NMR spectrum, δ_C, ppm: 83.0 (C^1), 72.4 (C^2), 37.4 (C^3), 30.7 (CH_3), 28.9 (C^6), 23.7 (C^5), 22.4 (C^4). Found, % C 56.35; H 8.86; Cl 23.77. $C_7H_{13}ClO$. Calculated, %: C 56.56; H 8.75; Cl 23.91.

2-Bromo-1(2)-methylcyclohexan-1-ol (3a, 3d) was prepared from 9.6 g (0.1 mol) of 1-methylcyclohex-1-ene **1a**. Yield 13.6 g (69.9%), the ratio of isomers **3a : 3d** = 82 : 18. bp 100–102.6°C (2 mmHg). Found, %: C 43.25; H 6.86; Br 41.21. $C_7H_{13}BrO$. Calculated, %: C 43.52; H 6.74; Br 41.45.

1-[2(1)-Chloro-1(2)-hydroxycyclohexyl]ethan-1-one (2b, 2e) was prepared from 3.1 g (25 mmol) of 1-(cyclohexenyl)ethan-1-one **1b**. Yield 3.2 g (72.6%), the ratio of isomers **2b : 2e** = 75 : 25, mp 73–75°C, bp 129–131°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3465 (OH), 2960 (CH_2), 2855 (CH_3), 1731 (C=O), 1450 (CH_2), 1100 (OH) 780, 760 (CCl). ^1H NMR spectrum, δ, ppm: 1.45–1.98 m (8H, CH_2), 2.15 s (3H, CH_3C=O), 3.68 br.s (1H, CH), 3.61 d.d (1H, HCOH, *J* = 10.8, 7.2 Hz); Found, %: C 54.54; H 7.45; Cl 19.97. $C_8H_{13}ClO_2$. Calculated, %: C 54.39; H 7.36; Cl 20.11.

1-[2(1)-Bromo-1(2)-hydroxycyclohexyl]ethan-1-one (3b, 3e) was prepared from 3.1 g (25 mmol) of 1-(cyclohexenyl)ethan-1-one **1b.** Yield 4.2 g (76%), the ratio of isomers **3b : 3e** = 83 : 17. mp 101–103.6°C, bp 146–148°C (1.5 mmHg). IR spectrum, ν, cm^{-1}: 3480 (OH), 2845 (CH_3), 2860 (CH_2) 1730 (C=O), 1470 (CH_2), 1345 (CH) 1100 (OH), 560–610 (CBr). ^1H NMR spectrum, δ, ppm: 1.40–2.0 m (8H, CH_2, **3b**), 1.45–1.76 m (6H, $3CH_2$, **3e**), 2.05–2.31 m (2H, CH_2, **3e**), 2.15 s (3H, CH_3C=O), 3.56 br.s (1H, $HOC_6H_9COCH_3$, **3e**), 3.63 br.s (1H, $HOHC_6H_8$, **3b**), 3.83 t (1H, HCBr, *J* = 7.2 Hz, **3e**), 3.71 t (1H, HC_6H_8OH, *J* = 7.1 Hz, **3b**); Found, %: C 43.16; H 5.93; Br 35.84. $C_8H_{13}BrO_2$. Calculated, %: C 43.44; H 5.88; Br 36.20.

2-Chloro-5(4)-ethenylcyclohexan-1-ol (2c, 2f) was prepared from 2.7 g (25 mmol) of 4-ethenylcyclohex-1-ene **1c**. Yield 2.7 g (67.3%), the ratio of isomers **2c : 2f** = 65 : 34. bp 112–114°C (3 mmHg). IR spectrum, ν, cm^{-1}: 3485, 3360 (OH), 3080, 3050 (CH_2), 1640 (C=C), 1460 (CH_2), 1125, 1095 (OH), 780, 760 (CCl). ^1H NMR spectrum, δ, ppm: 1.33–1.89 m (6H, $3CH_2$), 2.14 q (1H, $HC_6H_8CH{=}CH_2$, *J* = 6.8 Hz), 3.49 t (1H, HCOH, *J* = 7.3 Hz), 3.54 d (1H, HC(Cl)OH, *J* = 7.2 Hz), 3.61 br.s (1H, HOCH), 4.89 d.d (1H, H^aH^bC=CH, *J* = 10.2, 2.3 Hz), 4.91 d.d (1H, H^bH^aC=CH, *J* = 16.8, 2.2 Hz), 5.77 d.d (1H, $HC{=}CH_2$, *J* = 16.7, 10.3 Hz). Found, %: C 59.56; H 7.9; Cl 22.37. $C_8H_{13}ClO$. Calculated, %: C 59.81; H 8.1; Cl 22.12.

2-Bromo-5(4)-ethenylcyclohexan-1-ol (3c, 3f) was prepared from 2.7 g (25 mmol) of 4-ethenylcyclohex-1-ene **1c**. Yield 3.3 g (64.7%), the ratio of isomers **3c : 3f** = 61 : 39. bp 123–125.5°C (4 mmHg). IR spectrum, ν, cm^{-1}: 3492, 3350 (OH), 3050 (CH_2=), 1645 (C=C), 1085 (OH), 550–610 (CBr). ^1H NMR spectrum, δ, ppm: 1.33–2.09 m (6H, CH_2), 2.10 q (1H, H^5, *J* = 6.4 Hz), 3.48 d (1H, H^2, *J* = 7.3 Hz), 3.56 d (1H, HCOH, *J* = 7.2 Hz), 3.61 br.s (1H, HOCH), 4.89 d.d (1H, H^aH^bC=CH, *J* = 10.2, 2.3 Hz), 4.91 d.d (1H, H^bH^aC=CH, *J* = 16.8, 2.2), 5,77 d.d (1H, $HC{=}CH_2$, *J* = 16.7, 10.3 Hz). Found, % : C 47.12; H 6,43; Br 38.71. $C_8H_{13}BrO$. Calculated, %: C 46.83; H 6.34; Br 39.02.

General procedure for the synthesis of amino-alcohols from hydroxychlor(brom)ides. To the mixture of 2.97 g (20 mmol) of compound **2a** or 3.86 g (20 mmol) of **3a** 0.1 g KOH and 50–100 mL of 2-propanol was added. The mixture was heated for 1–1.5 h at 60–70°C with constant dropwise addition of 0.1 mol of amine. The reaction was monitored by GC (5–6 h). The formed precipitate was filtered, washed with 2-propanol, dried and crystallized from the mixture 2-propanol–water (2.5 : 1).

2-(Diethylamino)-1(2)-methylcyclohexan-1-ol (4a, 7a) was prepared from 2.97 g (20 mmol) of the mixture of isomers **2a** and **2d** or 3.86 g (20 mmol) **3a** and **3d** and 3.3 g (45 mmol) of diethylamine. Yield 2.1 g (56.7%, from **2a, 2d**), 2.3 g (62.2% from **3a, 3d**), the ratio of isomers **4a : 7a** = 83 : 17, mp 59–61°C, bp 127–129°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3496 (OH), 3340, 3236 (CN), 2960 (CH_3), 2855 (CH_2), 1666, 1658 (NC), 1460 (CH_2), 1128, 1110 (OH). ^1H NMR spectrum, δ, ppm: 1.13 t [6H, $N(CH_2C\underline{H}_3)_2$, *J* = 8.2 Hz], 1.23–1.77 m (8H, CH_2), 1.28 s (3H, CH_3, **4a**), 1.39 s (3H, $C\underline{H}_3$, **7a**), 2.44 d [4H, $N(C\underline{H}_2CH_3)_2$, *J* = 8.3 Hz], 2.66 d [1H, HCN, *J* = 7.2 Hz], 3.37 d (1H, HCOH, *J* = 7.0 Hz), 3.61 br.s (1H, OH). Found, %: C 70.86; H 12.61; N 7.39. $C_{11}H_{23}NO$. Calculated, %: C 71.35; H 12.43; N 7.57.

2-[Bis(2-hydroxyethyl)amino]-1(2)-methylcyclohexan-1-ol (4b, 7b) was prepared from 2.97 g (20 mmol) of the mixture of isomers **2a** and **2d** or 3.86 g (20 mmol) **3a** and **3d** and 4.73 g (45 mmol) of diethylamine. Yield 2.1 g (48.4%, from **2a, 2d**), 2.3 g (55.0%, from **3a, 3d**), the ratio of isomers **4b : 7b** = 82 : 18, mp 178–180°C. IR spectrum, ν, cm^{-1}: 3482 (OH), 3360, 3254 (CN), 2965 (CH_3), 2855 (CH_2), 1666, 1558 (CN), 1145, 1085 (OH). ^1H NMR spectrum, δ, ppm: 1.15–1.76 m (8H, CH_2), 1.31 s (3H, $C\underline{H}_3C_6H_9OH$), 2.57 t [4H, $N(CH_2)_2$, *J* = 7.2 Hz], 2.67 t [1H, HC_6H_8N, *J* = 7.1 Hz], 3.65 t [4H, $N(CH_2C\underline{H}_2OH)_2$, *J* = 7.2 Hz), 3.68 br.s (3H, $2CH_2O\underline{H}$ + $CH_3C_6H_9O\underline{H}$, **4b**), 3.59 br.s ($CH_3C_6H_9O\underline{H}$). Found, %: C 60.25; H

10.71; N 6.34. $C_{11}H_{23}NO_3$. Calculated, %: C 60.83; H 10.6; N 6.45.

1(2)-Methyl-2-(piperidin-1-yl)cyclohexan-1-ol (4c, 7c) was prepared from 2.97 g (20 mmol) of the mixture of isomers **2a** and **2d** or 3.86 (20 mmol) of **3a** and **3d** and 3.9 g (45 mmol) of piperidine. Yield 2.8 g (71.1%, from **2a, 2d**), 3.0 g (76.1%, from **3a, 3d**), the ratio of isomers **4c : 7c** = 75 : 25, mp 84–86°C. IR spectrum, ν, cm^{-1}: 3497 (OH), 3330, 3256 (CN), 2850 (CH_2), 1560, 1450 (NC), 1115, 1070 (OH). ^1H NMR spectrum, δ, ppm: 1.13–1.25 m (14H, CH_2), 1.31 s (3H, C<u>H</u>$_3C_6H_8OH$, **7c**), 1.39 s (3H, C<u>H</u>$_3C_6H_8OH$, **4c**), 2.48 t [4H, N$(CH_2)_2$, *J* = 7.2 Hz], 2.67 d [(1H, <u>H</u>C_6H_8N, *J* = 7.3 Hz, **4c**), 3.42 d (1H, <u>H</u>C_6H_8OH, *J* = 7.3 Hz, **7c**), 3.60 br.s (1H, OH). Found, %: C 72.86; H 11.88; N 6.93. $C_{12}H_{23}NO$. Calculated, %: C 73.10; H 11.68; N 7.11.

2-(Morpholin-4-yl)-1(2)-methylcyclohexan-1-ol (4d, 7d) was prepared from 2.97 g (20 mmol) of the mixture of isomers **2a** and **2d** or 3.86 (20 mmol) **3a** and **3d** and 4.35 g (50 mmol) of morpholine. Yield 1.8 g (45.2%, from **2a, 2d**), 2.4 g (60.3%, from **3a, d**), the ratio of isomers **4d : 7d** = 85 : 15, mp 99–101°C. IR spectrum, ν, cm^{-1}: 3493 (OH), 3375, 3320 (CN), 2950 (CH_2), 1620, 1596 (CN), 1465 (CH_2), 1380 (CH), 1240, 1180 (COC), 1130, 1089 (OH). ^1H NMR spectrum, δ, ppm: 1.13–1.25 m (8H, CH_2), 1.31 s (3H, C<u>H</u>$_3C_6H_9OH$, **4d**), 1.39 s (3H, C<u>H</u>$_3C_6H_9N$, **7d**), 2.62 t (1H, HC_6H_8N, *J* = 7.1 Hz, **4d**), 3.42 t (1H, <u>H</u>C_6H_8OH, *J* = 7.2 Hz, **7d**), 2.69 t [4H, N$(CH_2)_2$ *J* = 7.2 Hz], 3.60 br.s (1H, OH), 3.64 t [4H, O$(CH_2)_2$, *J* = 7.3 Hz], Found, %: C 65.78; H 10.76; N 6.83. $C_{11}H_{21}NO_2$. Calculated, %: C 66.33; H 10.55; N 7.04.

2-Anilino-1(2)-methylcyclohexan-1-ol (4e, 7e) was prepared from 2.97 g (20 mmol) of the mixture of isomers **2a** and **2d** or 3.86 (20 mmol) **3a** and **3d** and 4.2 g (45 mmol) of aniline. Yield 2.6 g (63.4%, from **2a, 2d**), 2.8 g (68.3%, from **3a, 3d**), the ratio of isomers **4d : 7d** = 82 : 18, mp 126–128°C. IR spectrum, ν, cm^{-1}: 3486 (OH), 3370, 3320 (CNH), 2890 (CH_2), 2849 (CH), 1665, 1580 (NC), 1395, 1350 (CH). ^1H NMR spectrum, δ, ppm: 1.13–1.24 m (8H, CH_2), 1.31 s (3H, C<u>H</u>$_3C_6H_9OH$, **4d**), 1.53 s (3H, C<u>H</u>$_3$ C_6H_9NH, **7d**), 2.67 t (1H, <u>H</u>C_6H_8NH, *J* = 7.2 Hz), 3.42 t (1H, <u>H</u>C_6H_8OH, *J* = 7.2 Hz), 3.60 br.s (1H, OH), 4.1 br.s (1H, HN), 6.78–6.85 m (4H, Ar), 7.25 d (2H, $H^{3,5}$, *J* = 7.6 Hz). Found, %: C 75.87; H 9.35; N 6.61. $C_{13}H_{19}NO$. Calculated, %: C 76.10; H 9.27; N 6.83.

1-(1(2)-(Diethylamino)-2(1)-hydrocyclohexenyl)-ethan-1-one (5a, 8a) was prepared from 3.53 g (20 mmol) of the mixture of isomers **2b** and **2d** or 4.42 g (20 mmol) of **3b** and **3d** and 2.9 g (40 mmol) of diethylamine. Yield 2.6 g (61.0%, from **2b, 2e**), 2.7 g (63.4%, from **3b, 3e**), the ratio of isomers **5a : 8a** = 78 : 28, mp 119–121.5°C. IR spectrum, ν, cm^{-1}: 3490 (OH), 3365, 3320, (CN), 2960 (CH_3), 2855 (CH_2), 2849 (CH), 1750, 1723 (C=O), 1660, 1580 (CN), 1395 (CH), 1120, 1095 (OH). ^1H NMR spectrum, δ, ppm: 1.05 s [6H, (C<u>H</u>$_3CH_2)_2N$], 1.15–2.23 m (8H, CH_2), 2.15 s (3H, O=CCH_3, *J* = 8.1 Hz), 2.43 q [4H, N(C<u>H</u>$_2CH_3)_2$, *J* = 8.2 Hz), 3.66 br.s (H, OH). Found, %: C 67.22; H 10.43; N 6.25. $C_{12}H_{23}NO_2$. Calculated, %: C 67.61; H 10.80; N 6.57.

1-{2(1)-Bis[(2-hydroxyethyl)amino]-2(1)-hydroxy-cyclohexenyl}ethan-1-one (5b, 8b) was prepared from 3.53 g of the mixture of isomers **2b** and **2e** or 4.42 g of **3b** and **3e** and 4.73 g (45 mmol) of diethanolamine. Yield 2.5 g (51.0%, from **2b, 2e**), 2.7 g (55.1%, from **3b, 3e**), the ratio of isomers **5b : 8b** = 85 : 15, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3460 (OH), 3345 (NC), 2960 (CH_3), 2855 (CH_2), 2849 (CH), 1750, 1723 (C=O), 1620, 1596 (NC), 1450 (CH_2), 1110, 1069 (OH). Found, %: C 57.84; H 9.56; N 5.62. $C_{12}H_{23}NO_4$. Calculated, %: C 58.78; H 9.39; N 5.71.

1-[1(2)-Hydroxy-2(1)-(piperidin-1-yl)cyclohexyl]-ethan-1-one (5c, 8c) was prepared from 3.53 g of the mixture of isomers **2b** and **2e** or 4.42 g **3b** and **3e** and 3.8 g (45 mmol) of piperidine. The ratio of isomers **5c : 8c** = 81 : 19. Yield 2.5 g (55.6%, from **2b, 2e**), 2.7 g (60.0%, from **3b, 3e**), mp 47–49°C. IR spectrum, ν, cm^{-1}: 3530, 3370 (OH), 2960 (CH_3), 2850 (CH_2), 1750, 1723 (C=O), 1620, 1596 (NC), 1450 (CH_2), 1110, 1069 (OH). Found, %: C 68.76; H 10.43; N 6.16. $C_{13}H_{23}NO_2$. Calculated, %: C 69.33; H 10.22; N 6.22.

1-[1(2)-Hydroxy-2(1)-(morpholin-4-yl)cyclo-hexyl]ethan-1-one (5d, 8d) was prepared from 3.53 g of the mixture of isomers **2b** and **2e** or 4.42 g **3b** and **3e** and 3.9 g (45 mmol) of morpholine. Yield 2.4 g (53.4%, from **2b, 2e**), 2.7 g (60.1%, from **3b, 3e**). The ratio of isomers **5d : 8d** = 80 : 20, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3510, 3486 (OH), 3367, 3289 (CN), 2950 (CH_3), 2855 (CH_2), 1750, 1723 (C=O), 1620, 1596 (NC), 1460 (CH_2), 1240, 1120 (COC) 1115, 1070 (OH). Found, %: C 62.79; H 9.08; N 5.87. $C_{12}H_{21}NO_3$. Calculated, %: C 63.44; H 9.25; N 6.17.

1-(2-Anilinohydroxycyclohexyl)ethan-1-one (5e, 8e) was prepared from 3.53 g of the mixture of isomers

2b and **2e** or 4.42 g of **3b** and **3e** and 4.21 g (45 mmol) of aniline. Yield 2.2 g (47.6%, from **2b, 2e**), 2.5 g (53.7%, from **3b, 3e**), the ratio of isomers **5e : 8e** = 84 : 16, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3470 (OH), 3320 (NH), 2867 (CH_2), 2680 (NC), 1750, 1723 (C=O), 1665 (NC), 1645 (C=C), 1450 (CH_2), 1395, 1350 (CH), 1145 (OH). Found, %: C 71.95; H 8.25; N 5.84. $C_{14}H_{19}NO_2$. Calculated, %: C 72.10; H 8.15; N 6.0.

2-Diethylamino-5(4)-ethenylcyclohexan-1-ol (6a, 9a) was prepared from 3.21 g (20 mmol) of **2c** and **2f** or 4.1 g (20 mmol) of **3c** and **3f** and 2.9 g (40 mmol) of diethylamine. Yield 2.2 g (56.5%, from **2c, 2f**), 2.4 g (61.4%, from **3c, 3f**), the ratio of isomers **6a : 9a** = 84 : 16, bp 130–131.5°C (1.5 mmHg). IR spectrum, ν, cm^{-1}: 3530, 3480 (OH), 3370 (CN), 3050 (CH_2=), 2960 (CH_3), 2855 (CH_2), 2849 (CH), 1640 (C=O), 1450 (CH_2), 1380, 1340 (CH), 1115, 1075 (OH). ^{1}H NMR spectrum, δ, ppm: 1.11 s [6H, ($C\underline{H}_3CH_2)_2N$], 1.34–1.78 m (6H, $3CH_2$), 2.15 d.d (1H, H^5, J = 6.3, 7.2 Hz), 2.43 d [2H, $N(C\underline{H}_2CH_3)_2$], 2.68 q (1H, H^1, J = 7.3 Hz), 3.45 d (1H, H^1, J = 7.3 Hz), 3.67 br.s (H, OH), 4.91 d.d (1H, H^{8a}, J = 2.3, 10.4 Hz), 4.96 d.d (1H, H^{8b}, J = 2.3, 16.5 Hz), 5.78 d.d (1H, H^7, J = 6.3, 16.7 Hz). Found, %: C 72.84; H 11.83; N 6.91. $C_{12}H_{23}NO$. Calculated, %: C 73.10; H 11.68; N 7.10.

2-[Bis(2-hydroxyethyl)amino]-5(4)-ethenylcyclohexan-1-ol (6b, 9b) was prepared from 3.21 g of the mixture of isomers **2c** and **2f** or 4.1 g of **3c** and **3f** and 2.9 g (40 mmol) of diethanolamine. Yield 1.9 g (41.5%, from **2c, 2f**), 2.1 g (45.8%, from **3c, 3f**), the ratio of isomers **6b : 9b** = 56 : 44, mp 160–162.5°C. IR spectrum, ν, cm^{-1}: 3510, 3493 (OH), 3370 (CN), 2950 (CH_3), 3080, 3050 (CH_2=), 1645 (C=C), 1560 (CN), 1135, 1100, 1075 (OH). Found, %: C 62.37; H 10.23; N 5.76. $C_{12}H_{23}NO_3$. Calculated, %: C 62.88; H 10.04; N 6.11.

5(4)-Ethenyl-2-(piperidin-1-yl)cyclohexan-1-ol (6c, 9c) was prepared from 3.21 g of the mixture of isomers **2c** and **2f** or 4.1 g of **3c** and **3f** and 3.9 g (45 mmol) of piperidine. The ratio of isomers **6c : 9c** = 84 : 16. Yield 2.2 g (52.6%, from **6c**), 2.4 g (57.4%, from **9c**). mp 67–69°C. IR spectrum, ν, cm^{-1}: 3460 (OH), 3370 (CN), 3080 (CH_2=), 2850 (CH_2), 1645 (C=C), 1560 (CN), 1450 (CH_2), 1110, 1069 (OH). Found, %: C 74.12; H 10.92; N 6.63. $C_{13}H_{23}NO$. Calculated, %: C 74.64; H 11.0; N 6.70.

5(4)-Ethenyl-2-(morpholin-4-yl)cyclohexan-1-ol (6d, 9d) was prepared from 3.21 g of the mixture of isomers **2c** and **2f** or 4.1 g of **3c** and **3f** and 3.9 g (45 mmol) of morpholine. Yield 2.2 g (47.4%, from **2c, 2f**), 2.5 g (54.5%, from **3c, 3f**), the ratio of isomers **6d : 9d** = 56 : 44, mp 82–84°C, bp 161–162.5°C (1.5 mmHg). IR spectrum, ν, cm^{-1}: 3495 (OH), 3370 (CN), 3080, 3050 (CH_2=), 2850 (CH_2), 1645 (C=C), 1620, 1596 (CN),1450 (CH_2), 1240, 1123 (COC), 1110, 1082 (OH). Found, %: C 67.93; H 10.22; N 6.58. $C_{12}H_{21}NO_2$. Calculated, %: C 68.25; H 9.95; N 6.63.

2-Anilino-5(4)-ethenylcyclohexan-1-ol (6e, 9e) was prepared from 3.21 g of the mixture of isomers **2c** and **2f** or 4.1 g of **3c** and **3f** and 4.2 g (45mmol) of aniline. Yield 3.1 g (71.4%, from **2c, 2f**), 2.2 g (50.7%, from **3c, 3f**), the ratio of isomers **6e : 9e** = 54 : 46, bp 108–110°C (1.5 mmHg). IR spectrum, ν, cm^{-1}: 3480 (OH), 3350 (NH), 3050 (CH_2=), 2950 (CH_2), 2680, 1665 (CN), 1640 (C=C), 1350, 1280 (ArN), 1110 (OH). Found, %: C 77.03; H 8.93; N 6.37. $C_{14}H_{19}NO$. Calculated, %: C 77.42; H 8.76; N 6.45.

General procedure for testing antimicrobial activity of aminoalcohols. Antimicrobial activity of the synthesized compounds **4a**–**6e** was determined by GOST 9.052-88 and 9.082-77. As test cultures, bacterial (*Mycobacterium lacticolum, Pseudomonas aeruginosa*), fungi (*Aspergillus niger, Cladosporium-resinae)* and yeast microorganisms (*Candida tropicalis*) were used. The microorganisms were cultivated at 28±2°C in special thermostat with 90–100% humidity: fungi for 5–7 days, bacteria for 2–3 days. As nutrients for bacteria meat-extract agar, for fungi and yeast cultures wort agar were used. As reference compounds, 8-oxyquinoline and sodium pentachlorophenolate were used. The results of tests are presented in Table 2.

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