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SYNTHESIS AND BIOLOGICAL ACTIVITY OF *N*-(2-HYDROXYETHYL)CYTISINE DERIVATIVES

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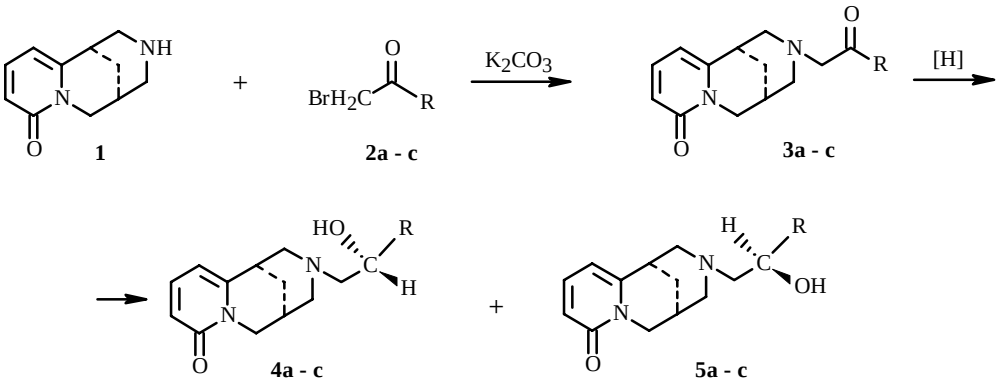
Derivatives of N-*(2-hydroxyethyl)cytisine,* N-*(2-hydroxypropyl)-,* N-*(2-hydroxy-2-(1-adamantyl)ethyl)-, and* N-*(2-hydroxy-2-phenylethyl)cytisine, were synthesized by reduction of* N-*(2-oxopropyl)-,* N-*(2-oxo-2-(1-adamantyl)ethyl)- and* N-*(2-oxo-2-phenylethyl)cytisine with metal hydrides. The antiarrhythmic and analgesic activities of the prepared compounds were investigated.*

Key words: cytisine, *N*-(2-hydroxyethyl)cytisine derivatives, reduction, metal hydrides, antiarrhythmic and analgesic activity.

Cytisine (**1**) and its derivatives are attractive to researchers owing to their broad spectrum of physiological activity (spasmolytic [1], insecticidal [2], cholinergic [3], analgesic [4]) and the ability to use them in catalytic reactions as optically active ligands [5]. We recently showed that *N*-(2-hydroxyethyl)cytisine has low toxicity and exhibits high antiarrhythmic activity compared with known antiarrhythmics [6, 7].

The goal of the present work was to synthesize new cytisine derivatives [8-11] and to study the structure—activity (antiarrhythmic) relationship for *N*-(2-hydroxyethyl)cytisine derivatives. Thus, we synthesized *N*-(2-hydroxypropyl)- (**4a**), *N*-(2-hydroxy-2-(1-adamantyl)ethyl)- (**4b**), and *N*-(2-hydroxy-2-phenylethyl)cytisine (**4c**) via reduction of the corresponding 2-alkyl- or 2-phenyl substituted *N*-(2-oxoethyl)cytisines **3a-c**, which were prepared by reacting **1** and bromoketones **2a-c**.



R = Me (**a**), Ad (**b**), Ph (**c**)

Ketones **3a-c** were prepared by reacting **1** with bromoketones [bromoacetone (**2a**), 1-adamantyl-2-bromomethylketone (**2b**), bromoacetophenone (**2c**)] in anhydrous acetone in the presence of K_2CO_3 for 1 h in 95-99% yields.

The reduction of these ketones with $NaBH_4$, $LiAlH_4$, $(i\text{-Bu})_2AlH$, and $AlH_3 \cdot N(Me)_3$ was studied in order to investigate the effect of the optically active center of cytisine and the nature of the metal hydride on the new asymmetric center formed by conversion of the carbonyl in **3a-c** into a secondary alcohol.

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TABLE 1. Reduction of **3c** by Metal Hydrides

Reductant	Ketone:hydride ratio	Solvent (vol. ratio)	Temperature, °C	Time, h	Overall yield, %	Ratio of diastereomers, %
$NaBH_4$	1:2	MeOH	20	1	99	50:50
$NaBH_4$-$CeCl_3 \cdot 7H_2O$*	1:2	MeOH	20	1	95	50:50
	1:2	*i*-PrOH	20	1	98	65:35
	1:2	EtOH-H_2O (2:3)	20	1	98	50:50
	1:2	*i*-PrOH-H_2O (35:1)	20	1	75	50:50
$NaBH_4$-$NdCl_3$	1:2	*i*-PrOH	20	1	75	50:50
$NaBH_4$-$RhCl \cdot 4H_2O$	1:2	*i*-PrOH	20	1	53	50:50
$NaBH_4$-Et_3N*						
(1:1)	1:1.25	*i*-PrOH	20	4	95	60:40
(1:2)	1:1.25	*i*-PrOH	20	4	99	65:35
(1:3)	1:1.25	*i*-PrOH	20	4	99	50:50
(1:4)	1:1.25	*i*-PrOH	20	4	99	50:50
$LiAlH_4$	1:2	CH_2Cl_2-Et_2O	20	2	55	55:45
	1:2	CH_2Cl_2-Et_2O	0	2	99	65:35
	1:2	CH_2Cl_2-Et_2O	-15	2	95	60:40
	1:2	CH_2Cl_2-Et_2O	-30	2	99	65:35
$LiAlH_4$-(-)-menthol						
(1:1)	1:2	CH_2Cl_2-Et_2O	0	2	44	55:45
(1:2)	1:1	CH_2Cl_2-Et_2O	0	2	0	-
(1:3)	1:2	CH_2Cl_2-Et_2O	0	2	0	-
(4:1)	1:2	CH_2Cl_2-Et_2O	0	2	80	50:50
(*i*-Bu)$_2$AlH	1:3	CH_2Cl_2	0	2	70	50:50
	1:8	CH_2Cl_2	0	2	99	45:55
$AlH_3 \cdot N(Me)_3$*	2:1	C_6H_6	20	2	95	45:55

*Reverse order of addition of reagents/reductants to ketone **3c**.

Reduction of **3a-c** by $NaBH_4$ in methanol for 1 h formed the corresponding aminoalcohols in high yields as mixtures of diastereomers **4a-c** and **5a-c**. There was practically no effect from the chiral centers. The ratio of diastereomers **4a-c** and **5a-c** did not depend on the structure of the starting ketone and was 1:1. Adding the bulky adamantyl substituent into *N*-(2-hydroxyethyl)cytisine changed slightly the stereoselectivity of the reaction. Aminoalcohols **4b** and **5b** were formed in a 60:40 ratio, respectively.

The stereochemistry of reduction of the ketone into the alcohol in the presence of various additives was studied in detail using reduction of **3c** by $NaBH_4$ as an example (Table 1).

Thus, reduction of **3c** by $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in isopropanol for 1 h produced a small excess of one of the diastereomeric alcohols **4c** + **5c**, which were obtained in a 65:35 ratio. Using CH_3OH, C_2H_5OH, C_2H_5OH:H_2O, and PrOH:H_2O as solvent decreased the yield of **4c** and **5c** although their ratio was practically unchanged.

Replacing $CeCl_3 \cdot 7H_2O$ by $NdCl_3$ or $RhCl_3 \cdot 4H_2O$ did not lead to preferential formation of one isomer. The overall yield decreased to 50-75%.

Reduction of **3c** by $NaBH_4$ in the presence of Et_3N [12] showed that adding a 2-fold molar excess of Et_3N to $NaBH_4$ produced aminoalcohols **4c** and **5c** in quantitative yield with a 65:35 ratio. Increasing the Et_3N content further to a 4-fold excess with respect to $NaBH_4$ did not affect the yield of aminoalcohols, which remained quantitative. However, it must be noted that the ratio of diastereomers was 1:1.

TABLE 2. Antiarrhythmic and Analgesic Activity of Synthesized Compounds

Compound	LD_{50}, iv, mg/kg	Antiarrhythmic effect ED_{50}, mg/kg, model		Antiarrhythmic index (LD_{50}/ED_{50}), model		LD_{50}, ip, mg/kg	Analgesic activity	
		calcium chloride	aconitine	calcium chloride	aconitine		dose, mg/kg	reduction of pain reaction, %
HCl (**4c+5c**)	98.0	0.4	0.52	245	188	306	2; 5	35; 50.4
HCl (**4a+5a**)	86.4	0.47	-	184	-	270	2; 27.0*	43; 40
HCl (**4b+5b**)	70.7	0.45	0.46	157	154	221	2; 22.1*	51; 21
Allapinine	6.0	0.32	0.07	19	86			
"Ketanov" (Ketorolac)						-	2	58

*1/10 of LD_{50}.

A study of the effect of temperature on reduction of **3c** by $LiAlH_4$ showed that the largest excess of one of the diastereomers (65:35) was observed at 0°C. The overall yield of **4c** and **5c** was 99%. Lowering the temperature further to -30°C had an insignificant effect on the stereoselectivity of the reaction.

We established that reduction of **3c** by $LiAlH_4$ and (-)-menthol (1:1 ratio), which performed very well in reduction of certain β-aminoketones [13], did not have a significant effect on the stereoselectivity of the reaction. In this instance the yield of **4c** and **5c** was less than 44% with a 55:45 ratio of diastereomers. Increasing the (-)-menthol content to a 3-fold molar excess relative to $LiAlH_4$ destroyed the reductant so that alcohols were not formed. Only **3c** was isolated from the reaction mixture.

In contrast with $NaBH_4$ and $LiAlH_4$, use of $(i\text{-Bu})_2AlH$ or $AlH_3 \cdot N(Me)_3$ as reductant led to formation of primarily the isomer of the opposite configuration. Thus, aminoalcohols were formed with a 45:55 ratio of diastereomers in quantitative yield with an 8-fold molar excess of $(i\text{-Bu})_2AlH$. The complex $AlH_3 \cdot N(Me)_3$ converted **3c** into diastereomers **4c** and **5c** at 20°C in benzene in practically quantitative yield (95%) and a 45:55 ratio of diastereomers.

The structures of the synthesized compounds were established using PMR and ^{13}C NMR spectra and homo- and heteronuclear two-dimensional $^1H—^1H$ COSY and CH-CORR NMR spectra.

The computer system PASS that was developed in the NIIBMKh of the RAMS was used to predict the potential physiological activity of the synthesized compounds. This showed that these aminoalcohols may exhibit antiarrhythmic, analgesic, and nootropic activity.

The hydrochlorides of the synthesized aminoalcohols were used as a mixture of diastereomers (**4a** + **5a**), (**4b** + **5b**), and (**4c** + **5c**) in a 1:1 ratio for tests of antiarrhythmic and analgesic activity. The antiarrhythmic activity was studied for two arrhythmia models induced by iv administration of aconitine and $CaCl_2$.

Tests using the aconitine atrial-ventricular arrhythmia model showed that the hydrochlorides (**4c** + **5c**) and (**4b** + **5b**) exhibited antiarrhythmic activity with iv administration at higher doses than the allapinine reference preparation and halved the duration of cardiac arrhythmia compared with the control (Table 2). For the $CaCl_2$ model, **4** and **5** at the studied doses had about the same antiarrhythmic activity as allapinine, providing a protective effect by avoiding lethal ventricular fibrillation. The LD_{50} for hydrochlorides (**4c** + **5c**) and (**4b** + **5b**) was more than 10 times greater than for allapinine.

Hydrochlorides (**4b** + **5b**) at a dose of 2 mg/kg and (**4c** + **5c**) at a dose of 5 mg/kg exhibited analgesic activity. Their analgesic activity was similar to the reference preparation of "Ketanov" (Table 2).

Thus, we synthesized *N*-(2-hydroxypropyl)-, *N*-(2-hydroxy-2-(1-adamantyl)ethyl)-, and *N*-(2-hydroxy-2-phenylethyl)cytisines via reduction of substituted *N*-(2-oxoethyl)cytisines and carried out the first screening of these compounds for antiarrhythmic and analgesic activity.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.45 MHz, respectively) with Me_4Si internal standard. IR spectra were obtained on a Specord M-80 instrument in mineral oil. Mass spectra were

measured in a MX-1300 spectrometer with inlet temperature 100°C at ionizing potential 12 and 70 eV. Melting points were determined on a Boetius microstage. TLC analysis was carried out on Silufol chromatography plates (Kavalier) and Sorbfil using C_6H_6:Et_2O:MeOH (10:5:2) with development in an iodine chamber.

We used pharmacopeic cytisine isolated from *Thermopsis lanceolata*. Compounds **2a** and **2c** [14] and $AlH_3 \cdot N(Me)_3$ [15] were prepared using the literature methods. Compound **2b** was obtained commercially (Aldrich); $(i\text{-Bu})_2AlH$, a commercial 73% solution (Redkin test plant). Solvents were purified as usual [16].

General Method for Preparing 3a-c. A mixture of cytisine (1.00 g, 5.26 mmol) and freshly calcined K_2CO_3 (1.26 g, 9.17 mmol) in absolute acetone (30 mL) was stirred vigorously, boiled, treated dropwise over 30 min with the appropriate bromoketone **2a-c** (5.26 mmol) in absolute acetone (10 mL), boiled and stirred for 1 h, cooled, and filtered to remove the precipitate, which was washed with $CHCl_3$ (30 mL). The filtrate was evaporated at reduced pressure. The solid was recrystallized from C_6H_6.

***N*-(2-Oxopropyl)cytisine (3a).** Bromoacetone (**2a**, 0.72 g) produced **3a** (1.23 g, 95%) as colorless crystals, mp 85-87°C, $[\alpha]_D^{20}$ -170.9° (*c* 1.51, $CHCl_3$), R_f 0.32, $C_{14}H_{18}N_2O_2$. Mass spectrum (*m*/*z*): 246 $[M]^+$. IR spectrum (ν, cm^{-1}): 1656 (C=O), 1708, 1352 (C=O), 1692, 740, 1432 (CH=CH), 800 (C=CH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.80 (3H, s, Me), 1.79 (1H, br.d, ^2J = 12.8, H_{anti}-8), 1.91 (1H, br.d, ^2J = 12.8, H_{syn}-8), 2.45 (1H, br.s, H-9), 2.54 (1H, br.d, ^2J = 10.5, H_{exo}-13), 2.60 (1H, br.d, J = 11.6, H_{exo}-11), 2.73 (1H, br.d, ^2J = 10.5, H_{endo}-13), 2.87 (1H, br.d, ^2J = 11.6, H_{endo}-11), 2.93, 3.01 (1H each, both d, ^2J = 15.8, H-14), 2.95 (1H, br.s, H-7), 3.87 (1H, dd, ^2J = 15.4, ^3J = 6.6, H_{exo}-10), 4.14 (1H, d, ^2J = 15.4, H_{endo}-10), 5.97 (1H, dd, ^3J = 6.8, ^3J = 1.3, H-5), 6.42 (1H, dd, $^3J_{3\text{-}4}$ = 9.0, $^3J_{3\text{-}5}$ = 1.3, H-3), 7.25 (1H, dd, $^3J_{4\text{-}5}$ = 6.8, $^3J_{4\text{-}3}$ = 9.0, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.21 (C-8), 26.78 (Me), 27.94 (C-9), 35.21 (C-7), 49.83 (C-10), 60.28, 60.40 (C-11, C-13), 68.04 (C-14), 104.53 (C-5), 116.69 (C-3), 138.55 (C-4), 150.83 (C-6), 163.40 (C-2), 208.68 (C-15).

***N*-(2-Oxo-2-(1-adamantyl)ethyl)cytisine (3b).** 1-Adamantylbromomethylketone (**2b**, 1.35 g) produced after 4 h **3b** (1.90 g, 99%) as colorless crystals, mp 146-148°C, $[\alpha]_D^{20}$ -171.79° (*c* 3.12, $CHCl_3$), R_f 0.60, $C_{23}H_{30}N_2O_2$. Mass spectrum (*m*/*z*): 366 $[M]^+$. IR spectrum (ν, cm^{-1}): 1708 (C=O), 1656, 1348 (C=O), 1462, 2856 (CH_2), 1692, 840 (C=CH), 1432, 736 (CH=CH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.57 [3H, d, $^2J_{B\text{-}A}$ = 11.6, H_B-(β-Ad)], 1.64 [6H, br.s, H-(σ-Ad)], 1.67 [3H, d, $^2J_{A\text{-}B}$ = 11.6, H_A-(β-Ad)], 1.78 (1H, br.d, ^2J = 12.7, H_{anti}-8), 1.88 (1H, br.d, ^2J = 12.7, H_{syn}-8), 1.92 [3H, br.s, H-(γ-Ad)], 2.43 (1H, br.s, H-9), 2.61 (1H, dd, ^2J = 10.7, $^3J_{13exo\text{-}7}$ = 2.3, H_{exo}-13), 2.63 (1H, br.d, ^2J = 10.8, H_{exo}-11), 2.81 (1H, br.d, ^2J = 10.7, H_{endo}-13), 2.88 (1H, br.d, ^2J = 10.8, H_{endo}-11), 2.93 (1H, br.s, H-7), 3.03 (1H, d, ^2J = 14.6, H_B-14), 3.23 (1H, d, ^2J = 14.6, H_A-14), 3.90 (1H, dd, ^2J = 15.4, $^3J_{10exo\text{-}9}$ = 6.7, H_{exo}-10), 4.08 (1H, d, ^2J = 15.4, H_{endo}-10), 5.97 (1H, dd, $^3J_{5\text{-}4}$ = 6.8, $^4J_{5\text{-}3}$ = 1.2, H-5), 6.42 (1H, dd, $^3J_{3\text{-}4}$ = 9.1, $^4J_{3\text{-}5}$ = 1.2, H-3), 7.26 (1H, dd, $^3J_{4\text{-}5}$ = 6.8, $^3J_{4\text{-}3}$ = 9.1, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.35 (C-8), 27.71 [C-(γ-Ad)], 27.91 (C-9), 35.23 (C-7), 36.27 [C-(σ-Ad)], 38.05 [C-(β-Ad)], 45.67 [C-(α-Ad)], 49.75 (C-10), 59.79 (C-11), 59.86 (C-13), 62.40 (C-14), 104.47 (C-5), 116.55 (C-3), 138.31 (C-4), 151.05 (C-6), 163.35 (C-2), 212.35 (C-15).

***N*-(2-Oxo-2-phenylethyl)cytisine (3c).** Phenacylbromide (**2c**, 1.05 g) produced **3c** (1.55 g, 95%) as colorless crystals, mp 130-131°C, $[\alpha]_D^{20}$ -188.3° (*c* 3.32, $CHCl_3$), R_f 0.38, $C_{19}H_{20}N_2O_2$. Mass spectrum (*m*/*z*): 308 $[M]^+$. IR spectrum (ν, cm^{-1}): 1654 (C=O), 1678, 1372 (C=O), 736, 1450, 1468, 1546, 1570 (Ph), 694, 1426 (CH=CH), 796 (C=CH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.80 (1H, br.d, J = 12.8, H_{anti}-8), 1.88 (1H, br.d, J = 12.8, H_{syn}-8), 2.43 (1H, br.s, H-9), 2.61 (1H, br.d, ^2J = 10.6, H_{exo}-11), 2.62 (1H, br.d, ^2J = 10.5, H_{exo}-13), 2.83 (1H, br.d, ^2J = 10.5, H_{endo}-13), 2.92 (1H, d, ^2J = 10.6, H_{endo}-11), 2.94 (1H, br.s, H-7), 3.52 (1H, ^2J = 14.5, H_B-14), 3.62 (1H, ^2J = 14.5, H_A-14), 3.82 (1H, dd, ^2J = 15.2, $^3J_{10exo\text{-}9}$ = 6.1, H_{exo}-10), 3.90 (1H, d, ^2J = 15.2, H_{endo}-10), 5.85 (1H, dd, $^3J_{5\text{-}4}$ = 6.5, $^3J_{5\text{-}3}$ = 1.2, H-5), 6.38 (1H, dd, $^3J_{3\text{-}4}$ = 9.0, $^3J_{3\text{-}5}$ = 1.2, H-3), 7.14 (1H, dd, $^3J_{4\text{-}3}$ = 9.0, $^3J_{4\text{-}5}$ = 6.5, H-4), 7.29 [2H, ddd, $^3J_{m\text{-Ph}—o\text{-Ph}}$ = 7.2, $^3J_{m\text{-Ph}—p\text{-Ph}}$ = 4.1, H-*m*-Ph)], 7.46 [1H, tt, $^3J_{p\text{-Ph}—m\text{-Ph}}$ = 7.4, $^4J_{p\text{-Ph}—o\text{-Ph}}$ = 1.4, H-(*p*-Ph)], 7.77 [2H, dd, $^3J_{o\text{-Ph}—m\text{-Ph}}$ = 7.2, $^4J_{o\text{-Ph}—p\text{-Ph}}$ = 1.4, H-(*o*-Ph)].

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.09 (C-8), 27.64 (C-9), 35.03 (C-7), 49.56 (C-10), 59.55, 59.91 (C-11, C-13), 65.30 (C-14), 104.17 (C-5), 116.46 (C-3), 128.03 [C-(*m*-Ph)], 128.12 [C-(*o*-Ph)], 133.05 [C-(*p*-Ph)], 135.18 [C-(*i*-Ph)], 138.18 (C-4), 150.60 (C-6), 163.10 (C-2), 197.91 (C-15).

General Method for Reduction of 3a-c by $NaBH_4$. A solution of $NaBH_4$ (0.12 g, 3.20 mmol) in MeOH (20 mL) at room temperature was constantly stirred, treated dropwise over 1 h with the appropriate ketone (**3a-c**, 1.60 mmol) in MeOH (50 mL), stirred for 1 h, treated with dry acetone (5 mL), stirred for another 15 min, and evaporated to dryness. The solid was

dissolved in $CHCl_3$ (70 mL) and filtered through a layer of Al_2O_3 (2 cm) to remove the insoluble solid. Solvent was removed in vacuo. The diastereomers were characterized as a mixture using NMR spectroscopy. Their quantitative composition was determined from the ratio of areas of the signals for the C-15 methine protons for **4a** + **5a** and **4c** + **5c** and for the C-10 H_{endo} protons for **4b** + **5b**.

***N*-(2-Hydroxypropyl)cytisines 4a + 5a.** Ketone **3a** (0.39 g) produced **4a** + **5a** (0.39 g, 98%) as light yellow crystals, R_f 0.23, $C_{14}H_{20}N_2O_2$. Mass spectrum (*m*/*z*): 248 $[M]^+$. IR spectrum (ν, cm^{-1}): 1640 (C=O), 1420, 740 (CH=CH), 810 (C=CH), 3370 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.00, 1.02 (3H each, d, $^3J_{16\text{-}15}$ = 5.0, Me), 1.86 (4H, m, H-8), 2.05-2.21 (6H, m, H-11, H-13, H-14), 2.47 (2H, br.s, H-9), 2.62 (2H, br.d, ^2J = 10.7, H-11, H-13), 2.84-2.92 (2H, m, H-11, H-13), 2.94-3.10 (4H, m, H-7, H-11, H-13), 3.47 (2H, br.s, OH), 3.60-3.75 (2H, m, H-15), 3.88-3.97 (2H, m, H_{exo}-10), 4.04, 4.12 (1H each, d, ^2J = 15.5, H_{endo}-10), 5.94-6.00 (2H, m, H-5), 6.39-6.46 (2H, m, H-3), 7.22-7.35 (2H, m, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 19.57 (Me), 25.29 (C-8), 27.31, 27.72 (C-9), 34.68, 35.15 (C-7), 49.49, 49.59 (C-10), 58.60, 58.76, 61.18, 61.75 (C-11, C-13), 64.40, 64.77 (C-15), 61.84, 62.36 (C-14), 104.41 (C-5), 116.11, 116.17 (C-3), 138.44 (C-4), 150.42, 150.65 (C-6), 162.92 (C-2).

***N*-(2-Hydroxy-2-(1-adamantyl)ethyl)cytisines 4b + 5b.** Ketone **3b** (0.58 g) produced **4b** + **5b** (0.577 g, 98%), R_f 0.54. IR spectrum (ν, cm^{-1}): 1088 (C–O), 1651 (C=O), 3100-3600 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.42-1.57 [12H, m, H-(β-Ad)], 1.58-1.75 [12H, m, H-(σ-Ad)], 1.77-1.75 [10H, m, H-8, H-(γ-Ad)], 2.15-2.42 (6H, m, H-14, H_{exo}-11, H_{exo}-13), 2.43-2.52 (2H, m, H-9), 2.55-2.67 (2H, m, H_{exo}-11, H_{exo}-13), 2.81-2.95 (2H, m, H_{endo}-11, H_{endo}-13), 2.97-3.14 (6H, m, H-7, H-15, H_{endo}-13, H_{endo}-11), 3.38 (2H, br.s, OH), 3.85-3.97 (2H, m, H_{exo}-10), 4.03, 4.12 (1H each, both d, ^2J = 15.4, H_{endo}-10), 5.93-6.02 (2H, m, H-5), 6.37-6.47 (2H, m, H-3), 7.21-7.32 (2H, m, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.85, 25.93 (C-8), 27.69, 28.21 [C-(γ-Ad)], 35.06, 35.17 [C-(α-Ad)], 35.18, 35.75 (C-7), 37.98, 38.03 [C-(β-Ad)], 37.23 [C-(σ-Ad)], 49.76, 49.90 (C-10), 57.63, 58.20, 58.54, 58.73, 62.12, 62.87 (C-11, C-13, C-14), 72.70, 73.56 (C-15), 104.64, 104.81 (C-5), 116.91 (C-3), 138.70, 138.88 (C-4), 150.34, 150.74 (C-6), 163.28 (C-2).

***N*-(2-Hydroxy-2-phenylethyl)cytisine 4c + 5c.** Ketone **3c** (0.49 g) produced **4c** + **5c** (0.491 g, 99%), R_f 0.23, $C_{19}H_{22}N_2O_2$. Mass spectrum (*m*/*z*): 310 $[M]^+$. IR spectrum (ν, cm^{-1}): 1648 (NC=O), 1378 (C=O), 742, 1456, 1486, 1546, 1564 (Ph), 700, 1426 (CH=CH), 802 (C=CH), 3400 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.78-2.00 (4H, m, H-8), 2.34-2.54 (8H, m, H_{exo}-11, H_{exo}-13, H-9, H-14), 2.55 (2H, m, H_{exo}-11, H_{exo}-13), 2.83-2.94 (2H, m, H_{endo}-11, H_{endo}-13), 3.11-3.19 (6H, m, H-7, H_{endo}-11, H_{endo}-13, OH), 3.85-3.98 (2H, m, H_{exo}-10), 4.06, 4.16 (both 1H, both d, ^2J = 15.6, H-10), 4.55, 4.62 (both 1H, both dd, $^3J_{15\text{-}14B}$ = 9.4, $^3J_{15\text{-}14B}$ = 9.8, $^3J_{15\text{-}14A}$ = 4.0, $^3J_{15\text{-}14A}$ = 3.9, H-15), 5.98-6.07 (2H, m, H-5), 6.43-6.50 (2H, m, H-3), 7.29-7.42 (12H, m, H-Ph, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.55, 25.63 (C-8), 27.62, 28.04 (C-9), 35.00, 35.44 (C-7), 49.70, 49.84 (C-10), 58.88 (C-11), 61.40, 61.99 (C-13), 65.30, 65.67 (C-14), 68.47, 69.07 (C-15), 104.64, 104.72 (C-5), 116.75, 116.83 (C-3), 125.50, 125.55 [C-(*m*-Ph)], 127.23 [C-(*o*-Ph)], 128.09 [C-(*p*-Ph)], 138.66, 138.72 (C-4), 141.64, 141.72 [C-(*i*-Ph)], 150.37, 150.68 (C-6), 163.25 (C-2).

General Method for Reduction of 3c by $NaBH_4$ in the Presence of Transition Metal Salts. **3c** (0.5 g, 1.60 mmol) and MCl_3 (0.80 mmol) were dissolved in *i*-PrOH (50 mL), stirred, treated dropwise over 30 min with $NaBH_4$ (48 mg, 1.28 mmol) in *i*-PrOH (25 mL), stirred for 30 min at room temperature, treated with acetone (1 mL), and stirred another 15 min. When the reaction was finished water (10 mL) and saturated NaCl solution (15 mL) were added. The mixture was extracted with ether (3 × 20 mL). The ether layer was dried over Na_2SO_4. Solvent was removed to produce **4c** + **5c** as white crystals, 0.485 g (98%) (MCl_3 = $CeCl_3 \cdot 7H_2O$); 0.372 g (75%) ($NdCl_3$); and 0.262 g (53%) ($RhCl_3 \cdot 4H_2O$).

General Method for Reduction of 3c by $NaBH_4$ in the Presence of Et_3N. **3c** (0.2 g, 0.65 mmol) was dissolved in *i*-PrOH (40 mL), treated with Et_3N (Et_3N:$NaBH_4$ mole ratio = 1:1, 2:1, 3:1, 4:1) and in one portion $NaBH_4$ (0.030 g, 0.81 mmol), and stirred for 4 h at room temperature. When the reaction was finished, the mixture was passed through a layer of Al_2O_3 (~3 cm). The filtrate was evaporated. The solid was dissolved in $CHCl_3$ (40 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na_2SO_4. Solvent was removed to produce **4c** + **5c** as white crystals, 0.19 g (95%, Et_3N:$NaBH_4$ = 1:1); 0.20 g (99%, Et_3N:$NaBH_4$ = 2:1); 0.20 g (99%, Et_3N:$NaBH_4$ = 3:1); 0.20 g (99%, Et_3N:$NaBH_4$ = 4:1).

General Method for Reduction of 3c by $LiAlH_4$ at Various Temperatures. An ether solution of $LiAlH_4$ (2.080 mL, 1.5604 M) was cooled to the appropriate temperature, treated dropwise over 15 min under a stream of Ar with **3c** (0.5 g,

1.62 mmol) dissolved in dry CH_2Cl_2 (10 mL), stirred, and held at the given temperature for 2 h. When the reaction was finished, the mixture was treated with NaOH solution (0.5 mL, 20%). The solid was filtered off and washed with hot $CHCl_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4. Solvent was removed to produce **4c** + **5c** as white crystals, mp 142-143°C, 0.28 g (55%, 20°C); 0.49 g (99%, 0°C); 0.48 g (95%, -15°C); 0.49 g (99%, -30°C).

Reduction of 3c by $LiAlH_4$ in the Presence of (-)-Menthol. A solution of (-)-menthol (0.50 g, 3.25 mmol) in dry CH_2Cl_2 (5 mL) at 0°C was stirred, treated with an ether solution (2.08 mL) of $LiAlH_4$ (1.56 M) and dropwise over 15 min under a stream of Ar with **3c** (0.5 g, 1.62 mmol) dissolved in dry CH_2Cl_2 (10 mL), stirred, held at 0°C for 2 h, cooled, treated dropwise at 0°C with water (5 mL) until hydrogen evolution stopped, and treated with HCl solution (10%) until aluminum hydroxide completely dissolved (pH 5-6). The ether layer was separated. The aqueous phase was adjusted to pH 7-8 and extracted with $CHCl_3$ (3 × 20 mL). Solvent was removed to produce **4c** + **5c** (0.221 g, 44%) as colorless crystals, mp 142-143°C.

Reduction of 3c by $(i\text{-Bu})_2AlH$. CH_2Cl_2 (10 mL) was cooled to 0°C, stirred vigorously under a stream of Ar, treated with $(i\text{-Bu})_2AlH$ solution (0.5 mL, 2.5 mmol), treated dropwise over 15 min with **3c** (0.1 g, 0.325 mmol) in CH_2Cl_2 (7 mL), stirred, and held at 0°C for 2 h. When the reaction was finished, the mixture was hydrolyzed with NaOH solution (10 mL, 40%), treated with water (20 mL), and extracted with $CHCl_3$ (3 × 20 mL). The organic phase was dried over Na_2SO_4. Solvent was removed to produce **4c** + **5c** (0.10 g, 99)) as colorless crystals, mp 142-143°C.

Reduction of 3c by $AlH_3 \cdot N(Me)_3$. A solution of **3c** (0.10 g, 0.32 mmol) in benzene (5 mL) under a stream of Ar was stirred, slowly treated dropwise with $AlH_3 \cdot N(Me)_3$ in benzene (0.17 mM), stirred for 2 h at 20°C, and treated with NaOH solution (10 mL, 5%) in MeOH. The reaction mixture was evaporated. The solid was dissolved in $CHCl_3$ (5 mL), treated with water (12 mL), and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried over Na_2SO_4. Solvent was removed to produce **4c** + **5c** (0.095 g, 95%) as crystals.

Determination of Toxicity of Aminoalcohol Hydrochlorides (4a + 5a), (4b + 5b), and (4c + 5c). Acute toxicity was studied in 64 mongrel mice for one-time ip and iv administration to unanesthetized mice. Animals were observed for 14 d, regularly recording their general condition and behavior.

Determination of Antiarrhythmic Activity of Aminoalcohol Hydrochlorides (4a + 5a), (4b + 5b), and (4c + 5c). Antiarrhythmic activity was studied in 138 mongrel anesthetized (urethane, 1 g/kg) rats (160-200 g) for rhythm disruption caused by iv administration of aconitine at a dose of 50 μg/kg and $CaCl_2$ at 250 mg/kg as a solution (10%). Rhythm disruptions were recorded in the second standard derivative. The studied compounds were administered sterilely to a tail vein 1-2 min before administering the arrythmogens [17]. The activity of the compounds was estimated from the prevention by them of disruptions of cardaic contractions and death of animals and from the elimination of lethal fibrillation. The effect of a studied compound was determined quantitatively by calculating the effective dose (ED_{50}) and the average lethal dose (LD_{50}) by the Litchfeld—Wilcoxon method [18]; the breadth of the therapeutic effect, by the antiarrythmic index (LD_{50}/ED_{50}).

Determination of Analgesic Activity of Aminoalcohol Hydrochlorides (4a + 5a), (4b + 5b), and (4c + 5c). The analgesic activity was studied for chemical irritation in 80 mongrel mice. The studied compounds were administered ip 1 h before administering acetic acid. The specific pain reaction, cramps (characteristic movements of animals including contraction of abdominal muscles alternating with their relaxation and extension of rear extremities and bending of the spine), was induced by ip administration of acetic acid (0.75%, 0.1 mL/10 g body mass). For the next 15 min after the injection, the number of cramps was measured for each animal (10 animals per group). The analgesic effect was estimated from the decrease in the number of cramps in percent of the control. The effectiveness criterion for the screening was a reduction of the pain reaction by at least 50%.

REFERENCES

1. A. M. Gazaliev, M. Zh. Zhurinov, and S. D. Fazylov, *New Bioactive Alkaloid Derivatives* [in Russian], Gylym, Almaty (1992), 206.
2. K. J. Blackhall, D. Hendry, R. J. Pryce, and S. M. Roberts, *J. Chem. Soc., Perkin Trans.*, No. 21, 2767 (1995).
3. M. D. Mashkovskii, *Medicinal Preparations* [in Russian], Vol. 1, Meditsina, Moscow (1998), 127.
4. T. W. Seale, R. Nael, S. Satendra, and G. Basmadjian, *NeuroReport*, 201 (1998).

5. R. M. Sultanova, M. D. Khanova, I. A. Dvornikova, A. V. Kuchin, V. A. Dokichev, Yu. V. Tomilov, and O. M. Nefedov, in: *Book of Abstracts of the VII Conference on the Chemistry of Carbenes and Related Intermediates*, Kazan (2003), p. 40.
6. Russ. Pat. No. 2,228,179 (2004).
7. R. Yu. Khisamutdinova, N. N. Yarmukhamedov, S. F. Gabdrakhmanova, D. T. Karachurina, G. A. Sapozhnikova, N. Z. Baibulatova, N. Zh. Baschenko, and F. S. Zarudii, *Khim.-Farm. Zh.*, 27 (2004).
8. I. P. Dubovik, M. M. Garazd, V. I. Vinogradova, and V. P. Khilya, *Khim. Prir. Soedin.*, 110 (2006).
9. M. V. Veselovskaya, M. M. Garazd, V. I. Vinogradova, and V. P. Khilya, *Khim. Prir. Soedin.*, 230 (2006).
10. A. S. Trifilenkov, A. P. Il′in, D. V. Kravchenko, M. V. Dorogov, S. E. Tkachenko, and A. V. Ivashchenko, *Izv. Vyssh. Zaved. Khim. Khim. Tekhnol.*, 96 (2005).
11. O. A. Pukhlyakova, N. Z. Baibulatova, I. O. Maidanova, T. V. Khakimova, V. A. Dokichev, and M. S. Yunusov, *Zh. Org. Khim.*, **36**, 1404 (2000).
12. A. Haiosh, *Komplexe Hydride*, Berlin (1966).
13. R. Andrisano, A. S. Angeloni, and S. Marzocchi, *Tetrahedron*, **29**, 913 (1973).
14. L. F. Tietze and T. Eicher, *Preparative Organic Chemistry* [translated from Ger., *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, Stuttgart (1991)], Mir, Moscow (1999), p. 69.
15. G. Brauer, ed., *Handbuch der Praeparativen Anorganischen Chemie in Drei Baenden*, Bd. 1, Enke, Stuttgart, Ger. (1975); Vol. 3, (1985), p. 891 [Russian translation].
16. A. J. Gordon and R. A. Ford, *A Chemist's Companion*, Wiley-Interscience, New York (1972).
17. V. P. Fisenko, ed., *Handbook of Experimental (Preclinical) Study of New Pharmacological Substances* [in Russian], ZAO IIA Remedium, Moscow (2000), pp. 209-217.
18. M. L. Belen′kii, *Elements of Quantitative Evaluation of Pharmacological Effects* [in Russian], Medgiz, Leningrad (1963), p. 152.