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SYNTHESIS AND STRUCTURE OF *N*-(2-(1-ADAMANTYL)-2-HYDROXYETHYL)CYTISINE DIASTEREOMERS

D. V. Shishkin,[1] E. R. Mukhamed′yarova,[1] N. Z. Baibulatova,[1] V. A. Dokichev,[1] and Yu. V. Tomilov[2]

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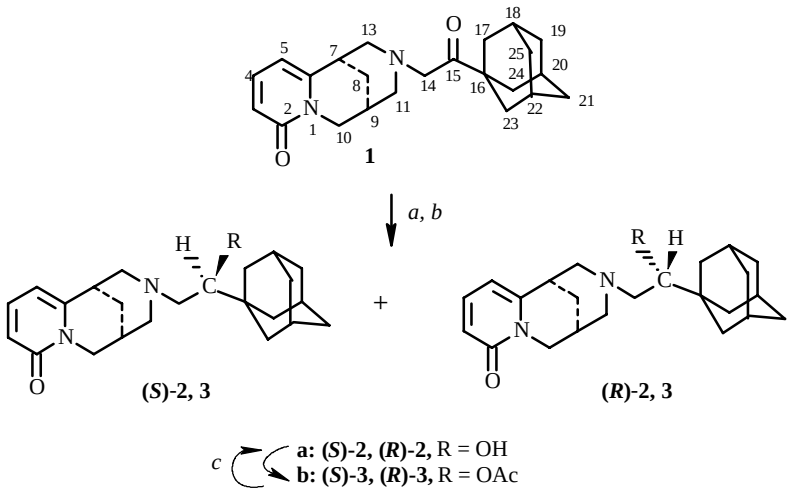
Diastereomers of N-*(2-(1-adamantyl)-2-hydroxyethyl)cytisine were synthesized by reduction of* N-*(2-(1-adamantyl)-2-oxoethyl)cytisine with* $NaBH_4$. *Their structures were established using x-ray structure analysis.*

Key words: synthesis, cytisine derivatives, diastereomers, 15(*R*)- and 15(*S*)-*N*-(2-(1-adamantyl)-2-hydroxyethyl)cytisine, x-ray structure analysis, PMR, ^{13}C NMR.

The high physiological activity (spasmolytic, insecticidal, analgesic, antiarrythmic, etc. [1-3]) of compounds containing the 3,7-diazabicyclo[3.3.1]nonane moiety is responsible for the development of new methods and techniques for preparing them. Efforts to synthesize new compounds of this class are intense. As a rule, they are prepared by reaction of aliphatic ketones, piperidin-4-ones [4], or nitrocompounds [5-7] with primary amines and formaldehyde under Mannich reaction conditions.

Targeted modification of natural alkaloids of this class of heterocycles, in particular cytisine, is of special interest. We prepared *N*-(2-hydroxyethyl)cytisine hydrochloride, which possesses high antiarrythmic activity in aconitine and calcium chloride models of arrythmia [8]. It is known that adamantane derivatives exhibit anti-Parkinsons activity, which is probably due to the ability of the bulky and highly lipophilic adamantane moiety to interact with biological membranes containing a lipid layer and with hydrophobic regions of proteins [9, 10].

Herein we report the synthesis of *N*-(2-(1-adamantyl)-2-hydroxyethyl)cytisine (**2**) and the structures of the resulting diastereomers that were established using x-ray structure analysis (XSA).



a. $NaBH_4$, *i*-PrOH, 20°C, 5 h; *b.* Ac_2O/AcOH, reflux 5h; *c.* KOH, MeOH, 20°C, 98%

1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, fax (347) 235 60 66, e-mail: dokichev@anrb.ru; 2) N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, fax (495) 135 63 90, e-mail: tom@ioc.ac.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 244-247, May-June, 2007. Original article submitted March 27, 2007.

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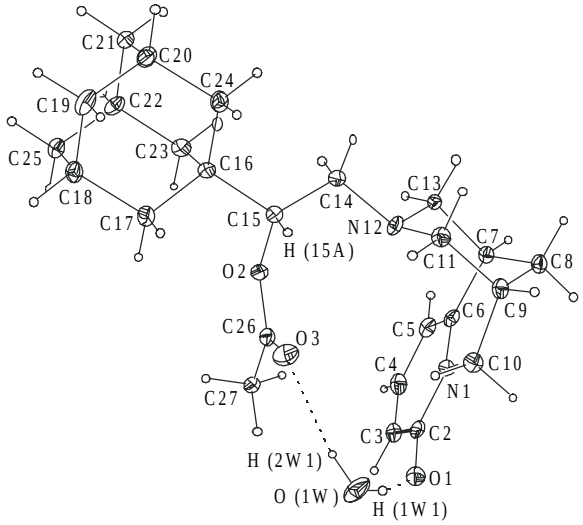

Fig.1.

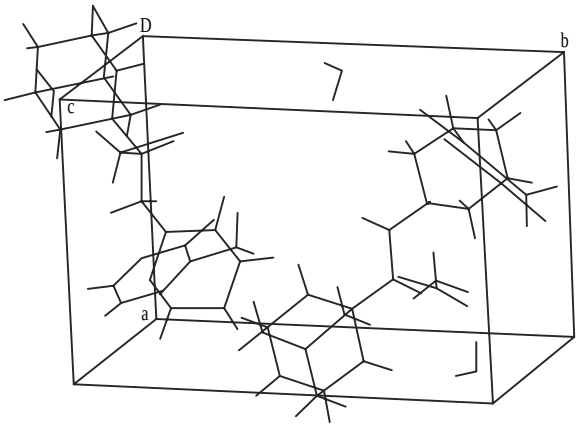

Fig. 2.

Fig. 1. Molecular structure of *N*-(2-(1-adamantyl)-2-acetoxyethyl)cytisine (***R***)-**3**.
Fig. 2. Crystal packing of *N*-(2-(1-adamantyl)-2-acetoxyethyl)cytisine (***R***)-**3**.

N-(2-(1-Adamantyl)-2-oxoethyl)cytisine (**1**) was prepared in 99% yield by reacting cytisine with an equimolar amount of 1-adamantylbromomethylketone in the presence of K_2CO_3 in absolute acetone. Reduction of **1** by $NaBH_4$ in isopropanol formed a difficultly separated mixture of the two diastereomers *N*-(2-(1-adamantyl)-2-hydroxyethyl)cytisine, (***S***)-**2** and (***R***)-**2**, in 98% overall yield and a 13:7 ratio, respectively. The configurations of the C-15 atoms in (***S***)-**2** and (***R***)-**2** were established using XSA of *N*-(2-(1-adamantyl)-2-acetoxyethyl)cytisine (***R***)-**3**, which was isolated by HPLC (MeOH:H_2O:AcOH eluent, 13:7:1) from a mixture of the acetylated aminoalcohols, (***S***)-**3** and (***R***)-**3**. According to XSA, (***R***)-**3** contains a water molecule in its structure despite the fact that (***R***)-**3** was dried at 70°C in vacuo (1 mm Hg) for 2 h after recrystallization from MeOH:H_2O (3:1 v/v). Alkaline hydrolysis of the acetates (***R***)-**3** or (***S***)-**3** by KOH produced in quantitative yield the pure alcohols (***R***)-**2** and (***S***)-**2**. This indicated that the configuration of C-15 did not change upon acetylation by acetic anhydride.

Figure 1 shows a general view of the molecular structure of (***R***)-**3**. The crystal structure contains intramolecular H-bonds between the water molecule and the carbonyl of the pyridone ring [bond length 2.855(2) Å, O–H = 0.96, C=O...H = 1.91(3) Å, O–H...O=C = 169(3)°] and the acetyl group [bond length 2.872(2) Å, O–H = 0.78(3), C=O...H = 2.11(3) Å, O–H...O=C = 165(3)°]. Figure 2 shows the packing of (***R***)-**3** in the crystal lattice.

Taking into account experimental uncertainty, the bond lengths and angles in the cytisine moiety deviate insignificantly from the literature values published for cytisine and its derivatives [11-14]. The cytisine moiety adopts the chair—chair conformation with an equatorial substituent on N-12. According to the XSA, C-15 has the *R*-configuration.

The structures of the synthesized compounds were confirmed by PMR and ^{13}C NMR spectra using homo- and heteronuclear two-dimensional HH-COSY and CH-CORR NMR spectra. Thus, magnetically equivalent C-17, C-23, and C-24 of the adamantyl and C-2, C-3, C-4, C-5, and C-6 of the pyridone ring, which appeared at δ_C 104-166 ppm, were determined unambiguously using the multiplicity and magnitude of chemical shifts in the ^{13}C NMR spectra. Assignment of signals for nonequivalent ring methylene protons H-10, H-11, and H-13, the positions of which in the PMR spectra could be affected significantly by conformational equilibria in solution (chair—boat), was more complicated. They were assigned by analyzing the SSCC. For example, the spin—spin splitting of H-11 with ^2J = 11.1 and $^3J_{1\text{-}9}$ = 1.9 suggested unambiguously that it was located in an *exo*-position. In all instances for the prepared compounds, *endo*-protons on both C-11 and C-13 as well as C-10 appeared at weak field compared with *exo*-protons. The methine proton on C-15 in the (***S***)-**3** isomer appeared in the PMR spectrum as a triplet at δ_H 4.48 ppm; in (***R***)-**3**, as a doublet of doublets at 4.56.

Thus, diastereomers of *N*-(2-(1-adamantyl)-2-hydroxyethyl)cytisine were synthesized and their structures were established.

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (300.13 MHz and 75 MHz) with Me_4Si internal standard. IR spectra in mineral oil were obtained on a Spekord M-80 instrument. Mass spectra were measured in a MX-1300 spectrometer at 100°C inlet and 12 and 70 eV ionization potential. TLC was carried out on Silufol and Sorbfil chromatographic plates using C_6H_6:Et_2O:MeOH (10:5:2) with development in an iodine chamber.

Compounds (***R***)-**3** and (***S***)-**3** were isolated pure using HPLC on a DuPont chromatograph with UV detection at 254 nm, Phenomenx Luna 250 × 10 mm column, silica gel with grafted C_{18}, 10 μm, 100 Å, with elution by MeOH:H_2O:AcOH (13:7:1), and isocratic mobile phase flow rate 4 mL/min.

XSA of (*R*)-3, $C_{25}H_{36}N_2O_4$, needle-like crystals from MeOH:H_2O (2:1). The XSA was performed at 100 K on a Bruker SMART APEX2 1000 CCD automated 3-circle diffractometer (Mo Kα-radiation, graphite monochromator, $2\theta_{max}$ $\mu \leq 56°$, $\lambda = 0.71073$ Å). The crystals were monoclinic, colorless, 0.60 × 0.35 × 0.23 mm, $a = 8.8844(15)$, $b = 12.728(2)$, $c = 9.9327(16)$ Å, $\beta = 96.930(4)°$, V = 1115.0(3) Å^3, $Z = 2$, $d_{calc} = 1.277$ g/cm^3, $\mu = 0.086$ mm^{-1}, F(000) = 464, space group $P2_1$. A total of 5786 reflections were measured, of which 4161 independent reflections were used in further calculations and refinement ($R_{int} = 0.0456$). The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms over F^2_{hkl}. H atoms were located in a difference electron-density synthesis and refined isotropically. The final agreement factors were $R = 0.527$ for 4161 reflections with $I > 2\sigma(I)$, $wR_2 = 0.0830$, and GOF = 1.003 over all reflections. All calculations were performed using the SHELXTL PLUS programs [15].

The complete crystallographic data were deposited in the Cambridge Crystallographic Database, No. CCDC 633710.

***N*-(2-(1-Adamantyl)-2-oxoethyl)cytisine (1).** A mixture of cytisine (0.37 g, 1.94 mmol) and freshly calcined KOH (0.60 g, 4.34 mmol) in absolute acetone (20 mL) was stirred vigorously, refluxed, and treated dropwise over 30 min with 1-adamantylbromomethylketone (0.50 g, 1.94 mmol) in absolute acetone (10 mL). The mixture was refluxed and stirred for 4 h and filtered to remove the precipitate. The precipitate was washed with $CHCl_3$ (30 mL). The solvent was removed at reduced pressure to afford **1** (0.71 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}): 1432, 1656, 1348, 1692, 1708.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.57 (3H, d, $^2J_{B\text{-}A} = 11.6$, H_B-17,23,24), 1.64 (6H, br.s, H-19,21,25), 1.67 (3H, d, $^2J_{A\text{-}B} = 11.6$, H_A-17,23,24), 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-18,20,22), 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-18,20,22), 27.91 (C-9), 35.23 (C-7), 36.27 (C-19,21,25), 38.05 (C-17,23,24), 45.67 (C-16), 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).

Reduction of 1 by $NaBH_4$. A solution of $NaBH_4$ (0.12 g, 3.20 mmol) in *i*-PrOH (20 mL) at room temperature was stirred and treated dropwise over 1 h with **1** (0.58 g, 1.60 mmol) in MeOH (50 mL). The mixture was stirred for 5 h, treated with dry acetone (5 mL), and stirred another 15 min. Solvent was removed at reduced pressure. The solid was dissolved in $CHCl_3$ (70 mL). The resulting solution was passed over a layer of Al_2O_3 (2 cm). Solvent was removed at reduced pressure to afford light yellow crystals (0.58 g, 98%) that were a mixture of (***S***)-**2** and (***R***)-**2** in a 13:7 ratio. The ratio of diastereomers was determined from the ratio of areas of the signals for the C-10 methylene *endo*-protons. Mass spectrum (*m*/*z*): 368 $[M]^+$. IR spectrum (ν, cm^{-1}): 952, 988, 1088, 1458, 1551, 1651, 2818-3000, 3100-3600.

***N*-(2-(1-Adamantyl)-2-hydroxyethyl)cytisine (*R*)-2.** PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.45 (6H, m, H-17,23,24), 1.59 (3H, br.d, $^2J = 12.0$, H_A-19,21,25), 1.68 (3H, br.d, $^2J = 12.0$, H_B-19,21,25), 1.80 (1H, br.d, $^2J = 12.5$, H_{anti}-8), 1.90 (1H, br.d, $^2J = 12.5$, H_{syn}-8), 1.92 (3H, br.s, H-18,20,22), 2.20 (1H, dd, $^2J = 12.3$, $^3J_{14B\text{-}15} = 10.3$, H_B-14), 2.23 (1H, br.d, $^2J = 12.0$, H_{exo}-11), 2.30 (1H, dd, $^2J = 12.3$, $^3J_{14A\text{-}15} = 3.2$, H_A-14), 2.40 (1H, br.s, OH), 2.45 (1H, br.s, H-9), 2.63 (1H, dd, $^2J = 10.6$, $^2J_{13exo\text{-}7} = 2.0$, H_{exo}-13), 2.83 (1H, br.d, $^2J = 10.6$, H_{endo}-13), 2.98 (1H, br.s, H-7), 3.00 (1H, dd, $^3J_{15\text{-}14B} = 10.3$, $^3J_{15\text{-}14A} = 3.2$, H-15), 3.08 (1H, br.d, $^2J = 11.0$, H_{endo}-11), 3.90 (1H, dd, $^2J = 15.5$, $^3J_{10exo\text{-}9} = 6.4$, H_{exo}-10), 4.03 (1H, d, $^2J = 15.5$, H_{endo}-10), 6.00 (1H, dd, $^3J_{5\text{-}4} = 6.8$, $^4J_{5\text{-}3} = 1.2$, H-5), 6.40 (1H, dd, $^3J_{3\text{-}4} = 9.1$, $^4J_{3\text{-}5} = 1.2$, H-3), 7.29 (1H, dd, $^3J_{4\text{-}3} = 9.1$, $^3J_{4\text{-}5} = 6.8$, H-4).

^{13}C NMR spectrum (CD_3OD, δ, ppm): 26.63 (C-8), 29.50 (C-9), 29.87 (C-18,20,22), 37.08 (C-16,7), 38.45 (C-19,21,25), 39.18 (C-17,23,24), 51.63 (C-10), 59.91 (C-14), 60.75 (C-11), 62.94 (C-13), 75.81 (C-15), 107.78 (C-5), 116.67 (C-3), 141.26 (C-4), 153.76 (C-6), 165.60 (C-2).

***N*-(2-(1-Adamantyl)-2-hydroxyethyl)cytisine (*S*)-2**, mp 184-185°C ($CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.45 (3H, br.d, ^2J = 11.9, H_A-17,23,24), 1.51 (3H, br.d, ^2J = 11.9, H_B-17,23,24), 1.60 (3H, br.d, ^2J = 11.8, H_A-19,21,25), 1.68 (3H, br.d, ^2J = 11.8, H_B-19,21,25), 1.82 (1H, br.d, ^2J = 12.5, H_{anti}-8), 1.93 (3H, br.s, H-18,20,22), 1.94 (1H, br.d, ^2J = 12.5, H_{syn}-8), 2.18 (1H, d, ^2J = 11.1, H_{exo}-13), 2.22 (1H, dd, ^2J = 12.0, $^3J_{14B-15}$ = 3.4, H_B-14), 2.33 (1H, dd, ^2J = 12.0, $^3J_{14A-15}$ = 10.9, H_A-14), 2.47 (1H, br.s, H-9), 2.59 (1H, br.d, ^2J = 10.6, H_{exo}-11), 2.89 (1H, br.d, ^2J = 10.6, H_{endo}-11), 2.98 (1H, br.s, OH), 2.99 (1H, br.s, H-7), 3.01 (1H, dd, $^3J_{15-14A}$ = 10.9, $^3J_{15-14B}$ = 3.4, H-15), 3.06 (1H, br.d, ^2J = 11.1, H_{endo}-13), 3.90 (1H, dd, ^2J = 15.4, $^3J_{10exo-9}$ = 6.4, H_{exo}-10), 4.12 (1H, d, ^2J = 15.4, H_{endo}-10), 6.00 (1H, dd, $^3J_{5-4}$ = 6.8, $^4J_{5-3}$ = 1.3, H-5), 6,42 (1H, dd, $^3J_{3-4}$ = 9.1, $^4J_{3-5}$ = 1.3, H-3), 7.28 (1H, dd, $^3J_{4-3}$ = 9.1, $^4J_{4-5}$ = 6.8, H-4).

^{13}C NMR spectrum (CD_3OD, δ, ppm): 26.55 (C-8), 29.70 (C-9), 29.78 (C-18,20,22), 36.80 (C7), 37.04 (C-16), 38.39 (C-19,21,25), 39.08 (C-17,23,24), 51.68 (C-10), 59.74 (C-11), 61.23 (C-14), 62.31 (C-13), 75.72 (C-15), 107.94 (C-5), 116.64 (C-3), 141.36 (C-4), 153.55 (C-6), 165.57 (C-2).

Acetylation of (*R*)-2 and (*S*)-2 Mixture. Diastereomers (***S*)-2** and (***R*)-2** (0.45 g, 1.22 mmol) in glacial acetic acid (45 mL) were treated with freshly distilled acetic anhydride (5 mL) and *p*-toluenesulfonic acid (1 mg) and refluxed for 5 h. Solvent and unreacted acetic anydride were removed at reduced pressure. The solid was dissolved in $CHCl_3$ (75 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na_2SO_4. Solvent was removed at reduced pressure to afford a mixture of (***S*)-3** and (***R*)-3** (0.47 g, 95%) in a 13:7 ratio as a brown oil. The mixture was separated by HPLC. The ratio of diastereomers was determined from the ratio of areas for the signals of the C-15 methine protons.

***N*-(2-(1-Adamantyl)-2-acetoxyethyl)cytisine (*R*)-3**, mp 163-164°C (MeOH:H_2O, 3:1).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.38 (3H, br.d, ^2J = 12.3, H_A-17,23,24), 1.45 (3H, br.d, ^2J = 12.3, H_B-17,23,24), 1.55 (3H, br.d, ^2J = 11.8, H_A-19,21,25), 1.65 (3H, br.d, ^2J = 11.8, H_B-19,21,25), 1.73 (1H ,br.d, ^2J = 12.7, H_{anti}-8), 1.80 (3H, s, Me), 1.81 (1H, br.d, ^2J = 12.7, H_{syn}-8), 1.89 (3H, br.s, H-18,20,22), 2.13 (1H, ddd, ^2J = 10.6, $^3J_{11exo-9}$ = 2.1, $^4J_{11exo-10exo}$ = 0.9, H_{exo}-11), 2.25 (1H, dd, ^2J = 13.1, $^3J_{14B-15}$ = 8.6, H_B-14), 2.36 (1H, br.s, H-9), 2.39 (1H, dd, ^2J = 13.1, $^3J_{14A-15}$ = 3.8, H_A-14), 2.41 (1H, dd, ^2J = 10.5, $^3J_{13exo-7}$ = 1.8, H_{exo}-13), 2.88 (1H, dddd, ^2J = 10.5, $^3J_{13endo-7}$ = 3.5, $^3J_{13endo-8syn}$ = 1.7, $^3J_{13endo-11endo}$ = 1.6, H_{endo} = 13), 2.92 (1H, br.s, H-7), 3.13 (1H, dddd, ^2J = 10.6, $^3J_{11endo-9}$ = 3.1, $^3J_{11endo-13endo}$ = 1.6, $^3J_{11endo-8endo}$ = 1.5, H_{endo}-11), 3.81 (1H, dd, ^2J = 15.3, $^3J_{10exo-9}$ = 6.7, H_{exo}-10), 4.01 (1H, d, ^2J = 15.3, H_{endo}-10), 4.56 (1H, dd, $^3J_{15-14B}$ = 8.6, $^3J_{15-14A}$ = 3.8, H-15), 5.98 (1H, dd, $^3J_{5-4}$ = 6.8, $^4J_{5-3}$ = 1.2, H-5), 6.42 (1H, dd, $^3J_{3-4}$ = 9.0, $^4J_{3-5}$ = 1.2, H-3), 7.26 (1H, dd, $^3J_{4-3}$ = 9.0, $^3J_{4-5}$ = 6.8, H-4).

^{13}C NMR spectrum (δ, ppm): 20.48 (Me), 25.97 (C-8), 27.91 (C-9), 28.08 (C-18,20,22), 35.29 (C-16), 35.76 (C-7), 37.00 (C-19,21,25), 38.19 (C-17,23,24), 49.51 (C-10), 57.08 (C-14), 59.06 (C-11), 62.02 (C-13), 75.56 (C-15), 104.47 (C-5), 116.52 (C-3), 138.42 (C-4), 151.52 (C-6), 163.39 (C-2), 170.53 (C-26).

***N*-(2-(1-Adamantyl)-2-acetoxyethyl)cytisine (*S*)-3.**

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.39 (3H, br.d, ^2J = 13.0, H_A-17,23,24), 1.44 (3H, br.d, ^2J = 13.0, H_B-17,23,24), 1.55 (3H, br.d, ^2J = 12.0, H_A-19,21,25), 1.65 (3H, br.d, ^2J = 12.0, H_B-19,21,25), 1.74 (1H, br.d, ^2J = 12.8, H_{anti}-8), 1.80 (3H, s, Me), 1.84 (1H, br.d, ^2J = 12.8, H_{syn}-8), 1.89 (3H, br.s, H-18,20,22), 2.15 (1H, dd, ^2J = 10.5, $^3J_{13exo-7}$ = 2.0, H_{exo}-13), 2.35 (2H, d, ^2J = 6.1, H-14), 2.39 (1H, dd, ^2J = 11.1, $^3J_{11exo-9}$ = 1.9, H_{exo}-11), 2.41 (1H, br.s, H-9), 2.89 (1H, br.d, ^2J = 11.1, H_{endo}-11), 2.91 (1H, br.s, H-7), 3.07 (1H, dddd, ^2J = 10.5, $^3J_{13endo-7}$ = 3.5, $^3J_{13endo-8syn}$ = 1.7, $^3J_{13endo-11endo}$ = 1.6, H_{endo}-13), 3.86 (1H, dd, ^2J = 15.4, $^3J_{10exo-9}$ = 7.3, H_{exo}-10), 4.02 (1H, d, ^2J = 15.4, H_{endo}-10), 4.48 (1H, t, $^3J_{15-14}$ = 6.1, H-15), 6.02 (1H, dd, $^3J_{5-4}$ = 6.9, $^4J_{5-3}$ = 1.3, H-5), 6.44 (1H, dd, $^3J_{3-4}$ = 9.0, $^4J_{3-5}$ = 1.3, H-3), 7.35 (1H, dd, $^3J_{4-3}$ = 9.0, $^3J_{4-5}$ = 6.9, H-4).

^{13}C NMR spectrum (δ, ppm): 20.57 (Me), 25.85 (C-8), 28.02 (C-18,20,22), 28.19 (C-9), 35.27 (C-7), 35.35 (C-16), 36.90 (C-19,21,25), 38.04 (C-17,23,24), 49.97 (C-10), 56.90 (C-14), 59.19 (C-13), 61.84 (C-11), 75.53 (C-15), 105.54 (C-5), 116.29 (C-3), 138.99 (C-4), 150.83 (C-6), 163.63 (C-2), 170.30 (C-26).

General Method for Alkaline Hydrolysis of (*R*)-3 or (*S*)-3. A solution of *N*-(2-(1-adamantyl)-2-acetoxyethyl)cytisine (28 mg, 0.068 mmol) in MeOH (6 mL) was treated with solid KOH (38 mg, 0.68 mmol) and stirred for 2 h at 20°C. Solvent was removed at reduced pressure. The solid was dissolved in hot CH_2Cl_2. The precipitate was filtered off. The filtrate was washed with water (3 × 5 mL) and dried over anhydrous Na_2SO_4. Solvent was removed at reduced pressure to afford (***R*)-2** (25 mg, 99%) as an oil and (***S*)-2** (25 mg, 99%) as colorless crystals, mp 184-185°C ($CHCl_3$).

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