SYNTHESIS AND CRYSTAL STRUCTURE OF *N*(12)-(2-HYDROXY-2-PHENYLETHYL)CYTISINE

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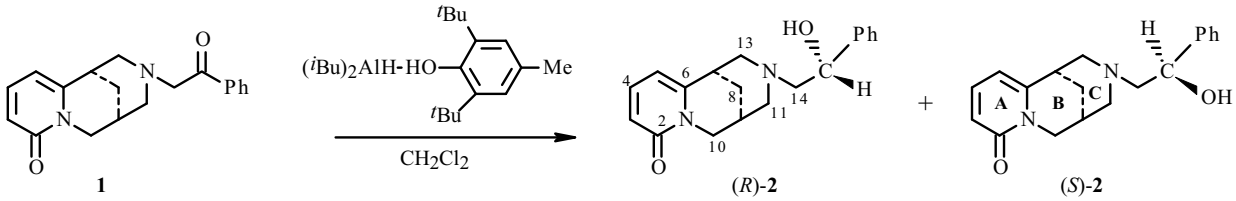
Diastereomers of N(12)-(2-hydroxy-2-phenylethyl)cytisine were synthesized by reduction of N(12)-(2-oxo-2-phenylethyl)cytisine by Yamamoto reagent. Their structures were solved using x-ray structure analysis.

Keywords: synthesis, cytisine derivatives, Yamamoto reagent, diastereomers, (15*R*)- and (15*S*)-*N*(12)-(2-hydroxy-2-phenylethyl)cytisine, x-ray structure analysis, PMR, ^{13}C NMR.

Nitrogenous heterocycles of the 3,7-diazabicyclo[3.3.1]nonane series are known to exhibit anti-arrhythmic activity [1]. However, such activity had not been reported at the start of our research for cytisine and its derivatives, which contain this fragment. We showed that introducing a 2-hydroxyethyl substituent in the *N*(12)-position of cytisine leads to the appearance in these compounds of anti-arrhythmic activity [2–4].

It was found earlier that the nature of the metal hydride had a decisive role in the stereoselective reduction of *N*(12)-(2-oxoethyl)cytisines [4]. Thus, reduction of ketone **1** by $NaBH_4$–$CeCl_3 \cdot 7H_2O$, $NaBH_4$–Et_3N, $LiAlH_4$, and $LiAlH_4$–(–)-menthol formed diastereomers (*R*)-**2** and (*S*)-**2** with a slight excess of the *R*-isomer (5–15%). Use of $(i\text{-Bu})_2AlH$ or $AlH_3 \cdot NMe_3$ as reductant formed primarily the (*S*)-**2** diastereomer with the *S*-configuration at the C-15 chiral center.



Herein we studied the reduction of **1** by Yamamoto reagent [$(i\text{-Bu})_2AlH$–2,6-di-*tert*-butyl-4-methylphenol] in order to increase the stereoselectivity of the reaction and to establish the absolute configuration of the diastereomers of **2**.

Thus, reduction of **1** by Yamamoto reagent [**1**:$(i\text{-Bu})_2AlH$:2,6-di-*tert*-butyl-4-methylphenol, 1:8:10] in CH_2Cl_2 at –78°C formed (15*R*)-(*R*)-**2** and (15*S*)-*N*(12)-(2-hydroxy-2-phenylethyl)cytisines (*S*)-**2** in a 3:7 ratio in overall yield 70%. Reduction of the amide of the pyridone ring of *N*(12)-(2-oxo-2-phenylethyl)cytisine was not observed under the conditions selected by us. The ratio of diastereomers (*R*)-**2** and (*S*)-**2** in the reaction mixture was determined from the ratio of resonance areas of the C-15 methine protons that appeared in the PMR spectrum as a doublet of doublets at δ_H 4.61 and 4.55 ppm, respectively.

A mixture of diastereomers (*R*)-**2** and (*S*)-**2** was separated into the pure compounds by preparative HPLC in order to establish the absolute configuration of aminoalcohols **2**. The absolute configuration of the C-15 chiral center for diastereomer (*R*)-**2** was established by an x-ray structure analysis (XSA) (Fig. 1).

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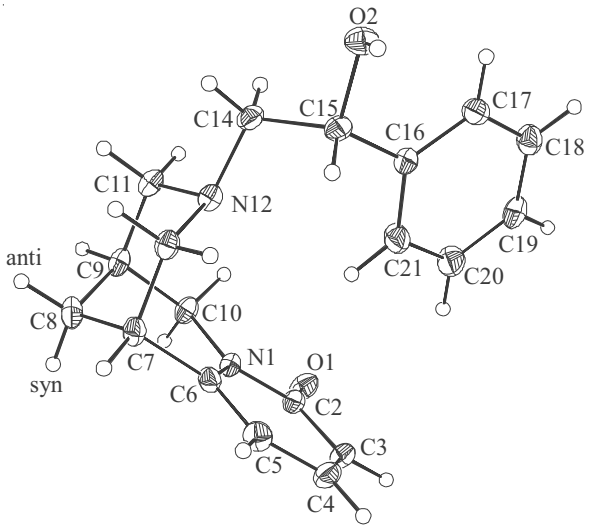

Fig. 1. Molecular structure of (7*R*,9*S*,15*R*)-*N*(12)-(2-hydroxy-2-phenylethyl)cytisine (*R*)-**2** from an XSA.

According to the XSA, the substituent on N-12 in the crystal phase of (*R*)-**2** occupied an equatorial position. The sum of the bond angles around N-12 (332.0°) indicated that the N atom had pyramidal coordination.

The structures of the synthesized compounds were confirmed by PMR and ^{13}C NMR data using homo- and heteronuclear two-dimensional HH-COSY and HETCOR NMR spectra.

Analysis of the spin–spin coupling constants showed that the 3,7-diazabicyclo[3.3.1]nonane fragment of cytisine in solution had a conformation close to that found in the XSA. The criteria that confirmed the chair-like conformation of the piperidine part were the observed (~1.3 Hz) through-space SSCC between H_{endo}-13, H_{endo}-11, and H_{syn}-8 in addition to those between H_{exo}-10, H_{exo}-11, H_{endo}-10, and H_{anti}-8. The SSCC between the apical proton on C-9 and the C-10 protons reflected the conformational state of ring B [5]. Values of $^3J_{9\text{-}10}$ of the order of 7 and 1 Hz corresponded to dihedral angles of ~31° and ~88°, which indicated that the chair-like conformation of ring B was flattened.

The significantly greater shielding of H_{exo}-11 and H_{exo}-13 (2.41–2.63 ppm) in (*R*)-**2** and (*S*)-**2** than in (-)-cytisine (3.00 and 3.01 ppm) was, according to the literature [6], due to increased electron density in the antiperiplanar position to the unshared electron pair on the N atom and indicated that the substituent on N-12 had an equatorial position. The presence in the IR spectra of (*R*)-**2** and (*S*)-**2** (in CCl_4 solution) of Boltzmann bands at 2850 and 2922 cm^{-1} also indicated that the unshared electron pair on the N atom had an axial position [7, 8].

Comparison of the spectra showed that the chemical shifts for C-11 and C-13 in addition to the *endo*- and *exo*-protons of C-11 and C-13 were distributed differently for the (*R*)-**2** and (*S*)-**2** diastereomers [9]. In (*R*)-**2**, the resonance of H_{exo}-11 (2.43 ppm) appeared at strong fields for *exo*-protons on C-11 and C-13. For the *endo*-positions, the resonance for H_{endo}-13 (2.86 ppm) appeared at stronger field. For (*S*)-**2**, H_{exo}-13 (2.41 ppm) and H_{endo}-11 (2.88 ppm) appeared at stronger fields. In the ^{13}C NMR spectra, C-13 (62.20 ppm) appeared at weaker field for (*R*)-**2** whereas C-11 (61.30 ppm) appeared at weaker field for (*S*)-**2**.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) with Me_4Si internal standard. IR spectra were obtained in mineral oil on a Spekord M-80 instrument and in a solution KBr cuvette with a 0.015 mm layer of CCl_4 ($c = 6.45\cdot10^{-3}$ M) on an IR Prestige-21 (Shimadzu). Mass spectra were taken in an MX-1300 spectrometer at 100°C inlet temperature and 70 eV ionizing potential. Melting points were determined on a Boetius microstage. Elemental analyses of the compounds were performed on a CHN-analyzer (HEKAtech GmbH Analysen-technik's Euro-EA). TLC analysis was carried out on silica gel 60 chromatographic plates (Merck) with development in an iodine chamber. Optical rotation angles were measured on a Perkin–Elmer 341 polarimeter (λ 589 nm) at 20°C. The XSA was performed at 100 K on a Bruker Smart Apex2 1000 CCD automated three-circle diffractometer (MoK_α-radiation, graphite monochromator, $2\theta_{max} \le 56°$, λ MoK_α = 0.71073 Å). Compounds (*R*)-**2** and (*S*)-**2** were separated pure by HPLC using a

Shimadzu LC-20 chromatographic system with a spectrophotometric diode-matrix detector (SPD-M20A) and a Bondapak Phenyl 300 × 3.9 mm, 10 μm column (Waters, USA). The mobile phase was H_2O:MeOH (60:40) at flow rate 1 mL/min. Detection was made at 330 nm.

Compound **1** was prepared as before [4]. Ketone **1** was reduced by the known method [10]. $(i\text{-Bu})_2AlH$ was purchased commercially as a 73% solution (OOO Redkin Pilot Plant).

XSA of (7*R*,9*S*,15*R*)-*N*(12)-(2-hydroxy-2-phenylethyl)cytisine (*R*)-2 ($C_{19}H_{22}N_2O_2$). Crystals grown from MeOH were orthorhombic, colorless, 0.15 × 0.05 × 0.02 mm, a = 9.3178(7), b = 10.6044(8), c = 15.8703(11) Å, $\alpha = \beta = \gamma = 90°$, V = 1568.1(2) Å^3, Z = 4, d_{calcd} = 1.315 g/cm^3, μ = 0.086 mm^{-1}, F(000) = 664, space group $P2_12_12_1$. Total number of measured reflections 18,776, of which 2597 independent reflections were used in further calculations and refinement (R_{int} = 0.0495). The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms over F^2_{hkl}. Hydrogen atoms were located in difference electron-density syntheses and refined isotropically. The final agreement factors were R = 0.0382 for 2597 reflections with $I > 2\sigma(I)$, wR_2 = 0.0918, and GOF = 1.018 over all reflections. All calculations were performed using the SHELXTL Plus programs [11]. Complete crystallographic data for (*R*)-**2** were deposited in the Cambridge Crystallographic Data Centre (No. CCDC 739257).

Reduction of 1 by Yamamoto Reagent. A solution of 2,6-di-*tert*-butyl-4-methylphenol (0.624 g, 3.246 mmol) in CH_2Cl_2 (7 mL) at 0°C was treated dropwise with a solution of $(i\text{-Bu})_2AlH$ (0.52 mL, 2.597 mmol) in CH_2Cl_2 (11 mL), stirred for 1 h at –10°C, cooled to –78°C, and slowly over 15 min treated dropwise with ketone **1** (0.10 g, 0.324 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at –78°C for 1 h, decomposed at –25°C by slow dropwise addition of HCl solution (1 mL of 37.4% in 9 mL H_2O). The temperature was adjusted to 0°C. Water (10 mL) was added dropwise. Water (20 mL) and CH_2Cl_2 (20 mL) were added at room temperature. The solution was washed with CH_2Cl_2 (3 × 30 mL). The acidic aqueous layer was neutralized with NaOH solution (10 mL, 15%, pH > 7) and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4. Solvent was removed to afford (*R*)-**2** and (*S*)-**2** (0.070 g, 70%) as crystals in a 3:7 ratio, respectively; R_f 0.23 (C_6H_6:Et_2O:MeOH, 10:5:2), $C_{19}H_{22}N_2O_2$. Mass spectrum: *m*/*z* 310 $[M]^+$. IR spectrum (ν, cm^{-1}): 700, 742, 802, 1378, 1426, 1456, 1486, 1546, 1564, 1648, 3200–3450.

(7*R*,9*S*,15*R*)-*N*(12)-(2-Hydroxy-2-phenylethyl)cytisine (*R*)-2, colorless crystals, mp 178–179°C (acetone), $[\alpha]_D^{20}$ –225 ± 3° (*c* 0.03, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.80 (1H, dddd, ^2J = 12.7, $^3J_{8anti\text{-}7}$ = 3.6, $^3J_{8anti\text{-}9}$ = 2.6, $^4J_{8anti\text{-}10endo}$ = 1.1, H_{anti}-8), 1.92 (1H, dtt, ^2J = 12.7, $^3J_{8syn\text{-}7}$ = 3.4, $^3J_{8syn\text{-}9}$ = 3.4, $^4J_{8syn\text{-}11endo}$ = 1.7, $^4J_{8syn\text{-}13endo}$ = 1.7, H_{syn}-8), 2.38 (1H, dd, ^2J = 12.7, $^3J_{14A\text{-}15}$ = 9.3, H_A-14), 2.43 (1H, ddd, ^2J = 11.2, $^3J_{11exo\text{-}9}$ = 2.4, $^4J_{11exo\text{-}10exo}$ = 1.2, H_{exo}-11), 2.47 (1H, m, H-9), 2.49 (1H, dd, ^2J = 12.7, $^3J_{14B\text{-}15}$ = 4.1, H_B-14), 2.61 (1H, dd, ^2J = 10.6, $^3J_{13exo\text{-}7}$ = 2.1, H_{exo}-13), 2.86 (1H, ddt, ^2J = 10.6, $^3J_{13endo}$-7 = 3.5, $^4J_{13endo\text{-}11endo}$ = 1.7, $^4J_{13endo\text{-}8syn}$ = 1.7, H_{endo}-13), 2.97 (2H, m, H-7, OH), 3.14 (1H, ddt, ^2J = 11.2, $^3J_{11endo\text{-}9}$ = 3.4, $^4J_{11endo\text{-}8syn}$ = 1.7, $^4J_{11endo\text{-}13endo}$ = 1.7, H_{endo}-11), 3.92 (1H, ddd, ^2J = 15.5, $^3J_{10exo\text{-}9}$ = 6.3, $^4J_{10exo\text{-}11exo}$ = 1.2, H_{exo}-10), 4.05 (1H, dt, ^2J = 15.5, $^3J_{10endo\text{-}9}$ = 1.1, $^4J_{10endo\text{-}8anti}$ = 1.1, H_{endo}-10), 4.61 (1H, dd, $^3J_{15\text{-}14A}$ = 9.3, $^3J_{15\text{-}14B}$ = 4.1, H-15), 5.99 (1H, dd, $^3J_{5\text{-}4}$ = 6.9, $^4J_{5\text{-}3}$ = 1.4, H-5), 6.46 (1H, dd, $^3J_{3\text{-}4}$ = 8.9, $^4J_{3\text{-}5}$ = 1.4, H-3), 7.19-7.28 (5H, m, H-(Ph)), 7.30 (1H, dd, $^3J_{4\text{-}3}$ = 8.9, $^3J_{4\text{-}5}$ = 6.9, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.82 (C-8), 27.88 (C-9), 35.70 (C-7), 49.89 (C-10), 59.10 (C-11), 62.32 (C-13), 65.91 (C-14), 69.31 (C-15), 104.68 (C-5), 117.10 (C-3), 125.75 (C-(*o*-Ph)), 127.48 (C-(*p*-Ph)), 128.31 (C-(*m*-Ph)), 138.75 (C-4), 141.92 (C-(*i*-Ph)), 150.79 (C-6), 163.41 (C-2).

(7*R*,9*S*,15*S*)-*N*(12)-(2-Hydroxy-2-phenylethyl)cytisine (*S*)-2, colorless crystals, mp 164–165°C (acetone), $[\alpha]_D^{20}$ –190 ± 1° (*c* 0.03, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.84 (1H, dtd, ^2J = 12.8, $^3J_{8anti\text{-}7}$ = 3.2, $^3J_{8anti\text{-}9}$ = 3.2, $^4J_{8anti\text{-}10endo}$ = 1.1, H_{anti}-8), 1.96 (1H, dtt, ^2J = 12.8, $^3J_{8syn\text{-}7}$ = 3.4, $^3J_{8syn\text{-}9}$ = 3.4, $^4J_{8syn\text{-}11endo}$ = 1.7, $^4J_{8syn\text{-}13endo}$ = 1.7, H_{syn}-8), 2.39 (1H, dd, ^2J = 12.6, $^3J_{14A\text{-}15}$ = 9.8, H_A-14), 2.41 (1H, dd, ^2J = 10.6, $^3J_{13exo\text{-}7}$ = 2.1, H_{exo}-13), 2.47 (1H, m, H-9), 2.49 (1H, dd, ^2J = 12.6, $^3J_{14B\text{-}15}$ = 3.9, H_B-14), 2.63 (1H, ddd, ^2J = 11.2, $^3J_{11exo\text{-}9}$ = 2.4, $^4J_{11exo\text{-}10exo}$ = 1.2, H_{exo}-11), 2.88 (1H, ddt, ^2J = 11.2, $^3J_{11endo\text{-}9}$ = 3.4, $^4J_{11endo\text{-}8syn}$ = 1.7, $^4J_{11endo\text{-}13endo}$ = 1.7, H_{endo}-11), 3.05 (2H, m, H-7, OH), 3.15 (1H, ddt, ^2J = 10.6, $^3J_{13endo\text{-}7}$ = 3.4, $^4J_{13endo\text{-}11endo}$ = 1.7, $^4J_{13endo\text{-}8syn}$ = 1.7, H_{endo}-13), 3.92 (1H, ddd, ^2J = 15.5, $^3J_{10exo\text{-}9}$ = 6.3, $^4J_{10exo\text{-}11exo}$ = 1.2, H_{exo}-10), 4.16 (1H, dt, ^2J = 15.5, $^3J_{10endo\text{-}9}$ = 1.1, $^4J_{10endo\text{-}8anti}$ = 1.1, H_{endo}-10), 4.55 (1H, dd, $^3J_{15\text{-}14A}$ = 9.8, $^3J_{15\text{-}14B}$ = 3.9, H-15), 6.03 (1H, dd, $^3J_{5\text{-}4}$ = 6.9, $^4J_{5\text{-}3}$ = 1.4, H-5), 6.47 (1H, dd, $^3J_{3\text{-}4}$ = 8.9, $^4J_{3\text{-}5}$ = 1.4, H-3), 7.21–7.30 (5H, m, H-(Ph)), 7.31 (1H, dd, $^3J_{4\text{-}3}$ = 8.9, $^3J_{4\text{-}5}$ = 6.9, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.94 (C-8), 25.34 (C-9), 35.27 (C-7), 50.02 (C-10), 59.11 (C-13), 61.71 (C-11), 65.56 (C-14), 68.70 (C-15), 104.75 (C-5), 117.22 (C-3), 125.69 (C-(*o*-Ph)), 127.48 (C-(*p*-Ph)), 128.34 (C-(*m*-Ph)), 138.83 (C-4), 141.85 (C-(*i*-Ph)), 150.47 (C-6), 163.47 (C-2).

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