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Synthesis and Structure Determination of Diastereoisomeric (1*R*,2*R*,6*S*)-6-(3-{[(1*RS*)-1-(1-Adamantyl)ethyl]amino}prop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diols

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Abstract—Epimeric (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol derivatives containing a rimantadine residue have been synthesized, and their steric structure has been determined using NOESY technique and DFT quantum chemical calculations.

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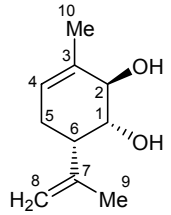
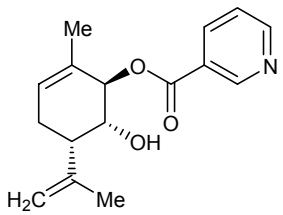
We previously found that diol **I** exhibits high anti-Parkinson [1, 2] and anticonvulsant activity [3]. Further studies have shown that chemical modification of diol **I** essentially affects its biological properties. The presence of two double bonds and two hydroxy groups is necessary for compound **I** to display pronounced anti-Parkinson effect [4]. Introduction of an oxygen- or nitrogen-containing substituent into position *9* of diol **I** sharply reduces or even eliminates anti-Parkinson activity, whereas it is retained if the substituent on C^9 is a sulfur- or carbon-containing group [5].

We recently revealed an appreciable activity of diol **I** against influenza A(H1N1) viruses. It was also found that nicotinic acid ester **II** is superior to **I** in the selectivity index with respect to influenza A(H1N1) viruses [6]. Rimantadine [**III**, (*RS*)-1-(1-adamantyl)ethanamine hydrochloride] is a well known antiviral drug whose action is based on inhibition of M2 ion channel necessary for the penetration of influenza viruses into cells [7, 8]. Some monoterpene derivatives containing a secondary amino group display similar properties [9]. Attachment of a rimantadine residue to diol **I** molecule seems to be promising from the viewpoint of studying antiviral [10] and other kinds of biological activity.



I



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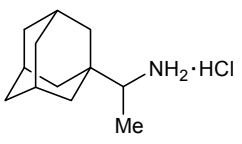
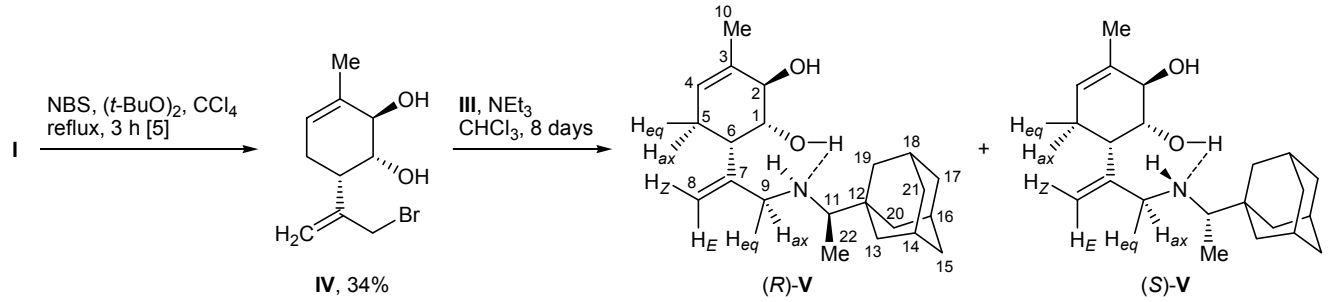


III

Taking into account the above stated, the goal of the present study was to synthesize rimantadine derivative of diol **I** at the 9-position.

We previously developed a procedure for the introduction of nitrogen-containing substituents into position *9* of diol **I** via allylic bromination and subsequent nucleophilic replacement of bromine in intermediate compound **IV** [5]. Following this procedure, by heating diol **I** with *N*-bromosuccinimide in boiling carbon tetrachloride in the presence of *tert*-butyl peroxide for 3 h we synthesized bromide **IV** in 34% yield (Scheme 1). Bromide **IV** was then brought into reaction with rimantadine (**III**) in chloroform in the presence of triethylamine (reaction time 8 days). By column chromatography we isolated a 1:1 mixture of stereoisomers (*R*)-**V** and (*S*)-**V** in an overall yield of 51%. The isomer mixture was subjected to repeated chromatographic separations. We thus succeeded in

Scheme 1.



isolating 5% of pure isomer (*R*)-**V** with *R* configuration of C^{11} and 8% of an epimer mixture enriched in (*S*)-**V** (*R*/*S* ratio 1 : 11, *de* 84%; Scheme 1).

Signals in the NMR spectra of stereoisomeric compounds **V** differing by configuration of the C^{11} atom were assigned as follows. Initially, preferred conformations of both stereoisomers were identified. Judging by the coupling constants between the 1-H and 2-H protons in both stereoisomers (^3J = 4.5 and 3.0 Hz), these protons occupy mainly pseudoequatorial positions; correspondingly, the hydroxy groups occupy pseudoaxial positions. Increased value of one of these coupling constants (4.5 Hz) is likely to result from appreciable contribution of the conformer with pseudoequatorial OH groups. We also tried to assign signals in the NMR spectra of the (*R*)- and (*S*)-diastereoisomers of **V** on the basis of DFT quantum chemical calculations. Preliminary conformational analysis led us to presume that the concentration of conformer with pseudoequatorial OH groups is higher for the (*R*)-diastereoisomer.

This assumption was additionally confirmed by comparison of the calculated (DFT) chemical shifts with the experimental values. The ^{13}C NMR spectra of both diastereoisomers were very similar: the maximum difference in the ^{13}C chemical shifts was ~2 ppm; therefore, we used ^1H chemical shifts as more informative. The largest differences in the chemical shifts were observed for geminal protons on C^5 and C^9. These differences were, respectively, 0.24 and 0.11 ppm for one isomer and 0.50 and 0.41 ppm, for the other. According to the calculation data, closer position of the 5-H signals may be determined by increased concentration of conformers with pseudoequatorial OH groups: the differences in the chemical shifts of 5-H_{eq} and 5-H_{ax} in the conformers with pseudoequatorial (*eq′*-OH) and pseudoaxial hydroxy groups (*ax′*-OH) have opposite signs. Closer position of signals from the C^9H_2 protons is expected only for the *R* configuration since the difference in the chemical shifts of protons on C^9 in the (*S*)-isomer almost does not change in going from *ax′*-OH to *eq′*-OH. Thus a combination of the experimental and calculation data suggests that conformers with pseudoaxial OH groups are most energetically favorable. However, the contribution of the conformer with pseudoequatorial OH groups may be appreciable in the case of the *R* configuration.

The hydrogen atom of the C^1OH group in the preferred conformers of both diastereoisomers is involved in intramolecular hydrogen bond with the nitrogen atom on C^9 (Scheme 1). The H-chelate ring thus formed fixes the conformation of the rimantadine residue, so that diastereotopic protons on C^9 can be denoted as pseudoequatorial (9-H_{eq}) and pseudoaxial (9-H_{ax}).

Taking into account the above data on preferred conformations of stereoisomers of **V**, we were able to unambiguously interpret the NOESY spectrum of a mixture of (*R*)-**V** and (*S*)-**V**. The spectrum clearly displayed a cross peak between 8-H_E and 9-H_{eq} in (*S*)-**V**, which was much more intense than the cross peak between 8-H_E and 9-H_{ax}. This means that the 8-H_E and 9-H_{eq} protons in the most energetically favorable conformer of (*S*)-**V** appear close to each other and that 8-H_E and 9-H_{ax} are distant from each other.

Stereoisomer (*R*)-**V** exists as two preferred conformers, one of which is characterized by close position of the 8-H_E and 9-H_{eq} protons, and the other, of 8-H_E and 9-H_{ax}. Correspondingly, the cross peaks due to nuclear Overhauser effects for these proton couples in the (*R*)-isomer are comparable in intensity. One conformer of (*R*)-**V** displayed in the NOESY spectrum cross peaks 5-H_{ax}/8-H_Z and 6-H/9-H_{ax}, whereas the corresponding protons in (*S*)-**V** are remote from each other, and no analogous nuclear Overhauser effects were observed. Cross peaks were also observed for 5-H_{ax}/9-H_{eq} and 1-H/22-H in (*R*)-**V** and for 5-H_{ax}/9-H_{ax} and 5-H_{ax}/22-H in (*S*)-**V**. These findings allowed us to unambiguously assign signals in the NMR spectra to particular diastereoisomers (*R*)-**V** and (*S*)-**V**.

EXPERIMENTAL

The spectral and analytical data were obtained at the Chemical Service Center (Siberian Branch, Russian Academy of Sciences). Quantum chemical calculations were performed at the Novosibirsk University Scientific Computing Center (*http://www.nusc.ru/*).

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500.13 and 125.76 MHz, respectively) and AV-600 spectrometers (600.3 and 150.96 MHz, respectively) from solutions in $CDCl_3$ using the residual proton and carbon signals of the solvent as reference ($CHCl_3$, δ 7.24; $CDCl_3$, δ_C 76.90 ppm). Signals in the NMR spectra were assigned using ^{1}H–^{1}H double resonance, *J* modulation (with off-resonance decoupling from protons), and two-dimensional heteronuclear ^{13}C–^{1}H correlation (C–H COSY and HSQC, $^{1}J_{CH}$ = 135 Hz; COLOC and HMBC, $^{2,3}J_{CH}$ = 10 Hz) and homonuclear ^{1}H–^{1}H correlation techniques (COSY and NOESY, mixing time 0.7 s). The high-resolution mass spectra (electron impact, 70 eV) were obtained on a DFS Thermo Scientific spectrometer (full scan mode; a.m.u range 0–500; direct sample admission into the ion source). The optical rotations $[\alpha]_D$ were measured on a PolAAr 3005 polarimeter.

Conformational analysis of stereoisomers (*R*)-**V** and (*S*)-**V** was performed using ChemAxon Marvin [11], VeraChem Vconf [12], and *conformers* programs [*http://limor1.nioch.nsc.ru/quant/program/conformers/*]. Quantum chemical calculations in terms of the density functional theory were performed with the use of PBE functional [13] and L1 (Λ01 [14], an analog of cc-pVDZ; structure optimization) or L22 basis set (Λ22, an analog of cc-pCVTZ; calculation of chemical shifts). Structure visualizations and Cartesian coordinates of atoms in all localized conformers are available at *http://limor1.nioch.nsc.ru/quant/conformers/Ad/*.

(1*R*,2*R*,6*S*)-6-(3-{[(1*R* and 1*S*)-1-(1-Adamantyl)-ethyl]amino}prop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diols (*R*)-V and (*S*)-V. A mixture of 0.170 g (0.688 mmol) of (4*S*,5*R*,6*R*)-6-(3-bromoprop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (**IV**), 0.144 g (0.585 mmol) of rimantadine, 0.25 ml (1.80 mmol) of triethylamine, and 30 ml of chloroform was kept for 8 days at room temperature. The solvent was distilled off, and the residue was subjected to column chromatography on 9 g of silica gel (60–200 μm, Macherey-Nagel) using hexane–chloroform (0 to 100% of the latter) and chloroform–ethanol (0 to 100% of the latter) with addition of 0.5% of triethylamine as eluents. We thus isolated 122 mg (0.354 mmol, 51%) of a mixture of (*R*)-**V** and (*S*)-**V** at a ratio of 1:1. The isomer mixture was separated by several consecutive chromatographic runs in a column charged with 4.5–9 g of silica gel (60–200 μm, Macherey-Nagel; hexane–chloroform, 20 to 50% of the latter, with addition of 0.5% of triethylamine) to obtain 20 fractions with different stereoisomer ratios. From these fractions we isolated 0.012 g (34.8 μmol, 5%) of pure isomer (*R*)-**V** and 0.019 g (55.1 μmol, 8%) of a mixture of (*S*)-**V** and (*R*)-**V** at a ratio of 11:1. The NMR spectra were recorded from a 2.3:1.0 mixture of (*R*)-**V** and (*S*)-**V**.

Isomer (*R*)-**V**. $[\alpha]_D^{27}$ = –27.5 (*c* = 0.40, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.03 d (3H, 22-H, $J_{22,11}$ = 6.5 Hz), 1.45–1.49 m and 1.52–1.57 m (3H each, 13-H, 19-H, 20-H), 1.58–1.62 m and 1.64–1.68 m (3H each, 15-H, 17-H, 21-H), 1.77 q (3H, 10-H, $J \leq$ 2.5 Hz), 1.94–1.97 m (3H, 14-H, 16-H, 18-H), 2.04 d.d.d.q (5-H_{eq}, ^{2}J = 17.5, $J_{5\text{-}eq,6\text{-}ax}$ = 5.3, $J_{5\text{-}eq,4}$ = 4.5, $J_{5\text{-}eq,10}$ = 1.5 Hz), 2.18 q (11-H, $J_{11,22}$ = 6.5 Hz), 2.28 d.d.m (5-H_{ax}, ^{2}J = 17.5, $J_{5\text{-}ax,6\text{-}ax}$ = 8.2 Hz), 2.69 m (6-H), 3.10 d (9-H_{eq}, ^{2}J = 11.5 Hz), 3.24 d (9-H_{ax}, ^{2}J = 11.5 Hz), 3.73 d.d (1-H, $J_{1,2}$ = 4.5, $J_{1,6}$ = 2.4 Hz), 3.84 br.d (2-H, $J_{2,1}$ = 4.5 Hz), 5.02 d (8-H_E), 5.05 d (8-H_Z), 5.53 m (4-H). ^{13}C NMR spectrum, δ_C, ppm: 12.68 q (C^{22}), 20.23 q (C^{10}), 27.56 t (C^{5}), 28.21 d (C^{14}, C^{16}, C^{18}), 35.81 s (C^{12}), 36.91 t (C^{15}, C^{17}, C^{21}), 38.35 t (C^{13}, C^{19}, C^{20}), 42.31 d (C^{6}), 52.79 t (C^{9}), 63.09 d (C^{11}), 72.65 d (C^{2}), 73.34 d (C^{1}), 117.22 t (C^{8}), 123.67 d (C^{4}), 132.77 s (C^{3}), 148.38 s (C^{7}). Found: *m*/*z* 345.2658 $[M]^+$. $C_{22}H_{35}O_2N$. Calculated: *M* 345.2662.

Isomer (*S*)-**V**. $[\alpha]_D^{27}$ = –0.93 (*c* = 0.43, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.99 d (3H, 22-H, $J_{22,11}$ = 6.5 Hz), 1.45–1.49 m and 1.52–1.57 m (3H each, 13-H, 19-H, 20-H), 1.58–1.62 m and 1.64–1.68 m (3H each, 15-H, 17-H, 21-H), 1.79 m (3H, 10-H, $J \leq$ 2.5 Hz), 1.84 d.d.d.q (5-H_{eq}, ^{2}J = 17.5, $J_{5\text{-}eq,6\text{-}ax}$ = 5.3, $J_{5\text{-}eq,4}$ = 4.5, $J_{5\text{-}eq,10}$ = 1.5 Hz), 1.94–1.97 m (3H, 14-H, 16-H, 18-H), 2.18 q (11-H, $J_{11,22}$ = 6.5 Hz), 2.28–2.34 m (5-H_{ax}), 2.68 m (6-H), 2.93 d (9-H_{eq}, ^{2}J = 11.5 Hz), 3.34 d (9-H_{ax}, ^{2}J = 11.5 Hz), 3.70 d.d (1-H, $J_{1,2}$ = 3.0, $J_{1,6}$ = 1.8 Hz), 3.88 br.d (2-H, $J_{2,1}$ = 3.0 Hz), 4.98 br.d (8-H_E, ^{2}J = 2.1 Hz), 5.05 d (8-H_Z, ^{2}J = 2.1 Hz), 5.58 m (4-H). ^{13}C NMR spectrum, δ_C, ppm: 73.50 d (C^{1}), 72.35 d (C^{2}), 132.27 s (C^{3}), 124.50 d (C^{4}), 25.80 t (C^{5}), 42.20 d (C^{6}), 148.83 s (C^{7}), 117.59 t (C^{8}), 51.08 t (C^{9}), 20.75 q (C^{10}), 62.66 d (C^{11}), 35.59 s (C^{12}), 38.35 t (C^{13}, C^{19}, C^{20}), 28.21 d (C^{14}, C^{16}, C^{18}), 36.91 t (C^{15}, C^{17}, C^{21}), 12.46 q (C^{22}).

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