Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Powder X-ray study of racemic (2*RS*,3*RS*)-5-amino-3-[4-(3-methoxyphenyl)piperazin-1-yl]-1,2,3,4-tetrahydronaphthalen-2-ol

Thaer Assaad and Mwaffak Rukiah*

Department of Chemistry, Atomic Energy Commission of Syria (AECS), PO Box 6091, Damascus, Syrian Arab Republic
Correspondence e-mail: cscientific@aec.org.sy

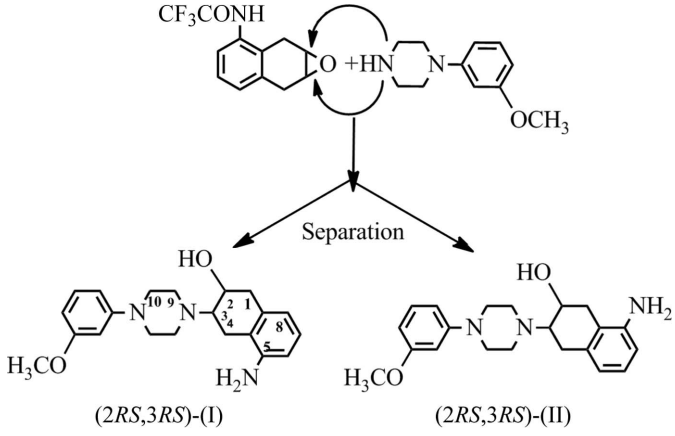
Received 8 September 2011
Accepted 4 October 2011
Online 31 October 2011

The structure of the title benzovesamicol analogue, $C_{21}H_{27}N_3O_2$, an important compound for the diagnosis of Alzheimer's disease, has been determined by X-ray powder diffraction. The title compound was firstly synthesized and characterized by spectroscopic methods (FT–IR, and ^{13}C and ^1H NMR). The compound is a racemic mixture of enantiomers which crystallizes in the monoclinic system in a centrosymmetric space group ($P2_1/c$). Crystallography, in particular powder X-ray diffraction, was pivotal in revealing that the enantio-resolution did not succeed. The piperazine ring is in a chair conformation, while the cyclohexene ring assumes a half-chair conformation. The crystal packing is dominated by intermolecular O—H···N hydrogen bonding which links molecules along the *c* direction.

Comment

(2*RS*,3*RS*)-5-Amino-3-[4-(3-methoxyphenyl)piperazin-1-yl]-1,2,3,4-tetrahydronaphthalen-2-ol, (2*RS*,3*RS*)-(I), is a benzovezamicol derivative, which is used in cholinergic nerve imaging for the diagnosis of Alzheimer's disease. Radiolabelled benzovesamicol analogues have been widely used as imaging probes in single photon emission computer tomography (SPECT) and positron emission tomography (PET), aimed at both *in vitro* and *in vivo* studies of Alzheimer's disease (Alfonso *et al.*, 1993; Efange *et al.*, 1997). For this aim, many efforts have focused on developing vesamicol derivatives as radiotracers using SPECT and PET (Rogers *et al.*, 1989; Jung *et al.*, 1990; Mulholland & Jung, 1992; Mulholland *et al.*, 1993; Van Dort *et al.*, 1993; Kuhl *et al.*, 1996; Sorger *et al.*, 2000; Bando *et al.*, 2000; Bando *et al.*, 2001; Auld *et al.*, 2002; Zea-Ponce *et al.*, 2005).

The title compound, (2*RS*,3*RS*)-(I), was prepared as presented in the Scheme. The synthesis began with the addition of 1-(3-methoxyphenyl)piperazine to 2,2,2-trifluoro-*N*-(1a,2,7,7a-tetrahydronaphtho[2,3-*b*]oxiren-3-yl)acetamide (Rogers *et al.*, 1989; Zea-Ponce *et al.*, 2005) to obtain two regioisomers, which were separated by flash chromatography (silica gel; Et_2O and Et_3N, 10:1 *v*/*v*). Compound (2*RS*,3*RS*)-(I) was characterized by FT–IR and ^{13}C and ^1H NMR spectroscopy and showed results consistent with the assigned structures. Moreover, since the specific binding of benzovezamicol derivatives is known to be highly enantioselective, enantiomeric resolution of racemic (2*RS*,3*RS*)-(I) was performed using (1*S*)-(+)-camphor-10-sulfonic acid [(+)-CSA] (see *Experimental*). The resulting compound, supposedly a pure enantiomer, crystallizes in the form of a very fine white powder. It seems impossible, to our knowledge, to grow single crystals of sufficient thickness and quality for single-crystal X-ray diffraction experiments. Thus, a crystal structure determination by powder X-ray diffraction was attempted for this compound.



(2*RS*,3*RS*)-(I) (2*RS*,3*RS*)-(II)

We employed in-house powder X-ray diffraction data to solve and refine the crystal structure of what we anticipated would be (2*R*,3*R*)-(I), but proved to be (2*RS*,3*RS*)-(I). This involves a 26-atom (non-H) problem, which requires careful measurement and interpretation of the data in order to optimize the quality of the results. In recent years, the crystal structures of a number of compounds of pharmaceutical interest have been determined by powder X-ray diffraction data as a last resort in the absence of single crystals of sufficient quality (Chan *et al.*, 1999; Shankland *et al.*, 2004; Chernyshev *et al.*, 2003; Kiang *et al.*, 2003; Rukiah *et al.*, 2004; Van der Lee *et al.*, 2005; Rukiah & Assaad, 2010; Al-Ktaifani & Rukiah, 2010; Rukiah & Al-Ktaifani, 2011).

The successful solution and refinement of the structure of the title compound showed that it crystallizes in the centrosymmetric space group $P2_1/c$, which of necessity means that the sample used for the powder diffraction analysis was racemic. To confirm this result, an analysis of the optical purity of the bulk material was performed by high-performance liquid chromatography (HPLC) and polarimetry. We used chiral HPLC to analyze the isolated product which was supposedly (2*R*,3*R*)-(I). The analysis of the optical purity was performed using semipreparative HPLC and a Chiracel column [4.6 × 150 mm; 5 µm, Zorpax, XDB (eXtra Dense Bonding)] and acetonitrile–H_2O–trifluoroacetic acid (80/20/0.1 *v*/*v*) as eluant at a flow rate of 1 ml min^{-1}. HPLC–UV

 doi:10.1107/S0108270111040844

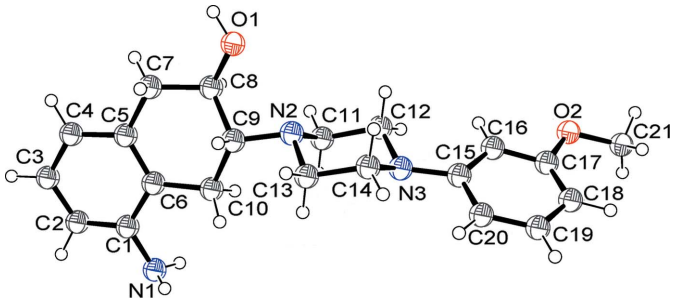


Figure 1
The molecular structure of (2*RS*,3*RS*)-(I), showing the atom-numbering scheme. Displacement spheres are drawn at the 50% probability level and H atoms are shown as small spheres of arbitary radii.

absorption was observed at 254 nm, which gave two peaks (retention times at 3.5 and 4.5 min) instead of one. A polarimeter was also used to measure the rotation of plane-polarized light. The net rotation of plane-polarized light is 0°, which means that the compound was optically inactive. These results mean that the enantiomeric resolution was not successful and the compound was indeed racemic.

An *ORTEP-3* (Farrugia, 1997) view of compound (2*RS*,3*RS*)-(I) with the atom labelling is shown in Fig. 1. Selected bond lengths and bond and torsion angles are reported in Table 1. Bond lengths and angles in compound (2*RS*,3*RS*)-(I) are in their normal ranges (Allen *et al.*, 1987). The molecule contains four six-membered rings (two benzene, a piperazine and a cyclohexene). The piperazine ring adopts a chair conformation, as shown by its puckering parameters

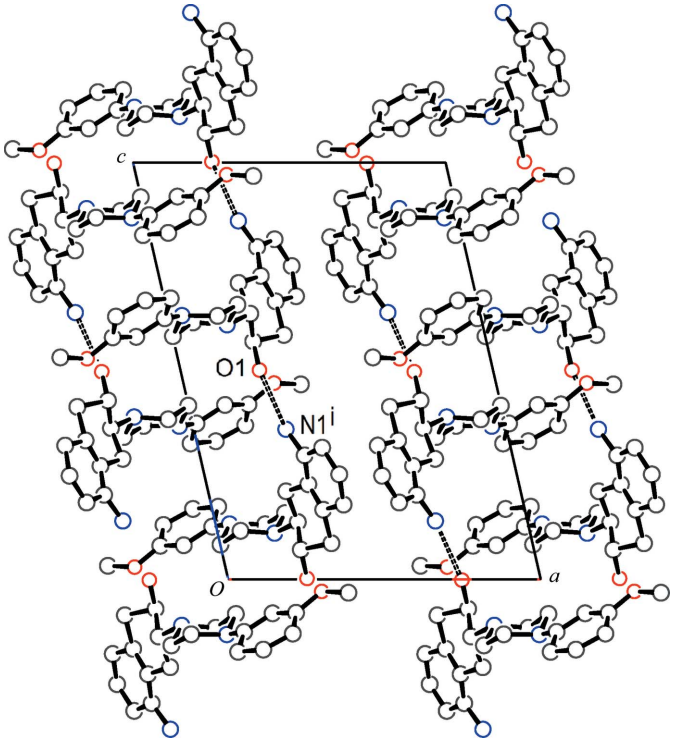


Figure 2
The crystal packing of (2*RS*,3*RS*)-(I), viewed normal to the *b* axis. O—H···N hydrogen bonds are shown as dashed lines. H atoms have been omitted for clarity. [Symmetry code: (i) $x, -y+\frac{3}{2}, z-\frac{1}{2}$.]

(Cremer & Pople, 1975) $Q = 0.578\ (13)$ Å, $\theta = 3.5\ (13)^\circ$ and $\varphi = 82\ (19)^\circ$. The bond lengths and angles around atoms C6 and C5 clearly confirm the presence of an aromatic bond. The cyclohexene ring assumes a conformation very similar to a half-chair [puckering parameters $Q = 0.560\ (14)$ Å, $\theta = 33.6\ (15)^\circ$ and $\varphi = 228\ (3)^\circ$], with the C5/C6/C7/C10 atoms nearly coplanar (the maximum deviation from the mean plane is 0.0157 Å for atom C5) and atoms C8 and C9 situated 0.546 (14) and 0.250 (13) Å below and above this mean plane, respectively. The cyclohexene ring is *trans*-fused to the first benzene ring (C1–C6) through atoms C5 and C6 to form a ten-membered ring system which is a tetrahydronaphthalene.

The crystal packing is characterized by an intermolecular head-to-tail O—H···N hydrogen bond involving the hydroxy H atom and the amine H atom (Table 2). The hydrogen bond forms a one-dimensional chain in the [001] direction (Fig. 2).

Experimental

2,2,2-Trifluoro-*N*-(1a,2,7,7a-tetrahydronaphtho[2,3-*b*]oxiren-3-yl)-acetamide was prepared according to a previously reported method (Rukiah & Assaad, 2010). The powder sample of compound (2*RS*,3*RS*)-(I) was ground lightly in a mortar, loaded between two Mylar foils and fixed in the sample holder with a mask of suitable internal diameter (8.0 mm). X-ray powder diffraction data were collected at room temperature with a Stoe transmission Stadi P diffractometer using monochromatic Cu $K_{\alpha 1}$ radiation (λ = 1.54060 Å) selected with an incident-beam curved-crystal germanium(111) monochromator, using the Stoe transmission geometry (horizontal set-up) with a linear position-sensitive detector (PSD). The pattern was scanned over the angular range 5–85° (2θ).

For the synthesis and enantiomeric resolution of (2*RS*,3*RS*)-(I), 1-(3-methoxyphenyl)piperazine (9.44 g, 49 mmol) was added to a solution of 1-amino-*N*-trifluoroacetyl-5,8-dihydronaphthalene oxide (4 g, 16 mmol) in ethanol (25 ml). The solution was refluxed for 16 h, and then kept for 24 h at room temperature to produce a powder solid. The solid was filtered off and dried under vacuum, then dissolved in methanol (25 ml) and treated with 1 *N* NaOH (15 ml). The mixture was stirred at room temperature for 16 h and then extracted with CH_2Cl_2 (3 × 25 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting regioisomers were separated by silica-gel chromatography with ethyl acetate–hexane (7:3 *v*/*v*) to give 900 mg (64%) of (2*RS*,3*RS*)-(I) (R_F = 0.65; m.p. 478–484 K).

The racemic mixture of (2*RS*,3*RS*)-(I) was separated into its enantiomers by complexation with (1*S*)-(+)-camphor-10-sulfonic acid [(+)-CSA]. Racemic (2*RS*,3*RS*)-(I) (500 mg, 1.41 mmol) and [(+)-CSA] (300 mg, 1.29 mmol) were dissolved in boiling acetonitrile. The mixture was stirred at room temperature for 16 h. The precipitate obtained on standing was filtered off and treated with 1 *N* NaOH and $CHCl_3$ (25 ml), while the aqueous layer was treated with $CHCl_3$ (3 × 25 ml). The combined organic extracts were washed with saturated brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to obtain what we anticipated would be (2*R*,3*R*)-(I) (m.p. 476–479 K) in 70% overall yield (350 mg). The filtrate was concentrated and the residue worked up as outlined above to obtain the anticipated (2*R*,3*R*)-(I) in 30% overall yield (150 mg) (this later proved to be a racemic mixture, see *Comment*).

Spectroscopic data for (2*RS*,3*RS*)-(I): ^{1}H NMR ($CDCl_3$): δ 2.48–2.55 (*m*, 2H, 2 H10), 2.71–3.00 (*m*, 6H, 2 H1, 2 H4, 2 H10), 3.25–3.35

(*m*, 6H, 4 H9, H3, OH), 3.60 (*s*, 2H, NH_2), 3.83 (*s*, 3H, CH_3), 3.88–3.92 (*m*, 1H, H2), 6.64–6.63 (*m*, 5H, $5H_{Ar}$), 7.02 (*t*, 2H, ^3J = 8 Hz), 7.22 (*t*, 2H, ^3J = 8 Hz, $2H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ 20.9 (2 C10), 38.0 (C1), 48.0 (C4), 49.8 (C3), 55.2 (CH_3), 65.2 (C2), 66.2 (2 C9), 95.58 (CH_{Ar}), 102.76 (CH_{Ar}), 104.64 (CH_{Ar}), 104.82 (CH_{Ar}), 109.1 (CH_{Ar}), 112.1 (CH_{Ar}), 129.82 (CH_{Ar}), 129.86 (CH_{Ar}), 134.78 (CH_{Ar}), 136.83 (CH_{Ar}), 144.41 (CH_{Ar}), 162.2 (C—CH_3); IR (KBr, ν, cm^{-1}): 3466.2 (OH), 3368.6 (NH_2), 3050 (CH═CH, Ar), 2910.4–2835.7 (CH_2, aliphatic), 1203 (OCH_3).

Crystal data

$C_{21}H_{27}N_3O_2$
M_r = 353.47
Monoclinic, $P2_1/c$
a = 12.6234 (3) Å
b = 8.90929 (16) Å
c = 17.2752 (3) Å
β = 102.8536 (11)°
V = 1894.18 (7) Å^3
Z = 4
Cu $K\alpha_1$ radiation
λ = 1.54060 Å
μ = 0.64 mm^{-1}
T = 298 K
flat sheet, 8 × 8 mm

Data collection

Transmission Stoe STADI P diffractometer
Specimen mounting: powder loaded between two Mylar foils
Data collection mode: transmission
Scan method: step
Absorption correction: for a cylinder mounted on the φ axis (*GSAS*; Larson & Von Dreele, 2004) T_{min} = 0.391, T_{max} = 0.502
$2\theta_{min}$ = 4.998°, $2\theta_{max}$ = 84.978°, $2\theta_{step}$ = 0.02°

Refinement

R_p = 0.019
R_{wp} = 0.024
R_{exp} = 0.017
$R(F^2)$ = 0.03232
χ^2 = 2.722
4000 data points
115 parameters
29 restraints
H-atom parameters constrained

For pattern indexing, the extraction of the peak positions was carried out using the program *WinPLOTR* (Roisnel & Rodriguez-Carvajal, 2001). Pattern indexing was performed using the program *DICVOL4.0* (Boultif & Louër, 2004). The first 20 lines of the powder pattern were completely indexed on the basis of a monoclinic cell. The absolute error on each observed line was fixed at 0.02° (2θ). The figures of merit are sufficient to support the obtained indexing results [M(20) = 23.1 and F(20) = 53.4 (0.0071, 53)]. The whole powder diffraction pattern from 5 to 85° (2θ) was subsequently refined with cell and resolution constraints (Le Bail *et al.*, 1988) in a space group without systematic extinctions in the monoclinic system, $P2/m$, using the 'profile matching' option of the program *FULLPROF* (Rodriguez-Carvajal, 2001). The best estimated space group in the monoclinic system was $P2_1/c$, which was determined with the help of the program *CHECKGROUP* interfaced by *WinPLOTR*. The number of molecules per unit cell was estimated to be Z = 4, and it can be concluded that the number of molecules in the asymmetric unit is Z' = 1 for the space group $P2_1/c$.

Some details of the solution and refinement of (2*RS*,3*RS*)-(I) merit a brief comment. Firstly, the structure was solved *ab initio* by direct methods using the program *EXPO2009* (Altomare *et al.*, 1999), but with no success. Therefore, the direct space method was used with the program *FOX* (Favre-Nicolin & Černý, 2002) to find the starting model, using the 'parallel tempering' algorithm of the Monte Carlo simulated-annealing method. The 2θ angular range was restricted from 5.0 to 55.0° in order to speed up the Monte Carlo calculations. The profile parameter needed for the program was calculated from preliminary profile-matching refinements carried out using *FOX* itself. The molecule of (2*RS*,3*RS*)-(I) has three independent torsion angles, so there are nine degrees of freedom to determine the starting model. The H atoms were not introduced in these calculations because they do not contribute significantly to the powder diffraction pattern, due to their low X-ray scattering power. After approximately 2 000 000 cycles, the agreement factor R_{wp} was near to 0.12. The calculations were continued with respect to preferred orientation in the (100) direction, and R_{wp} value decreased rapidly to 0.09 for a solution corresponding to a configuration which could constitute a relevant starting structural model in terms of crystal packing, the shortest contact distance between neighbouring molecules being 2.94 Å between the hydroxy group and the amine group, which is consistent with the presence of a hydrogen bond. The parameter G_1 of the March–Dollase (March, 1932; Dollase, 1986) function is 1.19 at the end of the calculations.

The model found by this program was introduced into the program *GSAS* (Larson & Von Dreele, 2004) implemented in *EXPGUI* (Toby, 2001) for Rietveld refinement. During Rietveld refinement, the effect of the asymmetry of the low-order peaks was corrected using a pseudo-Voigt description of the peak shape (Thompson *et al.*, 1987)

Table 1
Selected geometric parameters (Å, °).

C5—C6	1.369 (10)	C7—C8	1.573 (11)
C5—C7	1.563 (9)	C8—C9	1.510 (11)
C6—C10	1.589 (11)	C9—C10	1.496 (10)
C4—C5—C6	122.7 (13)	C1—C6—C5	112.8 (13)
C4—C5—C7	111.3 (15)	C1—C6—C10	122.7 (15)
C6—C5—C7	121.5 (14)	C5—C6—C10	120.7 (15)
C7—C5—C6—C1	176.6 (13)	C5—C6—C10—C9	28.4 (18)
C4—C5—C6—C10	−178.6 (14)	C5—C7—C8—C9	−61.2 (13)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O1···N1^{i}	0.82	2.50	3.099 (12)	131

Symmetry code: (i) $x, -y+\frac{3}{2}, z-\frac{1}{2}$.

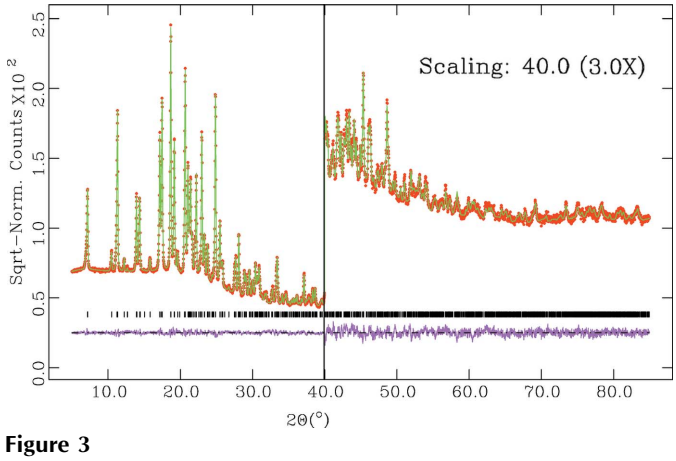


Figure 3
Final Rietveld plot for (2*RS*,3*RS*)-(I). Observed data points are indicated by dots, the best-fit profile (upper trace) and the difference pattern (lower trace) are solid lines. The vertical bars indicate the positions of Bragg peaks.

which allows for angle-dependent asymmetry with axial divergence (Finger *et al.*, 1994) and microstrain broadening as described by Stephens (1999). The two asymmetry parameters of this function, *S*/*L* and *D*/*L*, were both fixed at 0.0225 during Rietveld refinement. Soft restraints were imposed on bond lengths for the coordinates of the 26 non-H atoms. The target distances were taken from their normal values in similar compounds (Allen *et al.*, 1987). A global isotropic atomic displacement parameter was introduced for C, N and O atoms. Intensities were corrected for absorption effects with a μd value of 0.446. Before the final refinement, aromatic, methylene, methine and methyl H atoms were introduced from geometric arguments. The coordinates of these H atoms were refined with constraints to normal values on bond lengths and angles to the parent atoms (C—H = 0.99 Å for CH, 0.98 Å for CH_2 and 0.97 Å for CH_3). H atoms of the hydroxy and amine groups were located in a Fourier difference synthesis and refined with constraints on their bond lengths (O—H = 0.82 Å and N—H = 0.87 Å for NH_2) and angles. A spherical harmonic correction for preferred orientation (Von Dreele, 1997) was used with 14 coefficients. The use of the preferred orientation correction leads to better molecular geometry with better agreement factors. The final Rietveld plot of the X-ray diffraction pattern is given in Fig. 3.

Data collection: *WinXPOW* (Stoe & Cie, 1999); cell refinement: *GSAS* (Larson & Von Dreele, 2004); data reduction: *WinXPOW*; program(s) used to solve structure: *FOX* (Favre-Nicolin & Černý, 2002); program(s) used to refine structure: *GSAS*; molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *publCIF* (Westrip, 2010).

The authors thank Professor I. Othman, Director General, and Professor T. Yassine, Head of Chemistry, for their support and encouragement. Thanks are also due to Mr Raffat Ajaya and Madame Najwa Karajoli for their assistance with some of the laboratory work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CU3006). Services for accessing these data are described at the back of the journal.

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