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(*S*)-5,6-Dimethoxy-1,2,3,4-tetrahydro-2-naphthalenamine–L-(+)-Mandelic Acid (1/1): the Absolute Configuration of a Precursor of the Active Stereoisomer of 5,6-ADTN, an Important Dopaminergic Agonist

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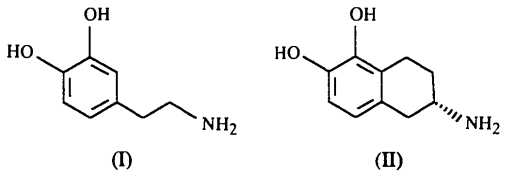
Abstract

The structure determination of the title compound, $C_{12}H_{18}NO_2^+.C_8H_7O_3^-$, has allowed the absolute configuration of the cation to be established. The demethylated base, (*S*)-5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenamine, or (2*S*)-5,6-ADTN, is responsible for the dopaminergic activity; this work shows that it has the same spatial arrangement as (6a*R*)-apomorphine.

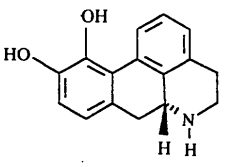
Comment

The physiological role of dopamine, (I), has been investigated extensively over the last 50 years and many studies on its analogues have been performed in order to define a dopaminergic pharmacophore (Kaiser & Jain, 1985; Ince, 1990). Many efforts have been made to reduce the conformational flexibility of the arylethylamine moiety; 5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenamine, (II) (Cannon, Kin, Aleem & Long, 1972; McDermed, McKenzie & Phillips, 1975; Sheppard, Burghardt & Long, 1978; Freedman, Templeton, Paot & Woodruff, 1981; Horn, Grol, Dijkstra & Mulder, 1978), and its *N*,*N*-dipropyl derivative, commonly known as 5,6-ADTN and 5,6-DPTN, respectively, emerged from this research. It is worthwhile noting the structural relation with (6a*R*)-apomorphine, (III) (Giesecke, 1973, 1977; Di Chiara & Gessa, 1978; absolute configuration by Kalvoda, Buchschacher & Jeger, 1955; Corrodi & Hardegger, 1955), an important compound endowed with a potent dopaminergic activity.



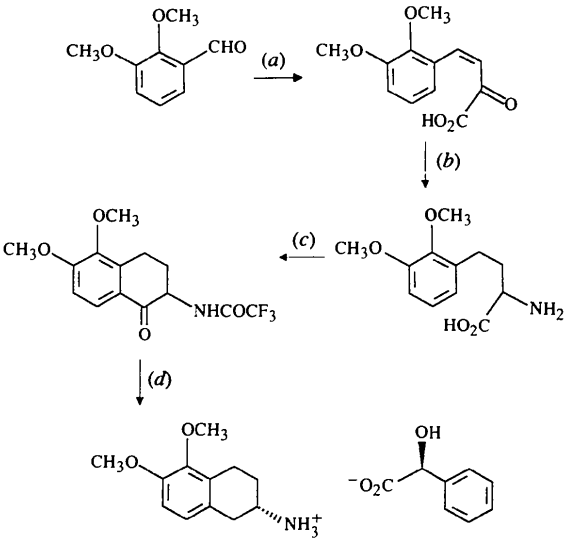
(I)

(II)



(III)

Racemic 5,6-ADTN has been synthesized in many laboratories (McDermed *et al.*, 1975; Horn *et al.*, 1978; Sprenger, Cannon, Barman & Burkman, 1969; Mitsuhashi, Adachi, Shimizu, Nomura & Shiotani, 1972; Cannon & Costal, 1977), but none of the synthetic routes seem to be suitable on a multigram scale owing to their overall low yield. To overcome this difficulty, we studied an alternative route which does not require any purification by chromatography and which gives an improved overall yield. Experimental details are reported in EPA (1992) and the general synthesis is shown in the scheme below.



(*a*) CH_3COCO_2H, piperidine, DMF;
(*b*) (i) $NH_2OH.HCl$, pyridine, ethanol; (ii) H_2, HCl/acetic acid, palladium on charcoal;
(*c*) $(CF_3CO)_2O$, CF_3COOH;
(*d*) (i) H_2, $HClO_4$/ethanol, palladium on charcoal; (ii) $NaBH_4$, ethanol; (iii) L-(+)mandelic acid.

Furthermore, a great pharmacological difference between the enantiomers of 5,6-ADTN was clearly demonstrated and great effort has been given to isolating and evaluating the pharmacological activity of each single enantiomer (Ince *et al.*, 1984). Considerations of the stereochemical requirements were used to model structural features of the dopamine receptor (see references cited by Kaiser & Jain, 1985) and it was demonstrated that most of the activity of 5,6-ADTN resides in the enantiomer with the absolute configuration *S*.

5,6-Dimethoxy-1,2,3,4-tetrahydro-2-naphthalenamine was resolved (Ince *et al.*, 1984) by HPCL separation of diastereomeric *N*-(*R*)-1-phenylethyl derivatives. Details of the assignment of the absolute configuration have not been published, although resolution of one intermediate in the synthesis was reported to have given a low yield (Grol, Jansen & Rollema, 1985). Confirmation of the absolute configuration of the compound with dopaminergic activity was therefore sought.

We therefore prepared the diastereoisomeric salt of racemic 5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenamine with L-(+)-mandelic acid, (IV), (IPA, 1991). Structure determination of this enantiomerically pure precursor of 5,6-ADTN clarifies for the first time the absolute configuration of this important class of compounds. Moreover, after demethylation we have confirmed that the dopaminergic activity mainly resides in the (2*S*)-5,6-ADTNs series (Montanari *et al.*, 1995) which has the same spatial arrangement as (6a*R*)-apomorphine.

The absolute configuration was defined to be *S* at C1 from the known *S* configuration of the mandelic acid used in the synthesis. Bond distances and angles are as expected (Allen *et al.*, 1987); in particular protonation of the aminic group increases the C1—N1 distance to 1.506 (4) Å, while deprotonation of the carboxyl group of mandelic acid makes the two C—O distances approximately equal. The α-hydroxycarboxylate moiety assumes a *gauche* conformation with respect to the phenyl ring.

The cyclohexene ring shows a total puckering amplitude (Cremer & Pople, 1975) of 0.525 (4) Å and a conformation intermediate between half-chair and sofa with a local pseudo twofold axis running along the midpoints of the C1—C10 and C3—C8 bonds and a pseudo mirror through C1···C8, as indicated by the following values of the displacement-asymmetry parameters (Nardelli, 1983*b*): Δ_2(C1—C10) = 0.053 (2) and Δ_m(C1) = 0.084 (2).

Worth noting is the orientation of the two methoxy groups which do not lie in the benzene plane as frequently found (Cacchi, Delmastro, Ianelli & Nardelli, 1992), but are twisted out of it, as indicated by the torsion angles C5—C6—O1—C11 = 12.8 (5) and C6—C7—O2—C12 = 84.7 (4)°, probably because of steric effects that prevent conjugation of these groups with the benzene aromatic system. As a consequence, the bond angles C6—O1—C11 [118.5 (3)°] and C7—O2—C12 [113.7 (3)°] are noticeably different.

The analysis of 'thermal' motion, carried out in terms of the Schomaker & Trueblood (1968) **TLS** rigid-body approximation using the *THMV* program (Trueblood, 1984), gave values of 0.123 and 0.106 for the residual error index, R_{wU}, for the cation and the anion, respectively. These values improve to 0.064 and 0.076 if the internal motions are considered according to Dunitz & Withe (1973).

The main interactions between the ions correspond to the hydrogen bonds involving the ammonium and α-hydroxy carboxylate groups whose geometries are given in Table 3.

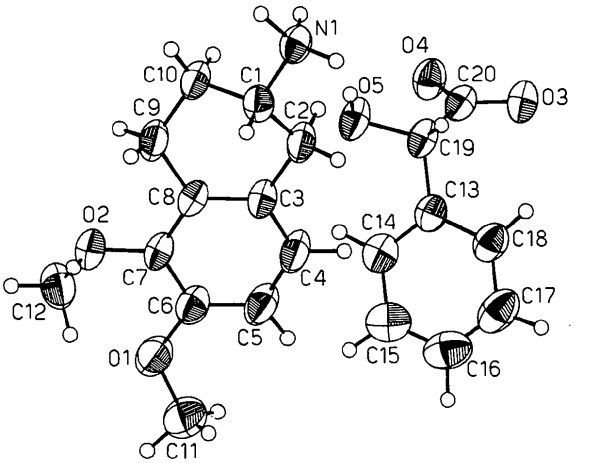


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the two ions. Displacement ellipsoids are drawn at the 50% probability level.

Experimental

The product was synthesized according to the procedure described in EPA (1992). M.p. 483–485 K (uncorrected), $[\alpha]^D$ = +28° (*c* = 1, 1N HCl). ^{1}H NMR (DMSO-d_6) δ 7.38–7.09 (*m*, 5H, aryl); 6.84 (*d*, 1H, J_{HN} = 8.4 Hz, CH-cathecol); 6.75 (*d*, 1H, CH-cathecol); 4.52 (*s*, 1H, CH–O); 3.74 (*s*, 3H, OCH_3); 3.66 (*s*, 3H, OCH_3); 3.30–3.16 (*m*, 1H, CH—N); 2.96–2.48 (*m*, 4H, CH_2—CH—CH_2—CH_2); 2.07–1.46 (*m*, 2H, CH—CH_2—CH_2). MS (CI isobutylene) *m/z* 208 (*M* + 1; amine; 100%); 153 (*M* + 1; acid). MS (EI, 70 eV) *m/z* 207 (M; amine); 176 (*M*—OCH_3; 100%). Elemental analysis: found C 66.99, H 7.11, N 3.89; calculated for $C_{20}H_{25}NO_5$ C 66.84, H 7.01, N 3.90%. The melting point was determined on a Büchi 535 melting-point apparatus. Specific rotation was determined at 293 K on a Perkin–Elmer 241-MC polarimeter. ^{1}H NMR spectrum was recorded on a Varian Gemini-200 (200 MHz) spectrometer. MS spectra were obtained using a Finnigan 4600 spectrometer by chemical ionization or by electron impact. Microanalysis was performed on a Fisons EA-1108 apparatus. The chiral HPCE analysis of (*S*)-5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenamine (Castelnuovo & Albanesi, 1995) showed an enantiomeric excess over 99.9%.

Crystal data

$C_{12}H_{18}NO_2^+.C_8H_7O_3^-$
M_r = 359.42
Orthorhombic
$P2_12_12_1$
a = 33.01 (3) Å
b = 7.915 (4) Å
c = 7.096 (4) Å
V = 1854 (2) Å^3
Z = 4
D_x = 1.288 Mg m^{-3}
D_m not measured

Cu *Kα* radiation
λ = 1.54178 Å
Cell parameters from 29 reflections
θ = 19.57–35.17°
μ = 0.757 mm^{-1}
T = 293 (2) K
Tablet
0.35 × 0.33 × 0.26 mm
Colourless

Data collection

Siemens AED single-crystal diffractometer
θ–2θ scans
Absorption correction: none
4006 measured reflections
2322 independent reflections
1396 observed reflections [$I > 2\sigma(I)$]
$R_{int} = 0.0277$
$\theta_{max} = 70.78°$
$h = -39 \rightarrow 40$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 8$
1 standard reflection monitored every 50 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.0302$
$wR(F^2) = 0.0602$
$S = 1.099$
2322 reflections
336 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0298P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.115$ e Å^{-3}
$\Delta\rho_{min} = -0.143$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0035 (3)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4
Absolute configuration: Flack (1983)
Flack parameter = 0.01 (30)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O1	0.50690 (7)	0.6968 (3)	0.0915 (3)	0.0786 (8)
O2	0.45772 (6)	0.6073 (3)	−0.1914 (3)	0.0614 (6)
O3	0.25083 (6)	0.2177 (3)	0.7785 (3)	0.0590 (6)
O4	0.26655 (7)	0.3416 (3)	0.5084 (3)	0.0625 (6)
O5	0.29457 (7)	0.0568 (3)	0.3578 (3)	0.0631 (6)
N1	0.28144 (9)	0.3852 (4)	0.1195 (4)	0.0546 (7)
C1	0.32580 (9)	0.4196 (4)	0.0876 (4)	0.0523 (8)
C2	0.34224 (10)	0.5338 (5)	0.2405 (4)	0.0603 (9)
C3	0.38602 (9)	0.5796 (4)	0.2006 (4)	0.0524 (8)
C4	0.41044 (11)	0.6379 (5)	0.3440 (4)	0.0677 (10)
C5	0.45062 (12)	0.6797 (5)	0.3136 (5)	0.0706 (11)
C6	0.46708 (10)	0.6655 (5)	0.1357 (4)	0.0583 (8)
C7	0.44232 (9)	0.6113 (4)	−0.0109 (4)	0.0516 (8)
C8	0.40208 (9)	0.5704 (4)	0.0192 (4)	0.0488 (7)
C9	0.37635 (11)	0.5171 (6)	−0.1461 (4)	0.0648 (10)
C10	0.33175 (10)	0.5027 (5)	−0.1028 (4)	0.0566 (8)
C11	0.53494 (15)	0.7132 (9)	0.2388 (7)	0.0890 (14)
C12	0.47952 (15)	0.4561 (6)	−0.2344 (7)	0.0817 (12)
C13	0.32839 (10)	0.0398 (4)	0.6609 (4)	0.0503 (7)
C14	0.36476 (11)	0.0670 (5)	0.5726 (5)	0.0701 (10)
C15	0.40131 (13)	0.0493 (7)	0.6692 (7)	0.0883 (13)
C16	0.40083 (15)	0.0051 (6)	0.8556 (7)	0.0836 (12)
C17	0.3649 (2)	−0.0213 (5)	0.9458 (6)	0.0800 (12)
C18	0.32843 (12)	−0.0033 (4)	0.8501 (4)	0.0619 (9)
C19	0.28869 (10)	0.0583 (4)	0.5565 (4)	0.0500 (8)
C20	0.26688 (9)	0.2179 (4)	0.6173 (4)	0.0488 (7)

Table 2. *Selected geometric parameters (Å, °)*

O1—C6	1.374 (4)	O4—C20	1.247 (4)
O1—C11	1.402 (6)	O5—C19	1.423 (3)
O2—C7	1.379 (3)	N1—C1	1.506 (4)
O2—C12	1.430 (6)	C13—C19	1.512 (5)
O3—C20	1.260 (3)	C19—C20	1.517 (4)
C6—O1—C11	118.5 (3)	O2—C7—C8	119.5 (3)
C7—O2—C12	113.7 (3)	O5—C19—C13	111.5 (2)
N1—C1—C10	109.8 (3)	C13—C19—C20	110.6 (3)
N1—C1—C2	110.4 (3)	O5—C19—C20	110.7 (2)
O1—C6—C5	124.9 (3)	O4—C20—C19	118.8 (3)
O1—C6—C7	116.5 (3)	O3—C20—C19	117.2 (3)
O2—C7—C6	119.1 (2)	O3—C20—O4	124.0 (3)
C11—O1—C6—C5	12.8 (5)		
C12—O2—C7—C6	84.7 (4)		
N1—C1—C10—C9	−172.8 (3)		
N1—C1—C2—C3	−175.6 (3)		
O5—C19—C20—O4	−18.7 (4)		
O5—C19—C20—O3	162.7 (3)		
C13—C19—C20—O4	105.4 (3)		
C13—C19—C20—O3	−73.1 (3)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O4	0.97 (3)	1.92 (3)	2.824 (4)	154 (3)
N1—H1N···O5	0.97 (3)	2.41 (3)	3.131 (4)	131 (2)
O5—H5O···O3^{i}	0.96 (4)	1.75 (5)	2.699 (3)	171 (4)
N1—H2N···O3^{ii}	0.86 (3)	2.82 (3)	3.505 (4)	138 (3)
N1—H2N···O4^{ii}	0.86 (3)	1.94 (3)	2.794 (4)	171 (3)
N1—H3N···O3^{iii}	1.00 (4)	1.96 (4)	2.938 (4)	165 (4)

Symmetry codes: (i) $\frac{1}{2}-x, -y, z-\frac{1}{2}$; (ii) $\frac{1}{2}-x, 1-y, z-\frac{1}{2}$; (iii) $x, y, z-1$.

Data collection: *AED Diffractometer Software* (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979). Cell refinement: *LQPARM* (Nardelli & Mangia, 1984). Data reduction: local programs. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965), *PLUTO* (Motherwell & Clegg, 1976). Software used to prepare material for publication: *PARST* (Nardelli, 1983*a*), *PARSTCIF* (Nardelli, 1991).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HA1167). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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(3*R**,4*S**)-4-[(*S**)-2-Cyclohexyl-2-(*tert*-butyldimethylsiloxy)ethyl]-3-hexyl-3-(trimethylsilyl)oxetan-2-one

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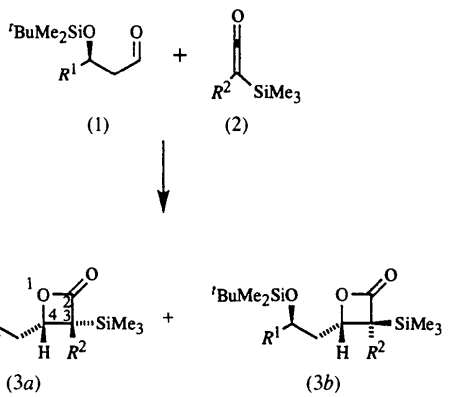
Abstract

The relative stereochemistry of the substituents of the oxetanone ring in the title compound, $C_{26}H_{52}O_3Si_2$, prepared by the highly diastereoselective [2+2] cycloaddition of a silylketene and a 3-alkoxy-substituted aldehyde, has been established.

Comment

In 1965, Shchukovskaya and co-workers (Shchukovskaya, Pal'chik & Lazarev, 1965) first prepared the remarkably stable (trimethylsilyl)ketene [(2), R^2 = H] and Zaitseva, Vinokurova & Baukov (1975) later showed that it undergoes [2+2] cycloaddition to benzaldehyde in the presence of boron trifluoride etherate to give 3-(trimethylsilyl)oxetanones (Pommier & Pons, 1993).



During a synthesis of the pancreatic lipase inhibitor tetrahydrolipstatin, Pommier, Pons, Kocienski & Wong (1994) found high 1,3-asymmetric induction in the analogous cycloaddition of *n*-hexyl(trimethylsilyl)ketene [(2), $R^2 = C_6H_{13}$] to the (*R*)-3-[(*tert*-butyldimethylsilyl)oxy]tetradecanal [(1), $R^1 = C_{11}H_{23}$]. Four diastereoisomers were generated in the ratio 80:10:8:2, in which the two major isomers having *S* stereochemistry at C-4 were assigned the structures (3*a*) (80%) and (3*b*) (10%). The relative stereochemistry at C-4 was determined from NMR experiments and chemical correlation, but the stereochemistry at C-3 could only be inferred from a sequence of subsequent transformations.

We now report that the [2+2] cycloaddition of the silylketene (2) ($R^2 = C_6H_{13}$) to the racemic aldehyde (1) ($R^1 = C_6H_{11}$), catalyzed by ethylaluminium dichloride, is also highly efficient and diastereoselective leading to only two diastereoisomers, *rac*-(3*a*) and *rac*-(3*b*) (9:1), according to high-field ^{1}H NMR analysis of the crude reaction mixture. The major isomer, *rac*-(3*a*), is crystalline (m.p. 359–361 K) and its relative stereochemistry was determined by X-ray crystallography. The structure (Fig. 1) was refined with anisotropic non-H atoms [isotropic for C(14)–C(19)] and shows the expected planar four-membered ring. As noted with related ring systems, the C—O bond adjacent to the C=O bond [1.381 (8) Å] is shorter than the other ring C—O distance [1.495 (7) Å]. The structure of (3*a*) confirms the sense of 1,3-asymmetric induction in the Lewis acid-catalyzed [2+2] cycloaddition of alkylsilylketenes to 3-alkoxy-substituted aldehydes (Pommier, Pons & Kocienski, 1995; Zemribo & Romo, 1995) and establishes for the first time the relative stereochemistry