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Resolution of (±)-nipecotic acid ((±)-3-piperidinecarboxylic acid) by separation of palladium(II) diastereomers containing orthometallated (*S*)-(−)-1-[1-(dimethylamino)ethyl]naphthalene

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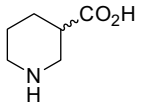
ABSTRACT

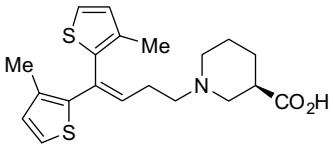
An efficient resolution of (±)-nipecotic acid has been achieved by the fractional crystallization of internally diastereomeric palladium(II) complexes containing the chelated carboxylate and orthometallated (*S*)-(−)-1-[1-(dimethylamino)ethyl]naphthalene. The configurationally pure enantiomers of the acid were recovered from the individual diastereomers of the complex by treatment with hydrochloric acid, which also regenerated the palladium(II) resolving agent. The crystal structure of the less-soluble diastereomer of the complex has been determined.

1. Introduction

(±)-Nipecotic acid (±)-**1** can be considered as a conformationally restricted γ-aminobutyric acid (GABA) analogue,[1] (*R*)-(−)-nipecotic acid is a more potent inhibitor of the uptake of GABA than the (*S*)-(+) isomer. The discovery that it displays in vitro activity as an inhibitor of [^{3}H]-GABA uptake has prompted its use as the basis for the design of centrally acting drugs, as in the potent *N*-alkylated derivative NNC 05-0328, Tiagabine.[2,3] The synthesis of novel GABA uptake inhibitors based on the nipecotic acid framework remains an active area of interest.[4]



(±)-**1**



Tiagabine

The usual method of resolution of (±)-nipecotic acid is by fractional crystallization of the L-(+)-hydrogen tartrate salts of the ethyl ester, the less-soluble diastereomer of the salt furnished by standard procedures (*R*)-(−)-ethyl nipecotate, $[\alpha]_D^{20} = -1.8$, and, subsequently, (*R*)-(−)-nipecotic acid, $[\alpha]_D^{21} = -3.4$; the corresponding (*S*)-(+) ester was obtained with use of D-(−)-tartaric acid in conjunction with enriched material from the original resolution.[5] The absolute configurations of the (*R*)-(−)-nipecotic acid and (*R*)-(−)-ethyl nipecotate have been inferred by ORD and CD spectroscopies[6] and by correlation with (*R*)-(−)-3-methylpiperidine, respectively.[7] (±)-Nipecotic acid can also be resolved via the use of enantiopure 10-camphorsulfonic acid.[8] Following our earlier resolution[9] of the α-amino acid (±)-2-piperidinecarboxylic acid [(±)-pipecolic acid] by the fractional crystallization of internal diastereomers formed in the reaction of the sodium salt of the acid with the readily prepared palladium(II) complex (*S*,*S*)-(+)-**2**·CH_2Cl_2,[10,11] we have resolved the β-amino acid (±)-**1** by a similar procedure. The resolution method, which is widely applicable to the resolution of chiral tertiary arsines and phosphines,[12] affords both enantiomers of the β-amino acid in >99% ee with recovery of the resolving agent. The related *ortho*-palladated *N*,*N*-dimethylbenzylamine complexes have been used for the determination of the absolute configurations and enantiomer ratios by NMR spectroscopy in α-amino-,[13] β-amino-, and γ-amino acids[14] with a variety of substitution patterns. The α-amino acid (*S*)-proline has been used for the resolution of *ortho*-palladated (±)-*N*,*N*-dimethyl-1-(2,5-dimethylphenyl)ethylamine.[15]

2. Results and discussion

A suspension of (*S*,*S*)-(+)-**2**·CH_2Cl_2 and sodium (±)-nipecotate (2 equiv) in methanol dissolved over 2 h to give a pale yellow solution of an equimolar mixture of (*S*),(*R*,S_N)-**3** and (*S*),(*S*,R_N)-**3** (Scheme 1). Concentration of the solution afforded (*S*),(*R*,S_N)-**3** as colorless microcrystals, which, after a single recrystallization from chloroform–methanol, formed colorless prisms (76% yield) having $[\alpha]_D$ = +184.2 (*c* 1.00, $CHCl_3$). The configurational homogeneity of the less-soluble (*S*),(*R*,S_N)-**3** was evident in the ^{1}H NMR spectrum,

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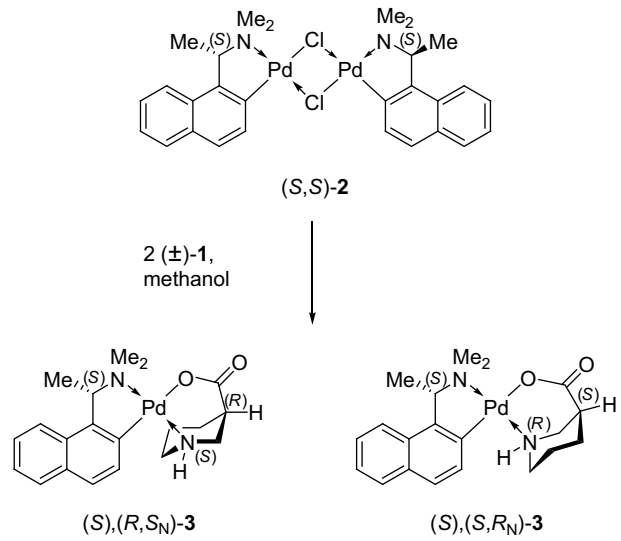

Scheme 1.

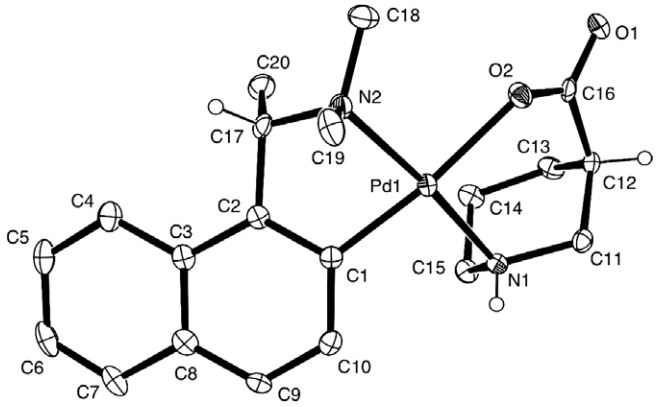

Figure 1. ORTEP drawing of (*S*),(*R*,S_N)-**3** with 30% probability ellipsoids shown. Hydrogen atoms bound to stereogenic centers have been included. Selected interatomic distances (Å) and angles (°) are as follows: Pd1–N1 2.064(5), Pd1–N2 2.091(4), Pd1–O2 2.128(4), Pd1–C1 1.979(5), N1–Pd1–N2 174.0(2), N1–Pd1–O2 91.4(2), O2–Pd1–C1 173.2(2), N2–Pd1–C1 80.5(2).

Table 1
Crystal data and experimental parameters for X-ray structure analysis

	(*S*),(*R*,S_N)-**3**·0.5H_2O
Formula	$C_{20}H_{26}N_2O_2Pd·H_1O_{0.5}$
M_r	441.86
Crystal system	Tetragonal
Space group	$P4_32_12$
a (Å)	9.216(2)
c (Å)	43.494(4)
Cell vol. (Å^3)	3694.1(11)
Z	8
D_c (g cm^{-3})	1.589
Crystal dim. (mm)	0.14 × 0.04 × 0.12
μ (mm^{-1})	8.25
Instrument	Rigaku AFC6R
Radiation	Cu-Kα
No. of unique rflns. (R_{int})	2335 (0.050)
No. of observed rflns. ($I > 3\sigma(I)$)	1759
Temperature (K)	213.2
Final *R*, R_w ($I > 3\sigma(I)$)	2.85, 2.94

where the doublet at δ 7.00 ($^3J_{HH}$ = 8.36 Hz) for the γ-naphthalene-ring proton adjacent to the orthometallated carbon was well separated from the corresponding resonance for (*S*),(*S*,R_N)-**3**, namely, δ 6.87 ($^3J_{HH}$ = 8.42 Hz). After removal of (*S*),(*R*,S_N)-**3**, the combined filtrates were evaporated to dryness and the residue was recrystallized from chloroform–diethyl ether. In this way, configurationally pure (*S*),(*S*,R_N)-**3** was isolated as fine needles (79% yield) having $[\alpha]_D = -36.8$ (*c* 1.00, $CHCl_3$).

The crystal structure of (*S*),(*R*,S_N)-**3** was determined. Colorless plates of the hemihydrate suitable for X-ray crystallography were grown by the slow addition of diethyl ether into a solution of the complex in dichloromethane. Crystal data for the complex are listed in Table 1 and an ORTEP diagram of the molecule is given in Figure 1. There are eight molecules in the unit cell of the crystal. The piperidine-*N* atom binds regioselectively to the palladium atom *trans* to dimethylamino-*N* atom of the orthometallated amine ligand. The palladium has a distorted square-planar coordination geometry, with the piperidine ring adopting a chair conformation and the six-membered nipicotate-*N*,*O* chelate ring an envelope conformation, as observed in the crystal structure of the racemate (±)-aquabis(nipecotato)copper(II).[16] The five-membered organometallic ring adopts a λ configuration, which is typical for this ring when it contains a carbon stereocenter with an (*S*)-configuration.[11]

The pure enantiomers of (±)-**1** were liberated from the individual diastereomers (*S*),(*R*,S_N)-**3** and (*S*),(*S*,R_N)-**3** by treatment of methanol solutions with concentrated hydrochloric acid; under these conditions, sparingly soluble (*S*,*S*)-**2** precipitated in each case in almost quantitative yield. The mother liquors were evaporated to dryness and the residues were extracted with water, thus furnishing the respective enantiomers of the (±)-nipecotic acid hydrochlorides (±)-**4** after removal of the water and recrystallization of the residues from methanol–diethyl ether. The hydrochlorides were subsequently treated with triethylamine in chloroform to afford the free acids. Thus, enantiomerically pure (*R*)-**1** having $[\alpha]_D = -4.6$ (*c* 1.00, H_2O) {lit.[5] $[\alpha]_D^{23} = -3.4$ (*c* 5, H_2O)} was obtained from (*S*),(*R*,S_N)-**3**, and (*S*)-**1** having $[\alpha]_D = +4.6$ (*c* 1.00, H_2O) {$[\alpha]_D^{21} = +3.6$ (*c* 5, H_2O)} was obtained from (*S*),(*S*,R_N)-**3**. The configurational purity of each enantiomer of (±)-**1** was subsequently confirmed by the re-preparation of the diastereomer of the complex from which it was liberated and recording of the ^1H NMR spectrum.

3. Experimental

^1H NMR spectra were recorded at 24 °C on a Varian Gemini 300 spectrometer operating at 300.075 MHz. Optical rotations were measured at 20 °C on the specified solutions in a 1 dm cell with a Perkin Elmer Model 241 polarimeter. Specific rotations were estimated to be within $\pm 0.5 \times 10^{-1}$ deg cm^2 g^{-1}. Elemental analyses were performed by staff within the Research School of Chemistry. Di-μ-[(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthalenyl-*C*^{2},*N*]dipalladium(II)-1-dichloromethane, (*S*,*S*)-(+)-**2**·CH_2Cl_2, was prepared and isolated as previously described.[11] (±)-Nipecotic acid was purchased from the Aldrich Chemical Company, Inc.

3.1. [*SP*-4-4]-(+)$_{589}$-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C^2,N][(*R*,S_N)-3-piperidinecarboxylato-*N*,*O*]palladium(II) (*S*),(*R*,S_N)-3

A mixture of (*S*,*S*)-(+)-**2**·CH_2Cl_2 (14.80 g, 19.34 mmol) and sodium (±)-nipecotate (5.85 g, 38.68 mmol) in methanol (300 mL) was stirred at room temperature until complete dissolution had occurred (ca. 2 h). The almost colorless solution was concentrated to ca. 100 mL, whereupon colorless (*S*),(*R*,S_N)-**3** crystallized. The crude compound was separated, washed with water and 5% methanol–diethyl ether, and dried in vacuo (7.31 g). A single recrystallization of this material from chloroform–methanol gave the pure

diastereomer as colorless prisms (6.40 g, 76%): mp 195 °C (decomp.); $[\alpha]_D$ = +184.2 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_2Pd$: C, 55.5; H, 6.1; N, 6.5. Found: C, 55.3; H, 6.1; N, 6.2. ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 2H, CH_2), 1.79 (d, 3H, ^3J = 6.41 Hz, CH*Me*), 2.35 (m, 1H, CH_2), 2.70–2.88 (m, 4H, CHCOO, CH_2), 2.76 (s, 3H, NMe), 2.80 (s, 3H, NMe), 3.17 (m, 1H, CH_2), 3.59 (br d, 1H, ^3J = 11.53 Hz, CH_2), 3.92 (br s, 1H, NH), 4.20 (q, 1H, ^3J = 6.41 Hz, C*H*Me), 7.00 (d, 1H, ^3J = 8.36 Hz, NpH), 7.39 (m, 2H, NpH and NpH), 7.52 (d, 1H, ^3J = 8.36 Hz, NpH), 7.62 (d, 1H, ^3J = 8.00 Hz, NpH), 7.78 (dd, 1H, ^3J = 8.40 Hz, ^3J = 1.65 Hz, NpH). Crystals of the *hemihydrate* suitable for X-ray crystallography were grown by the slow addition of diethyl ether (wet) to a dichloromethane solution of the pure diastereomer.

3.2. [*SP*-4-4]-(−)$_{589}$-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C^2,N][(*S*,*R*$_N$)-3-piperidinecarboxylato-*N*,*O*]palladium(II) (*S*),(*S*,*R*$_N$)-3

After separation of crystalline (*S*),(*R*,*S*$_N$)-**3** and concentration of the filtrate, (*S*),(*S*,*R*$_N$)-**3** crystallized as almost colorless prisms (3.92 g). The mother liquor, after evaporation to dryness and recrystallization of the residue from chloroform (50 mL) by dilution with diethyl ether, afforded additional material by seeding with crystals. Combined yield after drying in vacuo: 6.60 g (79%) having mp 207–209 °C; $[\alpha]_D$ = −36.8 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_2Pd$: C, 55.5; H, 6.1; N, 6.5. Found: C, 55.2; H, 6.0; N, 6.1. ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 1H, CH_2), 1.77 (d, 3H, ^3J = 6.47 Hz, CH*Me*), 1.84 (m, 1H, CH_2), 2.28 (br d, 1H, ^3J = 13.61 Hz, CH_2), 2.56 (m, 4H, C*H*COO, CH_2), 2.72 (s, 3H, NMe), 2.81 (s, 3H, NMe), 2.79–2.92 (m, 3H, CH_2), 3.57 (m, 2H, CH_2), 3.89 (br s, 1H, NH), 4.22 (q, 1H, ^3J = 6.35 Hz, C*H*Me), 6.87 (d, 1H, ^3J = 8.42 Hz, NpH), 7.39 (m, 2H, NpH and NpH), 7.50 (d, 1H, ^3J = 8.42 Hz, NpH), 7.63 (d, 1H, ^3J = 8.24 Hz, NpH), 7.78 (dd, 1H, ^3J = 8.10 Hz, ^3J = 1.38 Hz, NpH).

3.3. (*R*)-(−)$_{589}$-3-Piperidinecarboxylic acid hydrochloride (*R*)-4

Hydrochloric acid (10 M, 2.64 mL, 26.4 mmol) was added to a suspension of (*S*),(*R*,*S*$_N$)-**3** (5.70 g, 13.17 mmol) in methanol (60 mL). A bright yellow precipitate of (*S*,*S*)-**2** separated. After stirring for 30 min, the solid was filtered off, washed with water and 5% methanol–diethyl ether, and dried (2.07 g, 95%). The mother liquor was evaporated to dryness and the pale yellow residue was extracted with water, the extract filtered, and the water removed. Recrystallization of the residue from methanol–diethyl ether afforded colorless needles of the pure hydrochloride (1.94 g, 89%): mp 249–252 °C; $[\alpha]_D$ = −2.7 (*c* 1.00, H_2O). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.5; H, 7.3; N, 8.5. Found: C, 43.1; H, 7.0; N, 8.0. ^{1}H NMR (D_2O): δ 1.85 (m, 3H, CH_2), 2.11 (m, 1H, CH_2), 2.95 (m, 1H, CH_2), 3.08 (m, 1H, CH_2), 3.27 (m, 2H, CH_2), 3.48 (m, 1H, C*H*CO_2H).

3.4. (*R*)-(−)$_{589}$-3-Piperidinecarboxylic acid (*R*)-1

Freshly distilled triethylamine (1.46 mL, 10.50 mmol) was added to a suspension of (*R*)-**4** (1.66 g, 10.00 mmol) in dry dichloromethane (15 mL). After stirring for 1 h, the triethylamine hydrochloride was filtered off and washed with a small quantity of dichloromethane. The combined filtrates were evaporated to dryness and the residue was recrystallized from dichloromethane–diethyl ether to afford the pure acid (1.20 g, 81%): mp 258–260 °C; $[\alpha]_D$ = −4.6 (*c* 1.00, H_2O). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.8. Found: C, 55.6; H, 9.0; N, 10.7. ^{1}H NMR (D_2O): δ 1.72 (m, 2H, CH_2), 1.88 (m, 1H, CH_2), 2.01 (m, 1H, CH_2), 2.60 (m, 1H, CH_2), 3.06 (m, 2H, CH_2), 3.24 (m, 1H, CH_2), 3.35 (m, 1H, C*H*CO_2H).

3.4.1. (*S*)-(+)$_{589}$-3-Piperidinecarboxylic acid (*S*)-1

(*S*)-**1** was obtained from (*S*),(*S*,*R*$_N$)-**3** by identical procedures, having $[\alpha]_D$ = +4.7 (*c* 1.00, H_2O).

3.5. X-ray crystal structure determination

The structure of (*S*),(*R*,*S*$_N$)-**3**·0.5H_2O was solved by heavy-atom methods. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms (excluding those bound to the coordinated secondary amine and the water of crystallization) were included at calculated positions and were not refined. All calculations were performed using the TEXSAN structure analysis software.[17] Molecular graphic was produced with ORTEP-3.[18] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 689225. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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