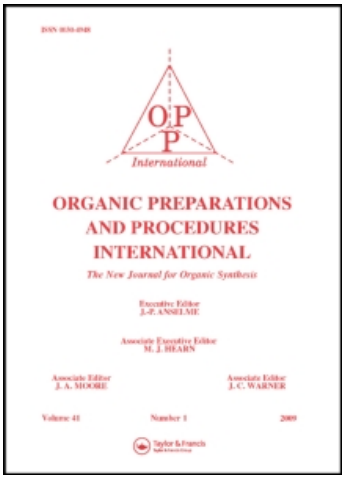

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A *cis*-1,2-DIAMINE FROM THE STEREOSELECTIVE REDUCTION OF AN α-AMINO ENAMINE

Stan V. D'andrea[a]; Shikai Zhao[a]; Stephen A. Mizsak[a]; Jeremiah P. Freeman[a]; Jacob Szmuszkovicz[b]
[a] Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN [b] The Upjohn Company, Kalamazoo, MI

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A *cis*-1,2-DIAMINE FROM THE STEREOSELECTIVE REDUCTION OF AN α-AMINO ENAMINE

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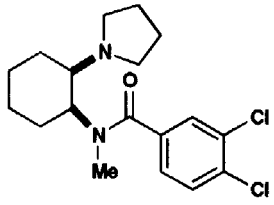
Stan V. D'Andrea, Shikai Zhao, Stephen A. Mizsak†, Jeremiah P. Freeman and Jacob Szmuszkovicz*

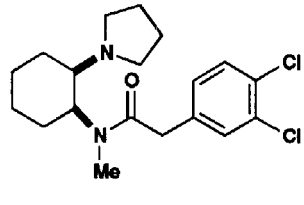
Department of Chemistry and Biochemistry
University of Notre Dame, Notre Dame, IN 46556

1,2-Aminoamides prepared from cycloalkyl-1,2-diamines exhibit a broad range of biological activity.[1] The activity and selectivity of these agents is sensitive to the stereochemistry of the 1,2-diamine functionality, the ring size of the carbon skeleton, and the ordering of the other substituents. *trans*-1,2-Aminoamides have shown potential as analgesics (μ and κ opiate agonists) and antidepressants.[2] In contrast, *cis*-1,2-aminoamides do not show significant opiate-like activity but are reported to show anticonvulsant and σ agonist activity.

U-54494 (**1**) is a structurally novel anticonvulsant[3] which was subjected to clinical trials. The related phenylacetamide **2** (1*S*,2*R*) is a potent and selective σ agonist.[4] Our interest in extending the *structure activity relationship* (SAR) in this *cis*-1,2-aminoamide series has led to the synthesis of the benzo-fused analogs **3**,[5] and this paper describes an alternative synthesis pathway for the *cis*-diamine **8**, precursor of **3**.



U-54494 (**1**)
(racemic)



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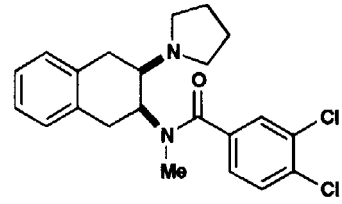
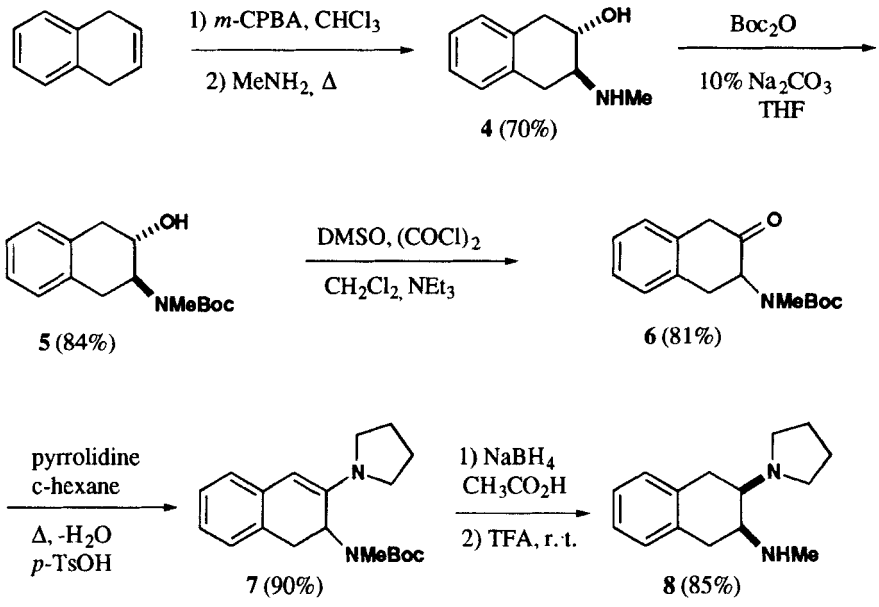


3

A recent report by Rice *et al.*[4] described the facile synthesis of various cyclohexane-*cis*-1,2-diamines by catalytic reductions of α-amino enamines. We felt that extension of this methodology to a tetraline system would give rise to amide **3** *via cis*-1,2-diamine **8**. The epoxide[6] generated from 1,4-dihydronaphthalene was not isolated but treated directly with 40% aq. methylamine to give the *trans*-amino alcohol **4**. Protection of compound **4** as its *t*-butyl carbamate gave the new amino alcohol **5**. PCC oxidation of **5** to the corresponding ketone **6** was inefficient, giving mixtures of starting material and ketone **6**. However, Swern oxidation of **5** provided **6** cleanly in 81% yield. Acid-catalyzed condensation of **6** with pyrrolidine proceeded readily in refluxing cyclohexane to give a yellow solid. The ^{1}H NMR spectra of this product is most consistent with enamine **7**.[7] Although catalytic reductions of α-amino enamines to *cis*-diamines are well documented, enamine **7** was unreactive under standard hydrogenation conditions[8] with Pd/C and no diamine **8** was obtained. Some limited success in this reduction was achieved by mimicking the transfer hydrogenation conditions (HCO_2NH_4) employed



for the cleavage of *N*-benzyl groups,[9] however the results were not always reproducible and some questions remain as to the stereochemistry of the resulting diamine. The use of an acid catalyst (i. e. $HClO_4$) to promote this hydrogenation[10] was also unsuccessful. However, the reduction of enamine **7** was achieved cleanly by $NaBH_4$ in AcOH.[11] After the reduction, the protecting group was removed by trifluoroacetic to give the *cis*-1,2-diamine **8**, fully characterized by NMR and the ^{13}C NMR spectra was identical with that of the compound obtained by the Diels-Alder reaction.[5] Compound **8** was converted to **3** according to the literature procedure.[5]

EXPERIMENTAL SECTION

The following chemicals were obtained from commercial sources and were used without further purification: triethylamine, di-*tert*-butyl dicarbonate, oxalyl chloride, 40% aq. methylamine, pyrrolidine (Aldrich), diethyl ether (Fisher, reagent ACS, anhydrous), methylene chloride (Fisher, certified ACS). Tetrahydrofuran (Fisher, certified) was purified by refluxing over sodium under nitrogen followed by distillation. DMSO was dried over 4Å molecular sieves and vacuum-distilled prior to use. 1,4-Dihydronaphthalene was prepared according to the literature procedure.[12]

***trans*-2-Hydroxy-3-methylamino-1,2,3,4-tetrahydronaphthalene (4).** 2,3-Epoxy-1,2,3,4-tetrahydronaphthalene was generated *in situ* as described previously[5] from 70% 1,4-dihydronaphthalene (30% naphthalene) (5.2 g, 28.0 mmol). The resultant CH_2Cl_2 solution of the epoxide was cooled to 0° and treated with 40% aq. methylamine (4 mL, 51.6 mmol). The methylene chloride was removed by rotary evaporation without external heating. An additional 4 mL (51.6 mmol) of 40% aq. methylamine was added and the heterogeneous reaction mixture was transferred to a sealed tube with the aid of 15 mL of THF. The reagents were stirred and heated at 50-60° for 18 hrs. The cooled reaction mixture

was partitioned between 100 mL of sat. aq. Na_2CO_3 and 100 mL of CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4), and concentrated to give 5.70 g of an off-white solid. The crude product was recrystallized from CH_2Cl_2-ether to afford 3.46 g (70%) of **4** as a white solid, mp. 178-179°; ^{1}H NMR (200 MHz): δ 2.59 (s, 3 H, NC<u>H</u>$_3$), 2.47-2.88 (m, 3 H, C<u>H</u> and C<u>H</u>$_2$), 3.18 (dd, *J* = 6, 16 Hz, 1 H), 3.24 (dd, 5, 15 Hz, 1 H), 3.72 (dt, *J* = 6, 10 Hz, 1 H, C<u>H</u>OH), 7.11 (s, 4 H, ArH); HRMS (EI) Calcd for $C_{11}H_{15}NO$: 177.1154. Found: 177.1156.

Amino Alcohol 5.- A solution of **4** (2.92 g, 16.5 mmol) in 10 mL of THF was diluted with 150 mL of 10% aq. Na_2CO_3 and treated with di-*tert*-butyl dicarbonate (3.60 g, 16.5 mmol). After stirring for 18 hrs, the THF was removed *in vacuo* and the residue was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried (Na_2SO_4), decanted, and concentrated to give 3.86 g (84%) of **5** as a tan solid, mp. (hexanes) 127°. ^{1}H NMR (200 MHz) δ 1.48 (s, 9 H, *tert*-butyl), 2.25 (br s, 1 H, O<u>H</u>), 2.87 (s, 3 H, NC<u>H</u>$_3$), 2.81-3.00 (m, 3 H), 3.25 (dd, *J* = 6, 16 Hz, 1 H, C<u>H</u>), 4.05 (m, 1 H, NC<u>H</u>), 4.30 (br s, 1H, C<u>H</u>OH), 7.12 (s, 4 H, ArH); MS (EI) m/z 277 (M^+).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.68; H, 8.69; N, 5.12

2-Tetralone 6.- A solution of DMSO (3.26 g, 41.7 mmol) in THF (150 mL) was cooled to -40° under N_2 and treated with oxalyl chloride (10.5 mL of a 2M CH_2Cl_2 solution, 20.9 mmol). After 30 min at -40°, the reaction was cooled to -78° and compound **5** (3.86 g, 13.9 mmol) in 50 mL of THF was added slowly. Stirring was continued for 10 min at -78° and for 30 min at -35°. Triethylamine (4.22 g, 41.7 mmol) was added and the reaction was held at -35° for 10 min and then allowed to warm to room temperature. After 1 hr at 22° the slightly green solution was cooled to 0° and diluted with an equal volume of ether. This organic solution was washed with cold water (3 x 100 mL), and cold 0.5 M $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated to give 3.83 g of an orange oil. The crude product was purified by column chromatography (silica gel, 1:1 ether-CH_2Cl_2) to give 3.10 g (81%) of **6** as a yellow oil which solidified on standing, mp 68-69°. IR (film): 1725 (CO), 1690 (CO) cm^{-1}. ^{1}H NMR (300 MHz) (2 conformers, 2:1) δ 1.47 and 1.52 (s, total of 9 H, *tert*-butyl), 2.94 and 2.97 (s, total of 3 H, NC<u>H</u>$_3$), 3.09 (dt, *J* = 6, 14 Hz, 1 H, C<u>H</u>), 3.46-3.89 (m, 3 H, C<u>H</u> and C<u>H</u>$_2$), 4.07 and 4.38 (dd, *J* = 6, 12 Hz, total of 1 H, C<u>H</u>NMeBoc), 7.24 (m, 4 H, ArH).

Anal. Calcd. for $C_{16}H_{21}NO_3 \cdot 1/4H_2O$: C, 68.67; H, 7.74; N, 5.01. Found: C, 68.49; H, 7.51; N, 4.89

Enamine 7.- To a solution of ketone **6** (2.82 g, 10.2 mmol) dissolved in 175 mL of cyclohexane was added pyrrolidine (3.64 g, 51.2 mmol) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol). This solution was connected to a Soxhlet extractor filled with 4Å molecular sieves and the system was placed under N_2. The reaction mixture was heated at reflux for 20 hrs, cooled to room temperature, diluted with 100 mL of ether and washed with sat. aq. $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), and concentrated to give 3.01 g (90%) of **7** as a tan solid: mp (hexanes) 152° (sublimes). IR (film) 1690 (broad, CO) cm^{-1}. ^{1}H NMR (300 MHz): δ 1.44 and 1.50 (s, total of 9 H, *tert*-butyl), 1.88 (m, 4 H, 2 x CH_2), 2.42 and 2.44 (s, total of 3 H, NCH_3), 2.85-3.37 (m, 6 H, 3 x CH_2), 4.86 and 5.09 (d, *J* = 7 Hz, total of 1 H, C<u>H</u>NMeBoc), 5.35 and 5.37 (s, total of 1 H, C=C<u>H</u>), 6.85 (m,

2H, ArH), 7.01 (m, 2 H, ArH); HRMS(EI) Calcd for $C_{20}H_{28}N_2O_2$: 328.2151. Found: 328.2151.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.74; H, 8.48; N, 8.32

***cis*-1,2,3,4-Tetrahydro-N-methyl-3-(1-pyrrolidinyl)-2-naphthalenamine (8).** Glacial acetic acid (5 mL) was added dropwise to a mixture of **7** (152 mg, 0.46 mmol) and $NaBH_4$ (200 mg) in THF (12 mL) in 1 min. at r.t. under nitrogen. The reaction mixture was thus heated at reflux temperature for 2 hrs. It was cooled to r.t., then poured into ice and basified by the addition of solid NaOH. The mixture was extracted with ether (3 x 30 mL), the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. The oil was dissolved in trifluoroacetic acid (1 mL) and the solution was stirred at r.t. for 1 hr. The reaction mixture was poured into ice, basified by the addition of solid NaOH, and extracted with ether (3 x 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a red oil (90 mg, 85%). ^{1}H NMR (500 MHz): δ 7.08 (m, 4 H, aromatic H's), 3.08 (dt, J = 3.6, 2.7 Hz, 1 H), 3.02 (dd, J = 17.0, 2.5 Hz, 1 H), 2.92 (dd, J = 17.0, 10.8 Hz, 1 H), 2.89 (dd, J = 16.2, 6.4 Hz, 1 H), 2.76 (dd, J = 17.0, 3.6 Hz, 1 H), 2.64 (m, 4 H), 2.45 (s, 3 H), 2.42 (ddd, J = 11.1, 6.6, 2.8 Hz, 1 H), 1.81 (m, 4 H). ^{13}C NMR (75 MHz) δ 134.66 (s), 133.69 (s), 129.34 (d), 129.08 (d), 125.79 (d), 125.57 (d), 63.69 (d), 56.08 (d), 51.83 (t), 34.89 (q), 32.08 (t), 31.41 (t), 23.21 (t).

A hydrochloride salt obtained from an ethereal solution of **8** and of HCl was recrystallized from methanol/ether to give an off-white solid: mp. >230°.

Anal. Calcd. for $C_{15}H_{22}N_2 \cdot 2HCl \cdot 0.2H_2O$: C, 58.71; H, 8.01; Cl, 23.11; N, 9.13

Found: C, 58.70; H, 8.15; Cl, 22.89; N, 9.15

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AROMATIC NITRATION OF 2-PHENYLHYDRAZONES OF 1,2-DICARBONYL COMPOUNDS USING CERIUM(IV) AMMONIUM NITRATE

Submitted by (11/23/92)

Himatkumar V. Patel,* Kavita A. Vyas, Sudhanshu P. Pandey and Peter S. Fernandes

N. S. R. Laboratory, Department of Chemistry
St. Xavier's College, Bombay 400001, INDIA

The reactions of organic compounds with salts of cerium(IV) have been studied under various conditions.[1] Reactions of cerium(IV) ammonium nitrate (CAN) with aromatic compounds, however, have not been as extensively investigated.[2] We now report herein our findings on nitration of 2-phenylhydrazones of 1,2-dicarbonyl compounds with CAN.

When 2-phenylhydrazones of 1,2-dicarbonyl compounds (**1**)[3] were treated with CAN in acetonitrile at room temperature for 1-3 hrs, a mixture of the corresponding 4-nitrophenyl and 2-nitrophenyl hydrazones[4-11] **2** and **3** respectively was obtained in good overall yields (Scheme). A slight excess (1.5 equiv.) of CAN was sufficient for complete nitration. All compounds isolated gave satisfactory analytical figures and were characterized by spectroscopic means (IR, mass and NMR); their mps were in agreement with those reported in literature.

A particularly important feature of this reaction is the prevailing mild conditions, as a result of which, neither carbonyl, ester, cyano, nitro groups nor the hydrazone portions undergo reaction with CAN. Thus exclusive formation of ring nitration products with the 4-nitro isomer (**2**) as the major product demonstrates the selectivity of this nitration.