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RESEARCH ARTICLES

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Anticonvulsant Properties of *N*-Substituted α,α-Diamino Acid Derivatives

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Received April 19, 1993, from the [†]*Department of Chemistry, University of Houston, Houston, TX 77204-5641,* [‡]*Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.* Accepted for publication November 24, 1993[⊗]. [§]Current address: Ligand Pharmaceuticals, 9393 Towne Center Dr., Suite 100, San Diego, CA 92121.

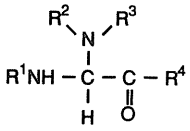
Abstract □ Recent studies have demonstrated that functionalized α,α-diamino acids (**1**) display excellent activity when evaluated in the maximal electroshock seizure (MES) test in mice. The synthesis and pharmacological evaluation of 14 select analogues within this series of compounds are detailed. Included in this survey were 10 *N*-acyl derivatives in which the basic C(α) *N*-group in **1** was replaced by a neutral *N*-substituent and four dipeptides where the amino acid fusion point was the α-carbon site. *N*-Acylation of **1** led to decreased anticonvulsant activity. The importance of these findings in relation to the requirements of the C(α) substituent for anticonvulsant activity in **1** are briefly discussed.

Introduction

Recent studies have shown that α,α-diamino acid derivatives (**1**) and related compounds are surprisingly stable and readily accessible materials.[1–5] Moreover, we have demonstrated that α-amino, α-hydrazino, and α-*N*-hydroxylamino adducts display excellent anticonvulsant activity when evaluated in the maximal electroshock seizure (MES) test in mice.[5] For example, the median effective dose (ED_{50}) values after intraperitoneal injection for the α-*N*-ethylamino (**2a**) (42.4 mg/kg) and α-N^2-(benzyloxycarbonyl)hydrazino (**2b**) (55.6 mg/kg) derivatives approached the ED_{50} of phenobarbital[6] (21.8 mg/kg), whereas the ED_{50}s of the α-methoxyamino (**2c**) (6.2 mg/kg) and the α-[(methoxymethyl)amino] (**2d**) (6.7 mg/kg) adducts exceeded the ED_{50} of phenytoin[6] (9.5 mg/kg). Both **2c** and **2d** exhibited these potent anticonvulsant effects at doses much lower than those which produced neuromotor impairment on the horizontal screen (HS) test (46.0 and 50.5 mg/kg were the ED_{50} doses for **2c** and **2d** on the HS test).[5] These findings prompted our investigation of the pharmacological activity of the racemic *N*-substituted α,α-diamino acid derivatives (**2e–r**) (Table 1). The *N*-acyl derivatives (**2e–n**) were evaluated to determine the effect of conversion of the *basic* C(α)-amino group in **2a–d** to a *neutral* C(α)-carbamate (**2e, 2f**), urea (**2g–2i**), thiourea (**2j, 2k**), amide (**2l, 2n**), or succinimide (**2m**) substituent on anticonvulsant activity. Also included in our study were the unique dipeptides **2o-r**, where the amino acid fusion point was the α-carbon site.

Experimental Section

Chemical Methods—Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Perkin-Elmer 1330 and 283 spectrometers and calibrated against the 1601-cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si and coupling constants (*J* values) are in hertz. Low-resolution mass spectra (MS) were recorded at an ionizing voltage of 70 eV from a Varian MAT CH-5 spectrometer at the Lilly Research Laboratories. Microanalyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. All compounds gave satisfactory elemental analyses (C, H, N) that were within ±0.4% of theoretical values. Thin-and thick-layer chromatography were run on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521) or silica gel GHLF (20 × 20 cm; Analtech 11187).



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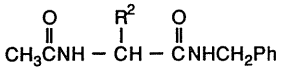
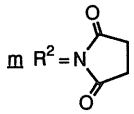


2a $R^2 = NHCH_2CH_3$
b $R^2 = NHNHCO_2CH_2Ph$
c $R^2 = NH(OCH_3)$
d $R^2 = N(CH_3)OCH_3$
e $R^2 = NHC(O)OCH_3$
f $R^2 = NHC(O)OPh$
g $R^2 = NHC(O)NHCH_3$
h $R^2 = NHC(O)NHPh$
i $R^2 = NHC(O)NHS(O_2)Ph$
j $R^2 = NHC(S)NHCH_3$
k $R^2 = NHC(S)NHPh$
l $R^2 = NHC(O)Ph(2'CO_2H)$



m $R^2 = N$

n $R^2 = NHC(O)CH_2NHC(O)OCH_2Ph$
o $R^2 = NHCH_2C(O)OCH_3$
p $R^2 = NHCH_2C(O)OCH_2CH_3$
q $R^2 = NHCH_2C(O)OCH_2Ph$
r $R^2 = \overset{+}{N}H_2CH_2CO_2^-$
s $R^2 = NH_2$
t $R^2 = Br$
u $R^2 = \overset{+}{N}(CH_3)_3, BF_4^-$
v $R^2 = NHC(O)CH_3$
w $R^2 = NHC(O)CF_3$

Chemical Synthesis—General Procedure for the Synthesis of Functionalized Amino Acid Derivatives 2e–k—A tetrahydrofuran (THF) solution containing **2s**[5] and either the acylating agent (1.06–1.10 equiv) and triethylamine (1.20 equiv) or the isocyanate (isothiocyanate) (1.0–1.1 equiv) was heated. The reaction was then filtered to remove any salts formed and purified, and the product was recrystallized if necessary. The reaction temperatures, times, and recrystallization solvents (if appropriate) were as follows: (**2e**) 55–60 °C, 2 h, EtOH; (**2f**) 45–50 °C, 2 h, MeOH; (**2g**) 45–50 °C, 2 h, MeOH; (**2h**) 45–50 °C, 2 h; (**2i**) 50–55 °C, 22 h; (**2j**) 65 °C, 4 h, EtOH; (**2k**) 65 °C, 3 h, EtOH.

Synthesis of *N*-[Acetamido(benzylcarbamoyl)methyl]phthalamic Acid (2l). To a warm pyridine solution (7.0 mL) containing **2s** (0.63 g, 2.83 mmol) was added phthalic anhydride (0.43 g, 2.87 mmol), and the reaction was stirred at 50–55 °C (5 h). Pyridine was removed by distillation *in vacuo* and the residue was treated with H_2O (20 mL). The aqueous mixture was extracted with EtOAc (2 × 20 mL) and then acidified with aqueous 1 N HCl solution. The white solid (0.70 g, 70%) that precipitated was filtered, washed with H_2O (10 mL), and dried; mp 186–188 °C.

Synthsis of 2-Acetamido-*N*-benzyl-2-(*N*-succinimidyl)acetamide (2m). A cooled (–78 °C) THF solution (150 mL) of **2t**[5] [prepared from 2-acetamido-*N*-benzyl-2-ethoxyacetamide[7,8] (2.00 g, 8.0 mmol) and BBr_3 (2.51 g, 10.05 mmol)] was added slowly into a cooled (–78 °C) THF suspension (50 mL) of sodium succinimide (3.06 g, 25.25 mmol). The

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1994.

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