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

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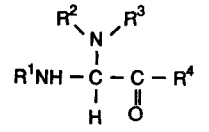
Abstract □ Recent studies have demonstrated that functionalized α,α-diamino acids (**1**) display excellent activity when evaluated in the maximal electroshock seizure (MES) test in mice. The synthesis and pharmacological evaluation of 14 select analogues within this series of compounds are detailed. 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.



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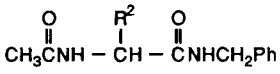

2a $R^2 = NHCH_2CH_3$
b $R^2 = NHNHCO_2CH_2Ph$
c $R^2 = NH(OCH_3)$
d $R^2 = N(CH_3)OCH_3$
e $R^2 = NHC(O)OCH_3$
f $R^2 = NHC(O)OPh$
g $R^2 = NHC(O)NHCH_3$
h $R^2 = NHC(O)NHPh$
i $R^2 = NHC(O)NHS(O_2)Ph$
j $R^2 = NHC(S)NHCH_3$
k $R^2 = NHC(S)NHPh$
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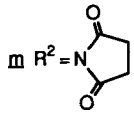
m $R^2 =$ 
n $R^2 = NHC(O)CH_2NHC(O)OCH_2Ph$
o $R^2 = NHCH_2C(O)OCH_3$
p $R^2 = NHCH_2C(O)OCH_2CH_3$
q $R^2 = NHCH_2C(O)OCH_2Ph$
r $R^2 = \overset{+}{N}H_2CH_2CO_2^-$
s $R^2 = NH_2$
t $R^2 = Br$
u $R^2 = \overset{+}{N}(CH_3)_3, BF_4^-$
v $R^2 = NHC(O)CH_3$
w $R^2 = NHC(O)CF_3$

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).

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

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reaction mixture was stirred at −78 °C (30 min) and at room temperature (90 min), and then treated with a 10% aqueous citric acid solution (50 mL). The resulting solution was neutralized with a saturated aqueous $NaHCO_3$ solution, and the reaction mixture extracted with EtOAc (3 × 100 mL). The combined extracts were dried (Na_2SO_4), and the volatile materials were removed by distillation *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel (6% MeOH/$CHCl_3$) to give 1.10 g (45%) of **2m**; mp 181–183 °C (recrystallized from EtOH).

Synthesis of *N*'-(Benzyloxy)-*N*-[acetamido(benzylcarbamoyl)-methyl]malondiamide (2n). 4-Methylmorpholine (0.35 g, 3.56 mmol) was added to a solution of *N*-CBZ-glycine (0.74 g, 3.55 mmol) in THF (75 mL) at −10 to −15 °C. The solution was stirred (5 min), and then isobutyl chloroformate (0.49 g, 3.55 mmol) was added and the mixture was stirred for an additional 20 min. A cooled (−10 °C) solution of **2s** (0.79 g, 3.55 mmol) in THF (125 mL) was then added slowly (30 min). The reaction mixture was stirred at this temperature (2 h) and then at room temperature (2 h). The insoluble materials were filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with EtOAc (20 mL) and the white solid (0.60 g) that remained was filtered, washed with H_2O, and dried to give **2n**. The initial insoluble material on trituration with H_2O gave an additional 0.40 g of **2n** to give a combined yield of 1.00 g (68%); mp 177–179 °C (recrystallized from EtOH).

Synthesis of Methyl *N*-[Acetamido(benzylcarbamoyl)methyl]-glycinate (2o). A methanolic solution (50 mL) containing **2u**[5] (1.00 g, 2.85 mmol) and methyl glycinate (prepared from methyl glycinate hydrochloride (1.01 g, 8.55 mmol), and NaOMe (0.38 g, 7.10 mmol)) was heated to reflux (2 h). The reaction was concentrated *in vacuo* to give an oily residue that was purified by flash column chromatography on SiO_2 gel (3% MeOH/$CHCl_3$) to give 0.60 g (72%) of **2o**; mp 144–146 °C (recrystallized from EtOAc).

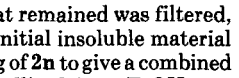
Synthesis of Ethyl *N*-[Acetamido(benzylcarbamoyl)methyl]-glycinate (2p). A methanolic solution (70 mL) containing **2u**[5] (1.50 g, 4.28 mmol) and ethyl glycinate [prepared from ethyl glycinate hydrochloride (3.10 g, 22.2 mmol) and NaOMe (1.17 g, 21.74 mmol)] was heated to reflux (2 h). The reaction was concentrated *in vacuo* to give an oily residue that was purified by flash column chromatography on SiO_2 gel (5% MeOH/$CHCl_3$) to give 0.60 g (46%) of **2p**; mp 125–127 °C (recrystallized from EtOAc).

Synthesis of Benzyl *N*-[Acetamido(benzylcarbamoyl)methyl]-glycinate (2q). A suspension of benzyl glycinate hydrochloride (5.00 g, 24.8 mmol) in THF (400 mL) containing Et_3N (4.90 g, 48.5 mmol) was stirred (4 h) at room temperature. The reaction mixture was cooled (−78 °C) and then a cooled (−78 °C) THF solution (150 mL) of **2t**[5] [prepared from 2-acetamido-*N*-benzyl-2-ethoxyacetamide[7,8] (4.00 g, 16.0 mmol) and BBr_3 (1 M in CH_2Cl_2, 20.0 mL, 20.0 mmol)] was added (30 min). The reaction mixture was stirred at −78 °C (30 min) and then at room temperature (16 h). The insoluble materials were filtered, the filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatrgraphy on SiO_2 gel (3% MeOH/$CHCl_3$) to give 1.56 g (26%) of **2q** as a white solid; mp 133–135 °C (recrystallized from EtOH).

Synthesis of *N*-[Acetamido(benzylcarbamoyl)methyl]glycine (2r). A solution of methyl *N*-[acetamido(benzylcarbamoyl)methyl]-glycinate (**2o**) (0.60 g, 2.05 mmol) and KOH (0.30 g, 5.36 mmol) in 90% aqueous EtOH (50 mL) was stirred at room temperature (48 h). The volatile materials were then removed *in vacuo*, and the residue dissolved in H_2O (10 mL). The aqueous solution was extracted with EtOAc (2 × 20 mL), and the aqueous layer was acidified to pH ~2.0 with aqueous 1 N HCl. A column containing ion-exchange resin Dowex 50X W4 was prepared using 10% aqueous pyridine. The column was thoroughly washed with H_2O. The acidic aqueous reaction solution was added to the top of the column, and the column was eluted with H_2O (300 mL or until the eluate was neutral). The column was then eluted with 10% aqueous pyridine (400 mL). The aqueous pyridine fraction was concentrated *in vacuo* to give a white solid, dried *in vacuo* and then triturated with absolute EtOH (7 mL). The insoluble materials that remained were filtered and dried to give 0.29 g (50%) of **2r**; mp 124–126 °C dec.

Pharmacological Evaluation—All tests were performed with male CF-1 mice from Charles River Breeding Laboratories (Portage, MI). All compounds were dissolved in 30% poly(ethylene glycol) 400 and administered in an injection volume of 1 mL/100 g of body weight. Initial anticonvulsant evaluation of **2e–r** was conducted with two dose levels (30, 100 mg/kg) administered intraperitoneally. Four mice at each dose level were tested at 0.5, 1, and 4 h after administration, unless otherwise indicated in Table 1, to determine if there was protection against MES seizures.

Table 1—Physical and Pharmacological Data in Mice for *N*-Substituted α,α-Diamino Acid Derivatives[a]

No.	R^2	mp[b]	MES[c] ED_{50}
2e	$NHC(O)OCH_3$	202–204	48.0 (37.7–56.7)
2f	NHC(O)OPh	201–203	>100
2g	$NHC(O)NHCH_3$	229–230	>100
2h	NHC(O)NHPh	242–244	>100
2i	$NHC(O)NHS(O_2)Ph$	188–191	>100
2j	$NHC(S)NHCH_3$	162–163	>100[d]
2k	NHC(S)NHPh	196–197	>100[d]
2l	NHC(O)Ph(2'-CO_2H)	186–188	>100
2m		181–183	>100
2n	$NHC(O)CH_2NHC(O)OCH_2Ph$	177–179	~30[e]
2o	$NHCH_2C(O)OCH_3$	144–146	>100
2p	$NHCH_2C(O)OCH_2CH_3$	125–127	>100
2q	$NHCH_2C(O)OCH_2Ph$	133–135	>100
2r	$^+NH_2CH_2CO_2^-$	124–126	>100[d]
phenytoin[f]			9.5 (8.1–10.4)
phenobarbital[f]			21.8 (15.0–22.5)
valproate[f]			272 (247–338)

[a] The compounds were administered intraperitoneally. ED_{50} values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. A dose–response curve was generated for all compounds that displayed sufficient activity. The dose–effect data for these compounds were obtained at 0.5 h ("time of peak effect"). [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. All compounds were suspended in 30% PEG. [d] The compound was tested only at 0.5 and 1 h due to insufficient supply of sample. [e] Unable to definitively define an ED_{50} value and confidence limits because of insufficient supply of sample. [f] Reference 6.

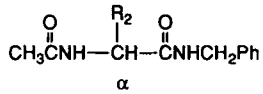
MES seizures were elicited by electrical current (ac, 60 cps, 50 mA, 0.2 s) applied via corneal electrodes. A drop of 0.9% saline was instilled on each eye prior to application of the electrodes to ensure electrical contact. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test. This is the identical protocol used by the Antiepileptic Drug Development Program of the Epilepsy Branch of NINCDS, NIH.[6,9]

After the time of peak anticonvulsant activity and the approximate dose range were determined, a dose–response curve was generated at the time of peak activity with at least three or four doses and 10–12 mice per dose. The MES ED_{50} is the calculated dose required to protect 50% of the mice in the MES test. For those compounds with significant anticonvulsant activity, the doses that caused neuromotor impairment on the horizontal screen (HS) test also were determined.[10] Previously trained mice were dosed with the compound and then placed individually on top of a square (13 × 13 cm) wire screen which was mounted on a vertical rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen in one minute were counted.

Results and Discussion

Chemistry—Several preparative routes were utilized for the construction of the targeted compounds. In most cases, 2-acetamido-*N*-benzyl-2-aminoacetamide[5] (**2s**) served as the starting material. Treatment of **2s** with the appropriate chloroformate, isocyanate, isothiocyanate, or anhydride, or use of the mixed anhydride protocol advanced for peptide synthesis,[11] led to the preparation of the *N*-acyl substituted adducts **2e–l** and **2n**. Correspondingly, the preformed α-bromo derivative[5] **2t** was

Table 2—Key Spectral Properties of *N*-Substituted α,α-Diamino Acid Derivatives



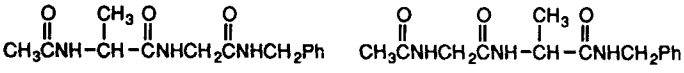
α

No.	IR[a]	^{1}H NMR[b] Cα*H*	^{1}H NMR[b] CH_2Ph	^{13}C NMR[c] C_α	^{13}C NMR[c] $C_\alpha NRC$	MS[d]
2e	1650	5.56 (t, 7.8)	4.27 (d, 5.6)	58.57	—[e]	279
2f	1630, 1700	5.66 (t, 7.6)	4.29–4.35 (m)	58.69	—[f]	341
2g	1630	5.59 (t, 7.8)	4.26 (d, 5.8)	57.92	157.30	279
2h	1600 (br)	5.67 (t, 7.6)	4.30 (d, 5.9)	57.59	153.98	340
2i	1630 (br)	5.47 (t, 7.7)	4.24 (d, 5.7)	57.14	150.36	405
2j	1620	6.10 (br, s)	4.27 (d, 5.8)	61.33	—[g]	294
2k	1620	5.24 (t, 6.9)	4.32 (d, 5.8)	61.18	180.02	356
2l	1620 (br)	5.92 (t, 7.2)	4.36 (d, 6.0)	57.44	—[h]	370
2m	1620 (br)	6.31 (d, 9.0)	4.23–4.36 (m)	55.19	176.33	304[i]
2n	1640 (br)	5.79 (t, 7.7)	4.28 (d, 5.8)	56.77	167.86	413
2o	1610, 1710	5.00 (t, 7.8)	4.28 (d, 6.0)	63.98	46.09	294
2p	1600, 1710	5.01 (t, 8.2)	4.28 (d, 5.8)	63.96	46.22	342
2q	1620, 1710	5.02 (t, 8.2)	4.27 (d, 6.1)	63.94	46.22	370
2r	1630	4.98 (d, 8.2)	4.29 (d, 5.7)	64.08	47.48	—[j]

[a] Infrared spectra were taken with KBr discs and values are reported in cm^{-1}. [b] All spectra were recorded with DMSO-d_6. The number in each entry is the chemical shift value (δ) observed in ppm relative to DMSO-d_6, followed by the multiplicity of the signal and the coupling constant in hertz. ^{1}H NMR spectra were recorded at 300 MHz. [c] ^{13}C NMR spectra were obtained at 75 MHz and the values referenced to DMSO-d_6. [d] All spectra were recorded using FD-MS unless otherwise indicated. Molecular ions reported refer to either M^+ or $M^+ + 1$ ions. [e] The carbamate carbonyl carbon resonance was not detected. The attached NHC(O)O*C*H$_3$ signal was observed at δ 51.46. [f] The carbamate carbonyl carbon resonance was not detected. The attached NHC(O)*C*$_6$H$_5$ signals were observed at δ 121.70, 125.18, 129.30, and 150.91. [g] The thiocarbonyl carbon resonance was not detected. The attached NHC(S)NH*C*H$_3$ signal was observed at δ 30.92. [h] The amide carbonyl resonance could not be readily assigned. Signals corresponding to four carbonyl peaks were observed at δ 167.85, 167.93, 168.48, and 169.47. [i] Value refers to $M^+ + 1$ ion observed by FAB-MS. [j] Spectrum was not taken.

employed as the immediate precursor for **2m** and **2q**, while 2-acetamido-*N*-benzyl-2-(trimethylammonio)acetamide tetrafluoroborate[5] (**2u**) was utilized for the synthesis of **2o** and **2p**. Finally, alkaline hydrolysis of **2o**, followed by neutralization of the dipeptide by passage through an ion-exchange resin yielded **2r**. Key spectral data (i.e., IR, ^{1}H NMR, ^{13}C NMR, MS) observed for **2e–r** are recorded in Table 2 and were consistent with both the proposed structures and previously reported trends.[5]

Pharmacological Evaluation—The *N*-substituted α,α-diamino acid derivatives **2e-r** were tested for anticonvulsant activity by using the procedures described by Krall et al.,[9] which have become standard testing procedures for the Antiepileptic Drug Development Program of the Epilepsy Branch of the National Institutes of Health. All compounds were administered intraperitoneally (ip) to mice. Table 1 lists the median effective dose (ED_{50}) values required to prevent seizures in the MES test by racemic **2**. Inspection of the results revealed several important observations. First, most of the *N*-acyl substituted derivatives (**2e–n**) evaluated were inactive in the MES test at doses of 100 mg/kg or less, and all were significantly less potent than **2c** and **2d**. Only **2e** and **2n** displayed noticeable activity. One noteworthy difference about the anticonvulsant effect of **2n** is that it also produced neuromotor impairment on the HS test at the same doses that blocked MES seizures. Thus, this anticonvulsant effect is qualitatively different than that previously seen with **2c** and **2d**.[5] These findings were of interest since the *N*-acyl derivatives **2e–n**, unlike **2a–d**, are not protonated at physiological pH values, thereby demonstrating that replacement of the basic C(α)-amino group in functionalized amino acids **2a–d** by the neutral C(α) *N*-substituents in **2e–n** did not lead to improved anticonvulsant activity. This observation was consistent with results previously obtained for two other *N*-acyl derivatives, 2,2-diacetamido-*N*-benzylacetamide (**2v**) and 2-acetamido-*N*-benzyl-2-(trifluoroacetamido)acetamide (**2w**).[5] Both **2v** and **2w** did not prevent maximal electroshock seizures at doses of 100 mg or less. Of the two active *N*-acyl derivatives, **2n** can also be viewed as a functionalized dipeptide as well as an *N*-acyl α,α-diamino acid adduct. Previously, we prepared and evaluated functionalized dipeptides **3** and **4**.[11] These compounds differed



3

4

from **2o–r** in that the two amino acid units were joined through an amide bond. Both **3** and **4** were inactive in both the maximal electroshock and subcutaneous pentylenetetrazole seizure tests[6,9] when administered to mice at dose levels up to and including 600 mg/kg.[12]

Conclusions

The composite data indicated that most structural modifications at the α-amino site in functionalized α,α-diamino acids led to a decrease in the anticonvulsant activity after intraperitoneal administration to mice when compared to the simple *N*-ethylamino adduct **2a**,[5] while none of the compounds approached the superior activity observed for the *N*-hydroxylamino derivatives **2c** and **2d**.[5] These results documented that excellent protection against MES-induced seizures by **1** can be achieved by incorporation of a *basic* C(α)-amino substituent.

References and Notes

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