# 3,3-Dialkyl- and 3-Alkyl-3-Benzyl-Substituted 2-Pyrrolidinones: A New Class of Anticonvulsant Agents

P. Amruta Reddy,[†] Bonnie C. H. Hsiang,[†] Tammy N. Latifi,[†] Matthew W. Hill,[‡] Karen E. Woodward,[§] Steven M. Rothman,[‡,||,⊥] James A. Ferrendelli,[§] and Douglas F. Covey*,[†]

*Departments of Molecular Biology and Pharmacology, Anatomy and Neurobiology, Neurology and Neurosurgery, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, and Division of Pediatric Neurology, St. Louis Children's Hospital, One Children's Place, St. Louis, Missouri 63110, and Department of Neurology, University of Texas Health Science Center, 6431 Fannin Street, Houston, Texas 77030*

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A series of 3,3-dialkyl- and 3-alkyl-3-benzyl-substituted 2-pyrrolidinones (lactams) have been prepared and evaluated for their anticonvulsant activities. In the pentylenetetrazole mouse seizure model, 3,3-diethyl lactam **7c** and 3-benzyl-3-ethyl lactam **7j** are the most effective anticonvulsants ($ED_{50}$ = 46 and 42 mg/kg, respectively) and have protective index (PI = $TD_{50}/ED_{50}$) values of 5.65 and 3.00, respectively. These protective index values compare favorably to those of the clinically used antiepileptic drugs ethosuximide ($ED_{50}$ = 161 mg/kg), phenobarbital ($ED_{50}$ = 22 mg/kg), and valproic acid ($ED_{50}$ = 133 mg/kg), which have PI values of 2.35, 4.00, and 2.12, respectively. The benzyl compounds [3-substituents are Bn, H (**7h**); Bn, Me (**7i**); and Bn, Et (**7j**)] are also very effective anticonvulsants against seizures induced by maximal electroshock ($ED_{50}$ = 41, 55, and 74 mg/kg, respectively) and have PI values of 3.51, 3.04, and 1.70, respectively. The corresponding PI values for phenobarbital and valproic acid are 1.37 and 5.18, respectively. As a class of anticonvulsants, the 3,3-disubstituted 2-pyrrolidinones have a broad spectrum of action and may be useful for the treatment of human epilepsies.

## Introduction

The neuroactive alkyl-substituted $\gamma$-butyrolactones (GBLs) have been reported to possess either convulsant or anticonvulsant properties depending upon the substitution pattern.[1] While the α-substituted GBLs with small alkyl groups are anticonvulsants capable of protecting mice against pentylenetetrazole-induced seizures,[1,2] the corresponding $\beta$-substituted compounds are convulsants.[3] Structure−activity studies of the effect of α-alkyl substituent size on neuroactivity have shown that the GBLs containing three or four carbon atoms in the α-alkyl group (branched alkyl or alkyl groups with one or two carbon atoms each or spiroalkyl groups) are anticonvulsants, whereas the compounds containing more than five carbon atoms in the α-alkyl group are convulsants.[4] Substitution of sulfur for the ring oxygen atom yields $\gamma$-thiobutyrolactones (TBLs). The TBLs have enhanced potencies, though their convulsant or anticonvulsant activity remains dependent on the alkyl substitution pattern.[4b,5] Finally, it was shown that alkyl-substituted cyclopentanones (i.e., compounds lacking a ring heteroatom) display similar structure−activity relationships for anticonvulsant and convulsant activity.[6]

The pharmacological actions of these compounds are believed due, at least in part, to complex interactions involving modulation of the picrotoxin binding site of the $\gamma$-aminobutyric acid type A ($GABA_A$) receptor−chloride ionophore complex. Thus, these compounds inhibit the specific binding of [$^{35}$S]-*tert*-butylbicyclophosphorothionate (TBPS),[7,8] a radioligand specific for the picrotoxin binding site, and modulate the actions of picrotoxin on $GABA_A$ receptor function.[9,10] The dual modulation of GABA-mediated chloride flux observed for some compounds has led to the hypothesis that interactions occur at two different sites on the $GABA_A$ receptor, one being identical to the picrotoxin or TBPS recognition site and the other an allosterically linked lactone site.[11] Consistent with this hypothesis, preliminary studies have shown that the potentiating effects of TBLs on GABA-mediated currents are retained by a picrotoxin-insensitive form of a rat $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptor.[12]

The neuroactivities of dialkyl-substituted 2-pyrrolidinones, the lactam analogues of the GBLS, have not been examined extensively. In part, this may be attributable to the lack of potent neuroactivity displayed by 3,3-dimethyl-2-pyrrolidinone and 4-ethyl-4-methyl-2-pyrrolidinone in our preliminary evaluations of this class of compounds.[3] The lack of literature reports of general methods for the preparation of 3,3-disubstituted 2-pyrrolidinones from suitable starting materials also curtailed our earlier efforts to evaluate these compounds. We now report general methods for the synthesis of these compounds, their anticonvulsant activities in two different animal seizure models, and preliminary studies of their pharmacological effects on $GABA_A$ receptor function.

## Chemistry

Among the compounds listed in the Table 1, 2-pyrrolidinone **(1)** and 3-methyl-2-pyrrolidinone **(2)** are commercially available. The published procedure for the preparation of lactam **2** from *N*-(trimethylsilyl)-2-pyrrolidinone **(3)**[13] was utilized for the preparation of the known 3-ethyl-2-pyrrolidinone **(4)**.[14] Thus, compound **3** was alkylated with ethyl iodide in presence of lithium diisopropylamide (LDA) in THF to give lactam **4** in 52% yield.

[†] Department of Molecular Biology and Pharmacology.
[‡] Department of Anatomy and Neurobiology.
[§] Department of Neurology.
[||] Department of Neurology and Neurosurgery.
[⊥] Division of Pediatric Neurology.
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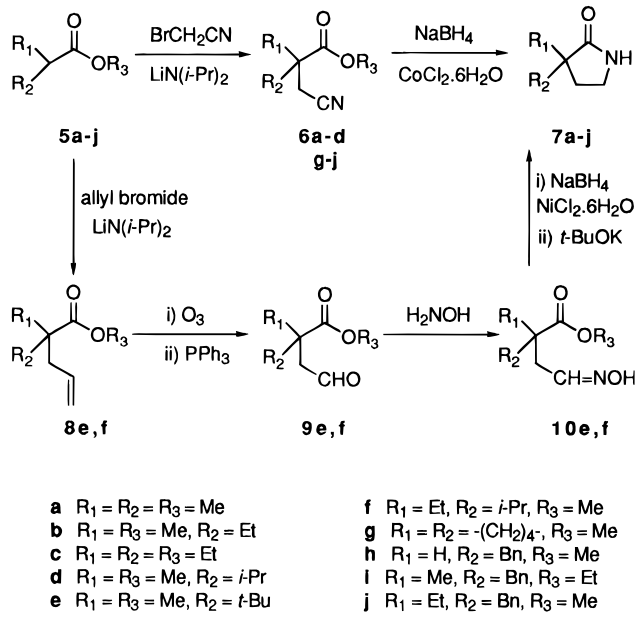
**Table 1.** Anticonvulsant activity, Neurotoxicity, and [$^{35}$S]TBPS Binding Data for 2-Pyrrolidinone Derivatives[a]

| compd | $R_1$ | $R_2$ | anticonvulsant potency: $ED_{50}$[b] (mg/kg) PTZ | MES | rotorod toxicity: $TD_{50}$[c] (mg/kg) | [$^{35}$S]TBPS displacement: $IC_{50}$[d] (mM) |
|---|---|---|---|---|---|---|
| **1** | H | H | >900 (0/6)[e] | >600 (0/6) | >900 (0/6) | 435 ± 32 |
| **2** | H | Me | >900 (2/6) | >750 (0/6) | >900 (3/6) | 215 ± 20 |
| **4** | H | Et | >750 (2/6) | 535 [517−657][f] | 260 [219−320] | 48.1 ± 1.8 |
| **7a** | Me | Me | >600 (2/6) | >600 (0/6) | >600 (0/6) | 32.4 ± 4.27 |
| **7b** | Me | Et | 226 [164−305] | 357 {175, 600}[g] | 622 [497−671] | 12.1 ± 0.99 |
| **7c** | Et | Et | 46 [30−63] | 174 [133−229] | 260 [219−320] | 5.81 ± 0.12 |
| **7d** | Me | *i*-Pr | 118 [69−192] | 220 {175, 300} | 307 {*175, 450*}[h] | 6.86 ± 0.55 |
| **7e** | Me | *t*-Bu | 178 {3,300} | 112 {10, 300} | >300 (1/6) | 3.26 ± 0.53 |
| **7f** | Et | *i*-Pr | 68 [49−90] | 112 [77−158] | 207 [167−255] | 2.62 ± 0.17 |
| **7g** | −(CH$_2$)$_4$− | | 238 [119−383] | | 307 {*100, 450*} | 12.1 ± 0.44 |
| **7h** | H | Bn | 71 [43−101] | 41 [20−63] | 144 [125−168] | 2.44 ± 0.17 |
| **7i** | Me | Bn | 63 [50−79] | 55 [42−102] | 167 [152−200] | 0.85 ± 0.05 |
| **7j** | Et | Bn | 42 [26−62] | 74 [67−93] | 126 [102−155] | 0.44 ± 0.06 |

[a] For the TBPS binding experiments, compounds **7c** and **7h**−**j** were dissolved in DMSO. The final DMSO concentration in the incubations did not exceed 2.5%, a concentration which had no effects on control TBPS binding. Other experimental details, including $IC_{50}$ values for TBPS and picrotoxinin, were as described previously.[4] [b] Dose at which 50% of the mice were protected from clonic seizures induced by pentylenetetrazole or tonic hindlimb seizures induced by maximal electroshock. At least four groups of six mice each were tested to obtain $ED_{50}$ values. Complete experimental details for these evaluations have been described previously.[4] [c] Dose at which 50% of the mice failed the rotorod toxicity test. The methods were as described previously.[4] [d] Binding data for compounds **7a**−**j** are presented as the mean ± SEM of at least three experiments performed in triplicate. Values reported for compounds **1**, **2**, and **4** are the mean ± range from duplicate experiments performed in triplicate. [e] Fractions in parentheses indicate number of mice protected/number of mice in group or number of mice toxic/number of mice in group at the dose reported. [f] Numbers in brackets are the 95% fiducial limits. [g] Numbers in braces are the lowest dose tested at which all mice were unprotected and the lowest dose tested at which all mice were protected, respectively. These values are given in place of 95% fiducial limits which could not be calculated from the data available. [h] Italicized numbers in braces are the lowest dose tested at which all mice were nontoxic and the lowest dose tested at which all mice were toxic, respectively. These values are given in place of 95% fiducial limits which could not be calculated from the data available.

**Scheme 1**




**a** $R_1 = R_2 = R_3 = Me$
**b** $R_1 = R_3 = Me$, $R_2 = Et$
**c** $R_1 = R_2 = R_3 = Et$
**d** $R_1 = R_3 = Me$, $R_2 = i\text{-}Pr$
**e** $R_1 = R_3 = Me$, $R_2 = t\text{-}Bu$
**f** $R_1 = Et$, $R_2 = i\text{-}Pr$, $R_3 = Me$
**g** $R_1 = R_2 = -(CH_2)_4-$, $R_3 = Me$
**h** $R_1 = H$, $R_2 = Bn$, $R_3 = Me$
**i** $R_1 = Me$, $R_2 = Bn$, $R_3 = Et$
**j** $R_1 = Et$, $R_2 = Bn$, $R_3 = Me$

The 2-pyrrolidinone derivatives **7a**−**j** listed in Table 1 were synthesized by the routes outlined in Scheme 1. Alkylation of esters **5** with bromoacetonitrile at −78 °C with LDA as base in THF or THF−HMPA afforded *β*-cyanoalkanoate esters **6** in yields ranging from 30 to 68%. The modest yields of cyano esters, especially in the case of **6d** (30%), are attributed to competing α-bromination reactions. Thus, the alkylation reaction of the ester **5d** also gave methyl 2-bromo-2,3-dimethylbutanoate in 35% yield.[15] The $NaBH_4$ reduction of nitriles **6** in THF−water (2:1, v/v) at 0 °C in the presence of $CoCl_2 \cdot 6H_2O$,[17] after 48 h of stirring at room temperature,[18] resulted in concomitant cyclization of the intermediate amino esters to form lactams **7** in good yields (56−81%). This method was utilized in the synthesis of the lactams **7a**−**d** and **7g**−**j**, in which **7a**,[19] **7g**,[20] and **7h**[13,21] are previously known compounds. The above reaction sequence was not successful in the synthesis of **7e** and **7f** due to the poor results obtained in the bromoacetonitrile alkylation step.

Alternatively, esters **5e,f** were alkylated with allyl bromide at −78 °C with LDA as base in THF−HMPA according to the procedure of MacPhee *et al.*[22] to give the olefinic esters **8e**,**f** in 70 and 82% yield, respectively. The olefinic esters **8e**,**f** were treated with ozone at −78 °C in $CH_2Cl_2$ and the ozonides reduced with $PPh_3$ for 4 h, resulting in the formation of the aldehydic esters **9e,f** (76−88% yield). Treatment of **9e,f** with $NH_2OH \cdot HCl$ in pyridine at 60 °C for 4 h afforded the oximes **10e,f** (86−92% yield) as the *syn* and *anti* mixtures. The $NaBH_4$ reduction of oximes **10e,f** in MeOH at −30 °C in the presence of $NiCl_2 \cdot 6H_2O$,[23] after 1 h of stirring at room temperature, afforded the amino esters which

without further purification were treated with *t*-BuOK in THF[24] for 16 h at room temperature to give the lactams **7e,f** in 57−77% yield.

## Pharmacology

Compounds were tested for anticonvulsant activity in mice against seizures induced by pentylenetetrazole (PTZ) or maximal electroshock (MES), and neurotoxicity in the animals was assessed by a rotorod test (Table 1). Unsubstituted lactam **1** did not have anticonvulsant activity, and it did not cause neurotoxicity at a dose as high as 900 mg/kg. Monoalkyl-substituted lactams **2** and **4** had very weak anticonvulsant activities, and lactam **4** was notably more neurotoxic than lactam **2**.

For the dialkyl compounds, anticonvulsant potency against PTZ-induced seizures was found to be dependent on the size and branching of the 3-alkyl groups. For compounds **7a**, **7b**, **7d**, and **7e**, which all contain a methyl substituent, anticonvulsant potency increases in the order **7a** ≪ **7b** < **7e** < **7d.** For compounds **7b**, **7c**, and **7f**, which all contain an ethyl substituent, anticonvulsant potency increases in the order **7b** < **7f** < **7c.** Thus, in each series an increase in branching of a second alkyl substituent initially increases and then decreases potency. Maximal activity was observed for diethyl compound **7c**. The spiro compound **7g,** which is a constrained analog of **7c**, is only as potent as compound **7b**.

Anticonvulsant potency against MES-induced seizures by the dialkyl compounds also was found to be dependent on the size and branching of the 3-alkyl groups. An analysis similar to that used immediately above indicates that in one series of compounds anticonvulsant potency increases in the order **7a** ≪ **7b** < **7d** < **7e**, and in the other series it increases in the order **7b** < **7c** < **7f**. Hence, in this animal seizure model anticonvulsant potency continuously increases with branching of the second alkyl substituent. Maximal activity was observed for compounds **7e** and **7f**.

Compounds **7h**−**j** all contain a benzyl group in place of a 3-alkyl group. Increasing the size of the other C-3 substituent increases the anticonvulsant potency of the compounds (**7h** < **7i** < **7j**) against PTZ-induced seizures, but decreases the anticonvulsant potency of the compounds (**7h** > **7i** > **7j**) against MES-induced seizures. Compound **7j**, which is the most potent of the benzyl-substituted lactams in the PTZ seizure model, has a potency equal to that of dialkyl lactam **7c** against PTZ-induced seizures. By contrast, all three compounds in the benzyl series are more potent than compounds in the dialkyl series at blocking MES-induced seizures, with compound **7h** being 4 times more potent than compound **7c**.

Results from the rotorod toxicity evaluations demonstrate that compounds **7h** and **7i** in the benzyl series have the best protective index (PI = $TD_{50}/ED_{50}$) for blocking MES-induced seizures (PI = 3.51 and 3.04, respectively), whereas compound **7c** in the dialkyl series has the best protective index (PI = 5.65) for blocking PTZ-induced seizures.

The interactions of each lactam with the picrotoxin binding site of the heterogeneous population of $GABA_A$ receptors[25] found in membranes prepared from rat brain was assessed by determining $IC_{50}$ values for displacement of [$^{35}$S]TBPS (Table 1). The benzyl compounds are more potent than the dialkyl compounds as displacers of [$^{35}$S]TBPS. Although for the benzyl compounds an increased ability to displace TBPS correlates with the rank order of potency for blocking PTZ-induced seizures, this correlation is not observed for the dialkyl series of compounds (e.g., compare compounds **7c** and **7e**). Lactams **1**, **2**, and **4** had extremely weak, but measurable, interactions with the picrotoxin site. On the basis of previous [$^{35}$S]TBPS binding studies of GBLs, TBLs, and cyclic ketones,[4b,6] no correlation was expected for lactam displacement of [$^{35}$S]TBPS and potency for blocking MES-induced seizures, and no correlation was observed.

The modulatory effects of compounds **7c** and **7j**, the best anticonvulsants against PTZ-induced seizures, on $GABA_A$ receptor function were examined in electrophysiological experiments carried out on cultured rat hippocampal neurons (Figure 1 and Table 2). A concentration-dependent increase in the chloride current mediated by 3 $\mu$M GABA was observed for each compound. Compound **7j**, which was a more potent displacer of [$^{35}$S]TBPS than compound **7c**, was more potent at increasing GABA-mediated current. As summarized in Table 2, the potentiating effects of each compound were reversed by the picrotoxin antagonist α-isopropyl-

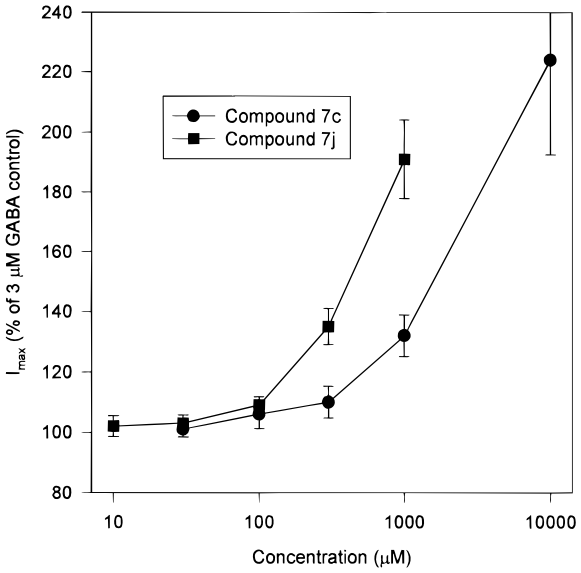



**Figure 1.** Concentration−response curves for the potentiation of 3 $\mu$M GABA-mediated chloride currents in cultured hippocampal neurons by compounds **7c** and **7j**. Data points are the mean ± SEM for at least four cells at each concentration tested.

**Table 2.** Antagonism of 2-Pyrrolidinone Derivative Induced Potentiation of 3 $\mu$M GABA-Mediated Current by the Picrotoxin Antagonist α-Isopropyl-α-methyl-γ-butyrolactone (α-IMGBL)

| compd | compd potentiation, % response relative to current produced by GABA[a] | $N$[b] |
|---|---|---|
| **7c** (1 mM) | 137 ± 6[c] | 8 |
| **7c** (1 mM) + α-IMGBL (3 mM) | 108 ± 2[d] | 8 |
| **7j** (300 $\mu$M) | 136 ± 8 | 5 |
| **7j** (300 $\mu$M) + α-IMGBL (3 mM) | 98 ± 2[d] | 5 |

[a] To calculate the percentage response, the magnitude of the peak current produced by 3 $\mu$M GABA plus compound(s) was normalized with respect to the peak current produced by 3 $\mu$M GABA alone on the same cell. A percentage response of 100% reflects no change in the current compared to 3 $\mu$M GABA alone. [b] $N$ = Number of cells examined. [c] Values are the mean ± SEM. [d] $p < 0.01$ by Student's $t$ test. Statistical significance calculated for test compound alone vs test compound and α-IMGBL.

α-methyl-γ-butyrolactone[9c] which indicates that these lactams modulate $GABA_A$ receptors in a manner similar to that found for GBLs.[9,10a]

## Discussion

Although anticonvulsant activity was not observed for 2-pyrrolidinone in this study, other investigators using an oral route of 2-pyrrolidinone administration and waiting 2 h before subcutaneously injecting PTZ (100 mg/kg) reported that 2-pyrrolidinone at a dose of 400 mg/kg protected 80% of the mice from PTZ-induced seizures.[26] The different results obtained for 2-pyrrolidinone in the two studies indicate the important role played by pharmacokinetic parameters in the screening of compounds for anticonvulsant activity and suggest that under a different set of test conditions the lactams studied herein may display even greater anticonvulsant activity. Nevertheless, even in the absence of comprehensive pharmacokinetic data, it is already clear from the results summarized in Table 1 that the anti-PTZ activity of 2-pyrrolidinone is markedly altered by substitution at C-3. Very weak anticonvulsant activity became evident with the introduction of a methyl or an ethyl substituent or dimethyl substituents at C-3 (compounds **2**, **4**, and **7a**, respectively), and further increases in anticonvulsant activity accompanied the introduction of larger substituents at this position. The previously reported failure to observe anticonvulsant activity for compound **7a**[2] appears to be attributable to the small size of the methyl substituents and not, as originally suggested, to protonation of the nitrogen at physiological pH.

Previous structure−activity studies of α,α-dialkyl-substituted TBLs have shown a good correlation ($r = 0.898$, $p = 0.01$, $n = 7$) between anticonvulsant potency in the PTZ test and the $IC_{50}$ value for displacement of [$^{35}$S]TBPS.[4b] As the results summarized in Table 1 demonstrate, no correlation between these experimental parameters was observed for the 3,3-dialkyl-substituted 2-pyrrolidinones. Moreover, while lactam **7c** is 2.8-fold more potent against PTZ-induced seizures than α-ethyl-α-methyl-γ-thiobutyrolactone ($ED_{50}$ = 128 mg/kg[4b,27]), the best of the earlier prepared GBL, TBL, and cyclopentanone congeners, lactam **7c** is < 17-fold as potent a displacer of [$^{35}$S]TBPS than the thiobutyrolactone ($IC_{50}$ = 0.33 mM[4b]). Additionally, lactam **7c** is ∼10-fold less potent at enhancing currents mediated by 3 μM GABA in cultured rat hippocampal neurons than α-ethyl-α-methyl-γ-thiobutyrolactone.[10a] These results suggest that mechanisms of anticonvulsant action which do not involve $GABA_A$ receptor modulation also contribute to the enhanced potency of lactam **7c** against PTZ-induced seizures.

Since structure−activity studies involving benzyl substituents were not carried out for the earlier studied GBLs, TBLs, and cyclopentanones, it is not possible to compare results for compounds having benzyl substituents in the different ring systems. However, because it was found previously that α-ethyl-α-*tert*-butyl-γ-butyrolactone was a convulsant,[4a] we expected that a substituent as large as benzyl would produce a lactam with convulsant properties. This was not found to be the case. Moreover, a benzyl substituent on the lactam ring enhanced a compound's ability to displace [$^{35}$S]-TBPS and in the one case examined, it gave a more potent enhancer of GABA-mediated currents (Figure 1). Lastly, the benzyl substituent increased, by an unknown mechanism of action, the anticonvulsant potency of the lactams against MES-induced seizures.

Overall, the results reported indicate that 3,3-disubstituted 2-pyrrolidinones have anticonvulsant activities against PTZ-induced seizures which are superior to those reported for the previously studied anticonvulsant GBLs, TBLs, and cyclopentanones, wherein the most potent of these compounds was α,α-diethyl-γ-thiobutyrolactone ($ED_{50}$ = 104 mg/kg and PI = 2.74).[4b] In the PTZ animal seizure model, lactams **7c** ($ED_{50}$ = 46 mg/kg) and **7j** ($ED_{50}$ = 42 mg/kg) have protective index values of 5.65 and 3.00, respectively. These protective index values compare favorably to those of the clinically used antiepileptic drugs ethosuximide ($ED_{50}$ = 161 mg/kg), phenobarbital ($ED_{50}$ = 22 mg/kg), and valproic acid ($ED_{50}$ = 133 mg/kg) which, when evaluated by the same methods, have protective index values of 2.35, 4.00, and 2.12 respectively.[27]

The benzyl compounds are also very effective against seizures induced by MES and the protective index values for **7h**, **7i**, and **7j** are 3.51, 3.04, and 1.70, respectively. The corresponding protective index values for phenobarbital and valproic acid are 1.37 and 5.18, respectively.[27] Whereas ethosuximide is not effective against seizures induced by MES, the phenyl-containing succinimide analogues phensuximide and methsuximide are effective anticonvulsants in this animal seizure model.[28] Thus, the introduction of aromatic substituents adjacent to a carbonyl group in either the succinimide or 2-pyrrolidinone ring systems produces compounds having anticonvulsant activity against MES-induced seizures. Direct comparisons of potency and PI values for lactams **7h**−**j**, phensuximide, and methsuximide are not possible since the succinimides have not been evaluated using the exact methods reported in this study.

Among the seizure models used here, the PTZ test is thought to be predictive of anticonvulsant drug efficacy against generalized absence and/or myoclonic seizures, while the MES test is thought to represent a valid model for generalized tonic−clonic seizures in humans.[29] As a class of anticonvulsants, the 3,3-disubstituted 2-pyrrolidinones have a broad spectrum of action and may be useful for the treatment of human epilepsies.

## Experimental Section

**General Methods.** Unless otherwise noted, the starting materials were obtained from commercial suppliers and used without further purification. Dichloromethane ($CH_2Cl_2$) was distilled over calcium hydride. Hexamethylphosphoramide (HMPA) was dried over activated 13X molecular sieves. Tetrahydrofuran (THF) was distilled over sodium−benzophenone. Ozonolysis was performed using a Model T-408 Welsbach Ozonator. A Varian model 3700 or 3400 CX gas chromatograph equipped with a glass column (0.25 in. i.d., 6 ft length) packed with 1% SP2401 on 80/100 mesh Supelcoport (Supelco, Inc.) was utilized to monitor the progress of the reactions and to assess the purity of the intermediate products. Thin-layer chromatography was performed on 250 μm Analtech silica gel plates containing a fluorescent indicator. Flash chromatography was carried out by using Scientific Adsorbents, Inc. 40 μm silica gel. Bulb-to-bulb distillations were performed using an Aldrich Kugelrohr apparatus. Melting points were determined with either Thomas-Hoover capillary or Kofler-type micro hot stage apparatus and are uncorrected. IR spectra were obtained with Perkin-Elmer 1710 FT-IR

instrument as thin films on NaCl plate, and NMR spectra ($^1$H and $^{13}$C) were recorded in $CDCl_3$ solutions on a Varian Gemini-300 spectrometer. Chemical shifts are expressed in parts per million ($\delta$) relative to tetramethylsilane as an internal standard. Elemental analyses were performed at M-H-W Laboratories in Phoenix, AZ.

**3-Ethyl-2-pyrrolidinone (4).** A solution of *N*-(trimethylsilyl)-2-pyrrolidinone (**3**, 11.0 g, 70.0 mmol)[13] in THF (10 mL) was added dropwise to a solution of LDA (prepared from diisopropylamine (7.07 g, 70.0 mmol) and *n*-butyllithium in hexanes (2.5 M, 28 mL, 70 mmol)) in THF (190 mL) at −78 °C in a nitrogen atmosphere. After 1 h, iodoethane (10.9 g, 70.0 mmol) was added, and the resulting solution was allowed to warm to room temperature (*ca*. 3 h) and stirred overnight. Water (75 mL) was added, the layers were separated, the aqueous phase was extracted with ether (3 × 50 mL), and the combined organic extract was dried over $MgSO_4$. The solvent was removed *in vacuo* to give 8.09 g of colorless oil, which upon flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **4** (4.14 g, 52%; 66% based on the 79% purity of the starting material) as a colorless solid: $R_f$ = 0.31 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 43−44 °C (hexanes at −5 °C) (lit.[14a] mp 38−39 °C; lit.[14b] mp 47−48.5 °C); IR 3257 (br, NH), 1693 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 6.95 (br, 1, NH), 3.38−3.27 (m, 2, NHC$H_2$), 2.36−2.22 (m, 2, NHCH$_2$C$H_2$) 1.93−1.73 (m, 2, diastereotopic H of C$H_2$CH$_3$, CHC═O), 1.50−1.35 (m, 1, diastereotopic H of C$H_2$CH$_3$), 0.98 (t, 6, $J$ = 7.5 Hz, CH$_2$C$H_3$); $^{13}$C NMR $\delta$ 180.06 (C═O), 42.34 (*C*HC═O), 40.40 (NHCH$_2$), 26.63 (NHCH$_2$*C*H$_2$), 23.67 (*C*H$_2$CH$_3$), 11.35 (CH$_2$*C*H$_3$).

**Methyl 3-Cyano-2,2-dimethylpropanoate (6a).** A solution of methyl isobutyrate (**5a**, 10.2 g, 100 mmol) in THF (10 mL) was added dropwise to a solution of LDA (prepared from diisopropylamine (11.1 g, 110 mmol) and *n*-butyllithium in hexanes (2.5 M, 44 mL, 110 mmol)) in THF (125 mL) at −78 °C in a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 1 h, and then a solution of bromoacetonitrile (14.4 g, 120 mmol) in THF (15 mL) was introduced slowly over a period of 30 min. (The reaction mixture starts getting darker as the addition progresses.) The resulting dark mixture was allowed to warm to room temperature (*ca*. 3 h) and stirred overnight. The reaction was quenched by addition of HCl (1 N, 150 mL) at 0 °C. The layers were separated, and the aqueous phase was further extracted with ether (3 × 75 mL). The combined organic extract was washed sequentially with 75 mL portions of saturated $NaHCO_3$, water (several times), and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 15.0 g of dark-colored liquid. Flash chromatography over silica gel (hexanes−EtOAc, 19:1) followed by short-path distillation afforded the nitrile **6a** (6.66 g, 47%) as a colorless liquid: bp 95−97 °C (20 mmHg); $R_f$ = 0.32 (hexanes−EtOAc, 17:3); IR 2248 (CN), 1735 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 3.74 (s, 3, OCH$_3$), 2.62 (s, 2, CH$_2$), 1.37 (s, 6, 2 × CH$_3$); $^{13}$C NMR $\delta$ 175.26 (C═O), 117.42 (CN), 52.46 (OCH$_3$), 40.84 (*C*C═O), 27.89 (CH$_2$), 24.67 (2 × CH$_3$). Anal. ($C_7H_{11}NO_2$) C, H, N.

**Methyl 2-(Cyanomethyl)-2-methylbutanoate (6b).** The reaction of methyl 2-methylbutyrate (**5b**, 13.34 g, 115.0 mmol) with bromoacetonitrile (16.56 g, 138.0 mmol) in the presence of LDA (prepared from diisopropylamine (12.78 g, 126.5 mmol) and *n*-butyllithium in hexanes (2.5 M, 50.6 mL, 126.5 mmol)) in THF (175 mL), as described above in the preparation of **6a**, gave 16.57 g of a dark-colored liquid. The crude product was vacuum distilled to give the nitrile **6b** (10.85 g, 61%) as a colorless liquid: bp 83−85 °C (10 mmHg); IR 2248 (CN), 1734 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 3.74 (s, 3, OCH$_3$), 2.68 (d, 1, $J$ = 16.8 Hz, diastereotopic H of CH$_2$CN), 2.58 (d, 1, $J$ = 16.8, Hz diastereotopic H of CH$_2$CN), 1.82−1.66 (m, 2, C$H_2$CH$_3$), 1.36 (s, 3, CH$_3$), 0.87 (t, 3, $J$ = 7.5 Hz, CH$_2$C$H_3$); $^{13}$C NMR $\delta$ 174.86 (C═O), 117.64 (CN), 52.45 (OCH$_3$), 44.95 (*C*C═O), 31.26 (*C*H$_2$CH$_3$), 25.45 (*C*H$_2$CN), 22.63 (CH$_3$), 8.95 (CH$_2$*C*H$_3$). Anal. ($C_8H_{13}NO_2$) C, H, N.

**Ethyl 2-(Cyanomethyl)-2-ethylbutanoate (6c).** The reaction of ethyl 2-ethylbutyrate (**5c**, 21.6 g, 150 mmol) with bromoacetonitrile (21.6 g, 180 mmol) in the presence of LDA (prepared from diisopropylamine (16.7 g, 165 mmol) and *n*-butyllithium in hexanes (2.5 M, 66 mL, 165 mmol)) in THF (225 mL), as described above in the preparation of **6a**, gave 27.8 g of a dark-colored liquid. After two vacuum distillations, the nitrile **6c** (12.4 g, 45%) was obtained as a colorless liquid (about 96% pure by GC): bp 84-85 °C (1.3 mmHg). An analytical sample was prepared by column chromatography over silica gel (hexanes−EtOAc, 19:1) followed by bulb-to-bulb distillation [pot temperature 80 °C (1 mmHg)]: $R_f$ = 0.36 (hexanes−EtOAc, 9:1); IR 2249 (CN), 1729 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 4.20 (q, 2, $J$ = 7.1 Hz, OC$H_2$CH$_3$), 2.68 (s, 2, CH$_2$CN), 1.91−1.79 (m, 2, diastereotopic H of each C$H_2$CH$_3$), 1.76−1.64 (m, 2, diastereotopic H of each C$H_2$CH$_3$), 1.28 (t, 3, $J$ = 7.1 Hz, OCH$_2$C$H_3$), 0.87 (t, 6, $J$ = 7.4 Hz, 2 × CH$_2$C$H_3$); $^{13}$C NMR $\delta$ 173.74 (C═O), 117.48 (CN), 61.08 (OCH$_2$), 48.84 (*C*C═O), 29.26 (2 × *C*H$_2$CH$_3$), 20.82 (*C*H$_2$CN), 14.11 (OCH$_2$*C*H$_3$), 8.59 (2 × CH$_2$*C*H$_3$). Anal. ($C_{10}H_{17}NO_2$) C, H, N.

**Methyl 2-(Cyanomethyl)-2,3-dimethylbutanoate (6d).** The reaction of methyl 2-methylisovalerate (**5d**, 19.5 g, 150 mmol)[30] with bromoacetonitrile (21.6 g, 180 mmol) in the presence of LDA (prepared from diisopropylamine (16.7 g, 165 mmol) and *n*-butyllithium in hexanes (2.5 M, 66 mL, 165 mmol)) in THF (225 mL), as described above in the preparation of **6a**, gave 20.6 g of the crude product as a dark-colored liquid. Vacuum distillation afforded 9.00 g of the nitrile as a colorless oil (about 90% pure): bp 89−92 °C (2.2 mmHg). Column chromatography over silica gel (hexanes−EtOAc, 19:1) followed by bulb-to-bulb distillation [pot temperature 85 °C (1 mmHg)] gave the pure nitrile **6d** (7.55 g, 30%) as a colorless oil: $R_f$ = 0.33 (hexanes−EtOAc, 9:1); IR 2247 (CN), 1733 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 3.74 (s, 3, OCH$_3$), 2.71 (d, 1, $J$ = 16.7 Hz, diastereotopic H of CH$_2$), 2.45 (d, 1, $J$ = 16.7 Hz, diastereotopic H of CH$_2$), 2.04 (septet, 1, C*H*(CH$_3$)$_2$), 1.33 (s, 3, CH$_3$), 0.91 (d, 6, $J$ = 7.1 Hz, CH(C$H_3$)$_2$); $^{13}$C NMR $\delta$ 174.73 (C═O), 118.10 (CN), 52.30 (OCH$_3$), 48.15 (*C*C═O), 34.81 (*C*H-(CH$_3$)$_2$), 24.23 (CH$_2$), 19.41 (CH$_3$), 17.55 (CH(*C*H$_3$)$_2$). Anal. ($C_9H_{15}NO_2$) C, H, N.

**Methyl 1-(Cyanomethyl)cyclopentanecarboxylate (6g).** A solution of methyl cyclopentanecarboxylate (**5g**, 5.12 g, 40.0 mmol) in dry THF (10 mL) was added dropwise to a solution of LDA (prepared from diisopropylamine (4.44 g, 44.0 mmol) and *n*-butyllithium in hexanes (2.5 M, 17.6 mL, 44 mmol)) in THF (60 mL) at −78 °C in a nitrogen atmosphere. The mixture was stirred at −78 °C for 45 min, and then a solution of bromoacetonitrile (5.76 g, 48.0 mmol) in THF (10 mL) and HMPA (3.5 mL, 20 mmol) was introduced slowly over a period of 15 min. The resulting dark mixture was allowed to warm to room temperature (*ca*. 3 h) and stirred overnight. The reaction was quenched by addition of HCl (1 N, 75 mL) at 0 °C. The layers were separated, and the aqueous phase was further extracted with ether (3 × 50 mL). The combined organic extract was washed with 75 mL portions of saturated $NaHCO_3$, water (several times), and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 6.50 g of dark-colored liquid, which after column chromatography over silica gel (hexanes−acetone, 19:1) followed by short-path distillation afforded the pure nitrile **6g** (3.87 g, 58%) as a colorless liquid: bp 97−99 °C (0.8 mmHg); $R_f$ = 0.28 (hexanes−acetone, 9:1); IR 2250 (CN), 1733 (C═O) cm$^{-1}$; $^1$H NMR $\delta$ 3.75 (s, 3, OCH$_3$), 2.66 (s, 2, CH$_2$CN), 2.24−2.11 (m, 2, CH$_2$), 1.85−1.68 (m, 6, 3 × CH$_2$); $^{13}$C $\delta$ NMR 175.81 (C═O), 118.15 (CN), 52.61 (OCH$_3$), 50.66 (*C*C═O), 36.62 (2 × CH$_2$), 26.04 (*C*H$_2$CN), 25.61 (2 × CH$_2$). Anal. ($C_9H_{13}NO_2$) C, H, N.

**Methyl 2-(Cyanomethyl)-3-phenylpropanoate (6h).** The reaction of methyl 3-phenylpropionate (**5h**, 4.10 g, 25.0 mmol) with bromoacetonitrile (3.60 g, 30.0 mmol) in the presence of LDA (prepared from diisopropylamine (2.78 g, 27.5 mmol) and *n*-butyllithium in hexanes (2.5 M, 11 mL, 27.5 mmol)) in THF (50 mL) and HMPA (2.2 mL, 12.5 mmol), as described above in the preparation of **6g**, gave 5.70 g of the crude product as a dark-colored liquid. Column chromatography over silica gel (hexanes−EtOAc, 17:3) followed by short-path distillation afforded the pure nitrile **6h** (1.70 g, 34%) as a colorless oil: bp 129−131 °C (0.3 mmHg); $R_f$ = 0.22; IR 2249 (CN), 1739 (C═O), 1604 (C═C) cm$^{-1}$; $^1$H NMR $\delta$ 7.36−7.16 (m, 5, ArH), 3.74 (s, 3, OCH$_3$), 3.17 (dd, 1, $J$ = 12.6, 5.0 Hz, diastereotopic H of CH$_2$Ph), 3.06−2.90 (m, 2, CHC═O and diastereotopic H of CH$_2$Ph), 2.52 (d, 2, $J$ = 6.2 Hz, CH$_2$CN); $^{13}$C $\delta$ NMR ($CDCl_3$)

172.26 (C=O), 136.60 (ArC), 128.85 (2 × ArC), 128.79 (2 × ArC), 127.17 (ArC), 117.66 (CN), 52.37 ($OCH_3$), 43.11 (*C*HC=O), 36.74 ($CH_2Ph$), 18.31 (*C*$H_2$CN). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

**Ethyl 2-(Cyanomethyl)-2-(phenylmethyl)propanoate (6i).** The reaction of ethyl 2-methyl-3-phenylpropionate (**5i**, 9.60 g, 50.0 mmol)[31] with bromoacetonitrile (9.00 g, 75.0 mmol) in the presence of LDA (prepared from diisopropylamine (6.06 g, 60.0 mmol) and *n*-butyllithium in hexanes (2.5 M, 24 mL, 60 mmol) in THF (150 mL) and HMPA (4.3 mL, 25 mmol), as described above in the preparation of **6g**, gave 12.0 g of the crude product as a pale yellow colored liquid. Flash chromatography over silica gel (hexanes−$CH_2Cl_2$, 3:2) afforded the pure nitrile **6i** (7.86 g, 68%) as a colorless viscous liquid. An analytical sample was prepared by bulb-to-bulb distillation [pot temperature 110−115 °C (0.9 mmHg)]: $R_f$ = 0.28 (hexanes−$CH_2Cl_2$, 1:1); IR 2247 (CN), 1729 (C=O), 1605 (C=C) $cm^{-1}$; $^1H$ NMR $\delta$ 7.32−7.24 (m, 3, ArH), 7.15−7.12 (m, 2, ArH), 4.18 (q, 2, $J$ = 7.1 Hz, OC*H*$_2$CH$_3$), 3.12 (d, 1, $J$ = 13.7 Hz, diastereotopic H of $CH_2Ph$), 2.90 (d, 1, $J$ = 13.7 Hz, diastereotopic H of $CH_2Ph$), 2.56 (d, 1, $J$ = 16.8 Hz, diastereotopic H of $CH_2CN$), 2.45 (d, 1, $J$ = 16.8 Hz, diastereotopic H of $CH_2CN$), 1.42 (s, 3, $CH_3$), 1.26 (t, 3, $J$ = 7.1 Hz, OCH$_2$C*H*$_3$); $^{13}C$ NMR $\delta$ 173.64 (C=O), 135.49 (ArC), 129.57 (2 × ArC), 128.32 (2 × ArC), 127.08 (ArC), 117.66 (CN), 61.29 (O*C*H$_2$CH$_3$), 45.54 (*C*C=O), 43.43 ($CH_2Ph$), 24.93 (*C*$H_2$CN), 23.09 (OCH$_2$*C*H$_3$), 13.84 ($CH_3$). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

**Methyl 2-(Cyanomethyl)-2-(phenylmethyl)butanoate (6j).** The reaction of methyl 2-ethyl-3-phenylpropionate (**5j**, 9.60 g, 50.0 mmol)[32] with bromoacetonitrile (7.20 g, 60.0 mmol) in the presence of LDA (prepared from diisopropylamine (5.56 g, 55.0 mmol) and *n*-butyllithium in hexanes (2.5 M, 22 mL, 55 mmol)) in THF (150 mL) and HMPA (4.3 mL, 25 mmol), as described above in the preparation of **6g**, gave 12.1 g of the crude product as a dark-colored liquid. Column chromatography over silica gel (hexanes−$CH_2Cl_2$, 3:2) afforded the pure nitrile **6j** (5.98 g, 52%) as a colorless viscous liquid. An analytical sample was prepared by bulb-to-bulb distillation [pot temperature 105 °C (0.5 mmHg)]: $R_f$ = 0.22; IR 2247 (CN), 1732 (C=O), 1605 (C=C) $cm^{-1}$; $^1H$ NMR $\delta$ 7.33−7.25 (m, 3, ArH), 7.16−7.12 (m, 2, ArH), 3.73 (s, 3, $OCH_3$), 3.22 (d, 1, $J$ = 14.1 Hz, diastereotopic H of $CH_2Ph$), 2.90 (d, 1, $J$ = 14.1 Hz, diastereotopic H of $CH_2Ph$), 2.60 (d, 1, $J$ = 16.5 Hz, diastereotopic H of $CH_2CN$), 2.46 (d, 1, $J$ = 16.5 Hz, diastereotopic H of $CH_2CN$), 2.07−1.94 (m, 1, diastereotopic H of C*H*$_2$CH$_3$), 1.86−1.75 (m, 1, diastereotopic H of C*H*$_2$CH$_3$), 0.91 (t, 3, $J$ = 7.5 Hz, CH$_2$C*H*$_3$; $^{13}C$ NMR $\delta$ 173.62 (C=O), 135.70 (ArC), 129.54 (2 × ArC), 128.65 (2 × ArC), 127.29 (ArC), 117.77 (CN), 52.21 ($OCH_3$), 50.44 (*C*C=O), 42.47 ($CH_2Ph$), 30.03 (*C*$H_2$CH$_3$), 20.77 (*C*$H_2$CN), 8.90 (CH$_2$*C*H$_3$). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

**3,3-Dimethyl-2-pyrrolidinone (7a).** A pink solution of $CoCl_2 \cdot 6H_2O$ (4.52 g, 19.0 mmol) and nitrile **6a** (5.36 g, 38.0 mmol) in THF (132 mL) and $H_2O$ (66 mL) was stirred vigorously and cooled to 0 °C while $NaBH_4$ (7.22 g, 190 mmol) was added in portions over 30 min in an atmosphere of $N_2$. The reaction was exothermic, producing a black precipitate and copious quantities of hydrogen. After the reaction mixture was stirred for 48 h at room temperature, 28% $NH_4OH$ (5 mL) was added, centrifuged, and the supernatant biphasic liquid was decanted. The sediment was washed with 15 mL of the same solvent mixture, and the combined supernatants were concentrated *in vacuo* to remove the bulk of THF. The aqueous residue was extracted with $CHCl_3$ (3 × 50 mL), and the combined $CHCl_3$ layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 3.73 g of a colorless viscous residue, which upon flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7a** (2.80 g, 65%) as a colorless solid: $R_f$ = 0.29 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 69−70 °C (pentane at −5 °C) (lit.[19] mp 65−67 °C); $^{13}C$ NMR $\delta$ 183.94 (C=O), 39.59 (*C*C=O), 38.71 ($NHCH_2$), 36.29 ($NHCH_2CH_2$), 24.14 (2 × $CH_3$).

**3-Ethyl-3-methyl-2-pyrrolidinone (7b).** The reaction of nitrile **6b** (7.36 g, 47.5 mmol) with $NaBH_4$ (9.030 g, 23.75 mmol) and $CoCl_2 \cdot 6H_2O$ (5.650 g, 23.75 mmol) in THF (166 mL) and $H_2O$ (83 mL), as described above in the preparation of **7a**, gave 5.79 g of the crude product as a colorless oily residue. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7b** (4.30 g, 71%) as a colorless solid: $R_f$ = 0.31 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 39−40 °C (pentane at −5 °C); IR 3214 (br, NH), 1693 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ 6.45 (br, 1, NH), 3.33−3.26 (m, 2, NHC*H*$_2$), 2.12−2.03 (m, 1, diastereotopic H of NHCH$_2$C*H*$_2$), 1.89−1.80 (m, 1, diastereotopic H of NHCH$_2$C*H*$_2$), 1.63−1.46 (m, 2, C*H*$_2$CH$_3$), 1.14 (s, 3, $CH_3$), 0.92 (t, 6, $J$ = 7.5 Hz, CH$_2$C*H*$_3$); $^{13}C$ NMR $\delta$ 183.11 (C=O), 43.26 (*C*C=O), 38.85 ($NHCH_2$), 32.88 ($NHCH_2CH_2$), 30.06 (*C*$H_2$CH$_3$), 22.46 ($CH_3$), 8.77 (CH$_2$*C*H$_3$). Anal. ($C_7H_{13}NO$) C, H, N.

**3,3-Diethyl-2-pyrrolidinone (7c).** The reaction of nitrile **6c** (8.24 g, 45.0 mmol) with $NaBH_4$ (8.55 g, 225 mmol) and $CoCl_2 \cdot 6H_2O$ (5.36 g, 22.5 mmol) in THF (158 mL) and $H_2O$ (79 mL) was carried out as described above in the preparation of **7a**. After the addition of $NaBH_4$, the reaction mixture was stirred and refluxed for 72 h and subjected to the usual workup to give 6.20 g of a colorless viscous residue. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7c** (4.42 g, 70%) as a colorless solid: $R_f$ = 0.34 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 52−53 °C (hexanes at −5 °C); IR 3199 (br, NH), 1679 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ 6.59 (br, 1, NH), 3.28 (t, 2, $J$ = 7.4 Hz, NHC*H*$_2$), 1.89 (t, 2, $J$ = 7.4 Hz, NHCH$_2$C*H*$_2$), 1.63−1.46 (m, 4, 2 × C*H*$_2$CH$_3$), 0.91 (t, 6, $J$ = 7.4 Hz, 2 × CH$_2$C*H*$_3$); $^{13}C$ NMR $\delta$ 182.51 (C=O), 47.44 (*C*C=O), 39.29 ($NHCH_2$), 29.37 ($NHCH_2CH_2$), 28.98 (2 × *C*$H_2$CH$_3$), 8.60 (2 × CH$_2$*C*H$_3$). Anal. ($C_8H_{15}NO$) C, H, N.

**3-Methyl-3-(1-methylethyl)-2-pyrrolidinone (7d).** The reaction of nitrile **6d** (6.42 g, 38.0 mmol) with $NaBH_4$ (7.22 g, 190 mmol) and $CoCl_2 \cdot 6H_2O$ (4.52 g, 19.0 mmol) in THF (132 mL) and $H_2O$ (66 mL), as described above in the preparation of **7a**, gave 4.35 g of the crude product as a colorless solid. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7d** (3.77 g, 70%) as a colorless solid: $R_f$ = 0.33 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 88−90 °C (hexanes at −5 °C); IR 3207 (br, NH), 1689 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ 6.53 (br, 1, NH), 3.36−3.21 (m, 2, NHC*H*$_2$), 2.18−2.05 (m, 1, diastereotopic H of NHCH$_2$C*H*$_2$), 1.92 (septet, 1, C*H*(CH$_3$)$_2$), 1.72−1.61 (m, 1, diastereotopic H of NHCH$_2$C*H*$_2$), 1.15 (s, 3, $CH_3$), 0.92 (d, 3, $J$ = 6.6 Hz, CH(C*H*$_3$)$_2$), 0.89 (d, 3, $J$ = 6.6 Hz, CH(C*H*$_3$)$_2$); $^{13}C$ NMR $\delta$ 183.61 (C=O), 46.86 (*C*C=O), 39.22 ($NHCH_2$), 32.87 (*C*H(CH$_3$)$_2$), 28.83 ($NHCH_2CH_2$), 22.26 ($CH_3$), 18.30 (CH(*C*H$_3$)$_2$), 17.01 (CH(*C*H$_3$)$_2$). Anal. ($C_8H_{15}NO$) C, H, N.

**2-Azaspiro[4.4]nonan-1-one (7g).** The reaction of nitrile **6g** (3.34 g, 20.0 mmol) with $NaBH_4$ (3.78 g, 100 mmol) and $CoCl_2 \cdot 6H_2O$ (2.38 g, 10.0 mmol) in THF (70 mL) and $H_2O$ (35 mL), as described above in the preparation of **7a**, gave 3.10 g of the crude product as a colorless solid. Column chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7g** (2.25 g, 81%) as a colorless solid: $R_f$ = 0.33 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 110−111 °C ($CH_2Cl_2$−hexanes) (lit.[20] mp 110 °C); IR 3200 (br, NH), 1678 (C=O) $cm^{-1}$; $^1H$ NMR $\delta$ 6.70 (br, 1, NH), 3.31 (t, 2, $J$ = 6.8 Hz, NHC*H*$_2$), 1.99 (t, 2, $J$ = 6.8 Hz, NHCH$_2$C*H*$_2$), 1.94−1.52 (overlapping m, 8, $(CH_2)_4$); $^{13}C$ NMR $\delta$ 184.08 (C=O), 50.17 (*C*C=O), 39.53 ($NHCH_2$), 36.41 ($NHCH_2CH_2$), 36.10 (2 × $CH_2$), 25.52 (2 × $CH_2$).

**3-(Phenylmethyl)-2-pyrrolidinone (7h).** The reaction of nitrile **6h** (3.05 g, 15.0 mmol) with $NaBH_4$ (2.85 g, 75.0 mmol) and $CoCl_2 \cdot 6H_2O$ (1.79 g, 7.50 mmol) in THF (54 mL) and $H_2O$ (27 mL), as described above in the preparation of **7a**, gave 2.37 g of the crude product as a colorless solid. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7h** (1.48 g, 56%) as a colorless solid: $R_f$ = 0.30 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 112−113 °C ($CH_2Cl_2$−hexanes) (lit.[13] mp 109−110 °C); $^{13}C$ NMR $\delta$ 180.17 (C=O), 139.53 (ArC), 128.90 (2 × ArC), 128.45 (2 × ArC), 126.26 (ArC), 42.96 (*C*HC=O), 40.43 ($NHCH_2$), 36.63 ($CH_2Ph$), 26.88 ($NHCH_2CH_2$).

**3-Methyl-3-(phenylmethyl)-2-pyrrolidinone (7i).** The reaction of nitrile **6i** (8.32 g, 36.0 mmol) with $NaBH_4$ (6.80 g, 180 mmol) and $CoCl_2 \cdot 6H_2O$ (4.28 g, 18.0 mmol) in THF (126 mL) and $H_2O$ (63 mL), as described above in the preparation **7c**, gave 6.78 g of the crude product as a pale brown colored solid. Flash chromatography over silica gel (1% MeOH in

$CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7i** (5.34 g, 78%) as a colorless solid: $R_f$ = 0.36 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 89−90 °C ($CH_2Cl_2$−hexanes); IR 3225 (br, NH), 1680 (C═O), 1604 (C═C) $cm^{-1}$; $^1H$ NMR $\delta$ 7.31−7.21 (m, 5, ArH), 6.08 (br, 1, NH), 3.18−3.11 (m, 1, diastereotopic H of $NHCH_2$), 2.98 (d, 1, $J$ = 13.3 Hz, diastereotopic H of $CH_2Ph$), 2.82−2.74 (m, 1, diastereotopic H of $NHCH_2$), 2.65 (d, 1, $J$ = 13.3 Hz, diastereotopic H of $CH_2Ph$), 2.21−2.12 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.84−1.75 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.21 (s, 3, $CH_3$); $^{13}C$ NMR $\delta$ 182.67 (C═O), 137.81 (ArC), 130.09 (2 × ArC), 128.13 (2 × ArC), 126.49 (ArC), 44.60 (*C*C═O), 43.37 ($CH_2Ph$), 38.87 ($NHCH_2$), 32.54 ($NHCH_2CH_2$), 23.65 ($CH_3$). Anal. ($C_{12}H_{15}NO$) C, H, N.

**3-Ethyl-3-(phenylmethyl)-2-pyrrolidinone (7j).** The reaction of nitrile **6j** (5.54 g, 24.0 mmol) with $NaBH_4$ (4.54 g, 120 mmol) and $CoCl_2 \cdot 6H_2O$ (2.86 g, 12.0 mmol) in THF (84 mL) and $H_2O$ (42 mL), as described above in the preparation of **7a**, gave 4.95 g of the crude product as a slightly brown colored oily residue. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7j** (3.69 g, 76%) as a colorless solid: $R_f$ = 0.44 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 89−90 °C (ether−hexanes at −5 °C); IR 3220 (br, NH), 1688 (C═O) $cm^{-1}$; $^1H$ NMR $\delta$ 7.31−7.17 (m, 5, ArH), 6.01 (br, 1, NH), 3.09−3.03 (m, 1, diastereotopic H of $NHCH_2$), 2.99 (d, 1, $J$ = 13.3 Hz, diastereotopic H of $CH_2Ph$), 2.64 (d, 1, $J$ = 13.3 Hz, diastereotopic H of $CH_2Ph$), 2.60−2.51 (m, 1, diastereotopic H of $NHCH_2$), 2.12−1.91 (m, 2, $NHCH_2CH_2$), 1.78−1.66 (m, 1, diastereotopic H of $CH_2CH_3$), 1.62−1.50 (m, 1, diastereotopic H of $CH_2CH_3$), 0.97 (t, 3, $J$ = 7.5 Hz, $CH_2CH_3$); $^{13}C$ NMR $\delta$ 181.76 (C═O), 137.83 (ArC), 130.08 (2 × ArC), 128.08 (2 × ArC), 126.46 (ArC), 48.87 (*C*C═O), 42.60 ($CH_2Ph$), 39.17 ($NHCH_2$), 30.26 ($NHCH_2CH_2$), 28.56 ($CH_2CH_3$), 8.80 ($CH_2CH_3$). Anal. ($C_{13}H_{17}NO$) C, H, N.

**Methyl 2-(1,1-Dimethylethyl)-2-methyl-4-pentenoate (8e).** A solution of methyl 2,3,3-trimethylbutyrate (**5e**, 38.9 g, 270 mmol)[34] in THF (30 mL) was added slowly to a solution of lithium diisopropylamide (prepared from diisopropylamine (40.9 g, 405 mmol) and *n*-butyllithium in hexanes (2.5 M, 154.4 mL, 386 mmol)) in THF (350 mL) at 0 °C in a nitrogen atmosphere, and the mixture was stirred for 45 min. The temperature was then reduced to −78 °C, and a solution of allyl bromide (51.3 g, 424 mmol) in THF (20 mL) and HMPA (40.3 mL, 232 mmol) was added over a period of 15 min. Stirring was continued for 2 h at −78 °C, and the system was allowed to warm to room temperature (*ca*. 6 h). The reaction was quenched by addition of HCl (3 N, 300 mL) at 0 °C. The layers were separated, and the aqueous phase was further extracted with ether (3 × 150 mL). The combined organic extract was washed with 100 mL portions of water, 5% $Na_2S_2O_3$, saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 48.9 g of brown-colored liquid, which upon two vacuum distillations afforded pure olefinic ester **8e** (34.9 g, 70%) as a colorless liquid: bp 87−89 °C (20 mmHg); IR 1730 (C═O), 1641 (C═C) $cm^{-1}$; $^1H$ NMR $\delta$ 5.72−5.58 (m, 1, CH═), 5.06−5.00 (m, 2, $=CH_2$), 3.65 (s, 3, $OCH_3$), 2.76 (dd, 1, $J$ = 13.2, 6.0 Hz, diastereotopic H of $CH_2$), 1.96 (dd, 1, $J$ = 13.2, 8.2 Hz, diastereotopic H of $CH_2$), 1.08 (s, 3, $CH_3$), 0.95 (s, 9, $C(CH_3)_3$); $^{13}C$ NMR $\delta$ 176.41 (C═O), 135.61 (CH═), 117.55 ($=CH_2$), 51.87-(*C*C═O), 51.02 ($OCH_3$), 38.39 ($CH_2$), 35.68 ($C(CH_3)_3$), 26.26 ($C(CH_3)_3$), 17.58 ($CH_3$). Anal. ($C_{11}H_{20}O_2$) C, H.

**Methyl 2-Ethyl-2-(1-methylethyl)-4-pentenoate (8f).** The reaction of methyl 2-ethyl-3-methylbutyrate (**5f**, 23.8 g, 165 mmol)[30] with allyl bromide (31.3 g, 259 mmol) in the presence of lithium diisopropylamide (prepared from diisopropylamine (25.0 g, 248 mmol) and *n*-butyllithium in hexanes (2.5 M, 94.4 mL, 236 mmol)) in THF (330 mL) and HMPA (24.7 mL, 142 mmol), as described above in the preparation of **8e**, followed by the vacuum distillation of crude product afforded the pure olefinic ester **8f** (24.9 g, 82%) as a colorless liquid: bp 92−94 °C (20 mmHg); IR 1728 (C═O), 1639 (C═C) $cm^{-1}$; $^1H$ NMR $\delta$ 5.85−5.71 (m, 1, CH═), 5.11−5.02 (m, 2, $=CH_2$), 3.67 (s, 3, $OCH_3$), 2.49 (dd, 1, $J$ = 14.5, 6.7 Hz, diastereotopic H of $CH_2$-CH═), 2.33 (dd, 1, $J$ = 14.5, 7.9 Hz, diastereotopic H of $CH_2$-CH═), 1.90 (septet, 1, $CH(CH_3)_2$), 1.82−1.50 (m, 2, $CH_2CH_3$), 0.91 (d, 6, $J$ = 7.1 Hz, $CH(CH_3)_2$), 0.83 (t, 3, $J$ = 7.5 Hz, $CH_2CH_3$); $^{13}C$ NMR $\delta$ 176.33 (C═O), 135.19 (CH═), 117.24 ($=CH_2$), 52.49 (*C*C═O), 51.13 ($OCH_3$), 35.92 ($CH_2CH$═), 33.01 ($CH(CH_3)_2$), 25.60 ($CH_2CH_3$), 18.20 ($CH(CH_3)_2$), 18.00 (CH-$(CH_3)_2$), 8.93 ($CH_2CH_3$). Anal. ($C_{11}H_{20}O_2$) C, H.

**Methyl 2-(1,1-Dimethylethyl)-2-methyl-4-oxobutanoate (9e).** A solution of olefinic ester **8e** (2.76 g, 15.0 mmol) in $CH_2Cl_2$ (60 mL) was reacted with ozone at −78 °C. When excess ozone was observed (blue coloration), $N_2$ was bubbled through the solution, and $Ph_3P$ (5.90 g, 22.5 mmol) was added in one portion while stirring. The system was allowed to warm to room temperature (*ca*. 2 h) and stirred for an additional 2 h. The solvent was removed *in vacuo* and the residue triturated with hexanes (150 mL). The precipitated $Ph_3PO$ (*ca*. 5.78g) was filtered off and the filtrate concentrated *in vacuo* to give 2.80 g of the crude product as a colorless viscous residue. Flash chromatography over silica gel (hexanes−EtOAc, 19:1) afforded 2.12 g (76%) of the aldehyde **9e** as a colorless oil:[35] $R_f$ = 0.32 (hexanes−EtOAc, 9:1); IR 2734 (aldehyde CH), 1725 (C═O) $cm^{-1}$; $^1H$ NMR $\delta$ 9.70 (d, 1, $J$ = 2.1 Hz, CHO), 3.69 (s, 3, $OCH_3$), 3.11 (d, 1, $J$ = 17.0 Hz, diastereotopic H of $CH_2$), 2.37 (dd, 1, $J$ = 17.0, 2.1 Hz, diastereotopic H of $CH_2$), 1.26 (s, 3, $CH_3$), 0.95 (s, 9, $C(CH_3)_3$); $^{13}C$ NMR $\delta$ 201.35 (CHO), 178.68 (C═O), 51.52 ($OCH_3$), 48.90 (*C*C═O), 48.23 ($CH_2$), 35.60 ($C(CH_3)_3$), 25.97 ($C(CH_3)_3$), 18.09 ($CH_3$).

**Methyl 2-Ethyl-2-(1-methylethyl)-4-oxobutanoate (9f).** The reaction of olefinic ester **8f** (9.20 g, 50.0 mmol) with ozone in $CH_2Cl_2$ (200 mL) at −78 °C, followed by the treatment of the resulting ozonide with $Ph_3P$ (19.7 g, 75.0 mmol) as described above in the preparation of **9e**, gave 14.4 g of an oily residue. Flash chromatography over silica gel (hexanes−EtOAc, 9:1) afforded the aldehyde **9f** (8.20 g, 88%) as a colorless oil:[35] $R_f$ = 0.40; IR 2742 (aldehyde CH), 1725 (C═O) $cm^{-1}$; $^1H$ NMR $\delta$ 9.86 (t, 1, $J$ = 2.6, 2.3 Hz, CHO), 3.73 (s, 3, $OCH_3$), 2.68 (dd, 1, $J$ = 16.3, 2.3 Hz, diastereotopic H of $CH_2$-CHO), 2.48 (dd, 1, $J$ = 16.3, 2.6 Hz, diastereotopic H of $CH_2$-CHO), 2.08 (septet, 1, $CH(CH_3)_2$), 1.88−1.67 (m, 2, $CH_2CH_3$), 0.89 (d, 6, $J$ = 6.7 Hz, $CH(CH_3)_2$), 0.87 (t, 3, $J$ = 7.5 Hz, $CH_2CH_3$); $^{13}C$ NMR $\delta$ 202.51 (CHO), 175.81 (C═O), 51.93 (*C*C═O), 51.74 ($OCH_3$), 45.50 ($CH_2CHO$), 33.64 ($CH(CH_3)_2$), 27.47 ($CH_2CH_3$), 18.49 ($CH(CH_3)_2$), 17.29 ($CH(CH_3)_2$), 9.21 ($CH_2CH_3$).

**Methyl 2-(1,1-Dimethylethyl)-2-methyl-4-oxobutanoate Oxime (10e).** A solution of aldehyde **9e** (2.05 g, 11.0 mmol) and $H_2NOH \cdot HCl$ (1.15 g, 16.5 mmol) in dry pyridine (10 mL) was stirred at 60 °C for 4 h in an atmosphere of $N_2$. After cooling it was poured into ice cold HCl (3 N, 50 mL) and extracted with ether (3 × 40 mL). The combined ether extract was washed successively with 40 mL portions of saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 2.30 g of pale brown colored viscous liquid. Flash chromatography over silica gel (hexanes−EtOAc, 4:1) followed by bulb-to-bulb distillation [pot temperature 100−105 °C (0.4 mmHg)] afforded the *anti* and *syn* oxime mixture **10e** (2.03 g, 92%) in the ratio of 58/42 as a colorless viscous liquid: $R_f$ = 0.27, 0.19; IR 3529 (br, OH), 1725 (C═O), 1660 (C═N) $cm^{-1}$; $^1H$ NMR major isomer, $\delta$ 8.50 (br, 1, OH), 7.32 (dd, 1, $J$ = 8.4, 4.4 Hz, CH═), 3.68 (s, 3, $OCH_3$), 2.85 (dd, 1, $J$ = 13.8, 4.4 Hz, diastereotopic H of $CH_2$), 2.17 (dd, 1, $J$ = 13.8, 8.4 Hz, diastereotopic H of $CH_2$), 1.12 (s, 3, $CH_3$), 0.95 (s, 9, $C(CH_3)_3$); Minor isomer, $\delta$ 8.50 (br, 1, OH), 6.62 (t, 1, $J$ = 5.4 Hz, CH═), 3.69 (s, 3, $OCH_3$), 2.72 (d, 2, $J$ = 5.4 Hz, $CH_2$), 1.16 (s, 3, $CH_3$), 0.97 (s, 9, $C(CH_3)_3$); $^{13}C$ NMR $\delta$ 175.78 (C═O), 150.62 (CH═), 150.54 (CH═), 51.47 ($OCH_3$), 50.93 (*C*C═O), 50.53 (*C*C═O), 35.87 ($CH_2$), 29.53 ($CH_2$), 34.04 ($C(CH_3)_3$), 26.19 ($C(CH_3)_3$), 26.13 ($C(CH_3)_3$), 17.97 ($CH_3$), 17.92 ($CH_3$). Anal. ($C_{10}H_{19}NO_3$) C, H, N.

**Methyl 2-Ethyl-2-(1-methylethyl)-4-oxobutanoate Oxime (10f).** The reaction of aldehyde **9f** (8.00 g, 43.0 mmol) and $H_2NOH \cdot HCl$ (4.78 g, 68.8 mmol) in dry pyridine (40 mL), as described above in the preparation of **10e**, gave 8.20 g of slightly yellowish viscous liquid. Column chromatography over silica gel (hexanes−EtOAc, 4:1) followed by bulb-to-bulb distillation [pot temperature 110 °C (0.6 mmHg)] afforded the *anti* and *syn* oxime mixture **10f** (7.47 g, 86%) in the ratio of 60/40 as a colorless viscous liquid: $R_f$ = 0.45, 0.39 (hexanes−EtOAc, 7:3); IR 3400 (br, OH), 1728 (C═O), 1660 (C═N) $cm^{-1}$;

$^1$H NMR characteristic signals in major isomer, $\delta$ 7.52 (dd, 1, $J$ = 7.3, 6.0 Hz, CH=), 3.70 (s, 3, $OCH_3$), 2.56 (dd, 1, $J$ = 14.8, 6.0 Hz, diastereotopic H of $CH_2CH$=), 2.45 (dd, 1, $J$ = 14.8, 7.3 Hz, diastereotopic H of $CH_2CH$=); minor isomer, $\delta$ 6.89 (dd, 1, $J$ = 5.0, 6.0 Hz, CH=), 3.71 (s, 3, $OCH_3$), 2.76 (dd, 1, $J$ = 14.8, 6.0 Hz, diastereotopic H of $CH_2CH$=), 2.64 (dd, 1, $J$ = 14.8, 5.0 Hz, diastereotopic H of $CH_2CH$=); other signals belonging to both isomers, $\delta$ 2.06−1.92 (m, 2, 2 × $CH(CH_3)_2$), 1.84−1.52 (m, 4, 2 × $CH_2CH_3$), 0.93−0.83 (m, 18, 2 × $CH(CH_3)_2$) and 2 × $CH_2CH_3$); $^{13}$C NMR $\delta$ 176.07 (C=O), 175.89 (C=O), 150.84 (CH=), 150.44 (CH=), 52.29 ($C$C=O), 51.72 ($C$C=O), 51.55 ($OCH_3$), 33.80 ($CH(CH_3)_2$), 33.64 ($CH(CH_3)_2$), 31.29 ($CH_2CH$=), 27.17 ($CH_2CH_3$), 26.73 ($CH_2CH_3$), 18.38 (2 × $CH(CH_3)_2$), 17.53 ($CH(CH_3)_2$), 17.43 ($CH(CH_3)_2$), 9.08 ($CH_2CH_3$), 8.99 ($CH_2CH_3$). Anal. ($C_{10}H_{19}NO_3$) C, H, N.

**3-(1,1-Dimethylethyl)-3-methyl-2-pyrrolidinone (7e).** A green solution of $NiCl_2 \cdot 6H_2O$ (4.76 g, 20.0 mmol) and oximes **10e** (2.01 g, 10.0 mmol) in MeOH (100 mL) was stirred vigorously and cooled to −30 °C while $NaBH_4$ (3.80 g, 100 mmol) was added in portions over 30 min in an atmosphere of $N_2$. The reaction was exothermic, producing a black precipitate and copious quantities of hydrogen. The cooling bath was removed and the mixture stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, the black precipitate was dissolved in HCl (6 N, 100 mL), and then the acidic solution was made alkaline (pH 8−9) by the addition of 28% $NH_4OH$ (*ca*. 35 mL) at 0 °C. Then it was extracted with $CH_2Cl_2$ (3 × 40 mL), and the combined $CH_2Cl_2$ layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed i*n vacuo* to give the crude methyl 4-amino-2-(1,1-dimethylethyl)-2-methylbutyrate (1.62 g , 87%) as a colorless semisolid: IR 3359 (br, NH), 1722 (C=O) cm$^{-1}$.

To a stirred solution of the above amino ester (1.62 g, 8.66 mmol) in THF (18 mL) was added *t*-BuOK (7.57 g, 67.6 mmol) at 0 °C in an atmosphere of $N_2$. The cooling bath was removed, and the mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$ (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extract was washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 1.37 g of a colorless solid. Column chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7e** (1.19 g, 77%) as a colorless solid: $R_f$ = 0.35 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 179−181 °C (ether−hexanes); IR 3194 (br, NH), 1673 (C=O) cm$^{-1}$; $^1$H NMR $\delta$ 6.39 (br, 1, NH), 3.31−3.18 (m, 2, $NHCH_2$), 2.32−2.22 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.75−1.67 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.16 (s, 3, $CH_3$), 1.02 (s, 9, $C(CH_3)_3$); $^{13}$C NMR $\delta$ 182.76 (C=O), 48.08 ($C$C=O), 38.69 ($NHCH_2$), 34.80 ($C(CH_3)_3$), 31.73 ($NHCH_2CH_2$), 25.65($C(CH_3)_3$), 19.26 ($CH_3$). Anal. ($C_9H_{17}NO$) C, H, N.

**3-Ethyl-3-(1-methylethyl)-2-pyrrolidinone (7f).** The reaction of the oximes **10f** (7.04 g, 35.0 mmol) with $NaBH_4$ (13.3 g, 350 mmol) and $NiCl_2 \cdot 6H_2O$ (16.7 g, 70.0 mmol) in MeOH (250 mL), as described above in the preparation of **7e**, gave the crude methyl 4-amino-2-ethyl-2-(1-methylethyl)butyrate (7.59 g) as a dark-colored liquid: IR 3350 (br, NH), 1725 (C=O) cm$^{-1}$.

The reaction of above amino ester with *t*-BuOK (15.29 g, 136.5 mmol) in THF (70 mL), as described above in the preparation of **7e**, gave 7.14 g of a dark-colored semisolid. Flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the pure lactam **7f** (3.11 g, 57% based on the oximes) as a colorless solid: $R_f$ = 0.41 (2% MeOH in $CHCl_3$−EtOAc, 1:1); mp 63−64 °C (hexanes at −5 °C); IR 3188 (br, NH), 1682 (C=O) cm$^{-1}$; $^1$H NMR $\delta$ 6.01 (br, 1, NH), 3.32−3.20 (m, 2, $NHCH_2$), 2.13−2.03 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.95 (septet, 1, $CH(CH_3)_2$), 1.84−1.75 (m, 1, diastereotopic H of $NHCH_2CH_2$), 1.57 (q, 2, $J$ = 7.4 Hz, $CH_2CH_3$), 0.92 (t, 3, $J$ = 7.4 Hz, $CH_2CH_3$), 0.90 (d, 3, $J$ = 6.9 Hz, $CH(CH_3)_2$), 0.88 (d, 3, $J$ = 6.9 Hz, $CH(CH_3)_2$); $^{13}$C NMR $\delta$ 182.07 (C=O), 50.89 ($C$C=O), 39.60 ($NHCH_2$), 32.48 ($CH(CH_3)_2$), 29.12 ($NHCH_2CH_2$), 25.60 ($CH_2CH_3$), 18.27 ($CH(CH_3)_2$), 16.80 ($CH(CH_3)_2$), 8.80 ($CH_2CH_3$). Anal. ($C_9H_{17}NO$) C, H, N.

**Neurological Evaluations and [$^{35}$S]TBPS Binding**. The methods used have been described previously.[4]

**Electrophysiology**. Neurons were voltage-clamped at −60 mV using a Dagan Model 8900 amplifier and exposed to GABA, or GABA and the compound were dissolved in extracellular fluid by a gravity-driven application system for 400 ms. Application pipets were positioned 10−30 $\mu$m away from cells. GABA was applied 30 s before and 30 s after GABA and compound application. Data were discarded if GABA response after drug application was <90% of GABA response prior to compound application. The maximum current is expressed as a percentage of the response to GABA alone. Extracellular fluid contained 140 mM NaCl, 3 mM KCl, 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.3), 5 mM $MgCl_2$, and 5.5 mM glucose. Intracellular fluid contained 130 mM CsCl, 10 mM tetraethyl ammonium chloride, 10 mM HEPES pH 7.3, 2 mM QX-314 (lidocaine *N*-ethyl bromide), 5.5 mM glucose, and 2 mM MgATP. Additional details for cell culture and electrophysiological methods can be found in ref 11.

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