Synthesis and Anticonvulsant Activities of 3,3-Dialkyl- and 3-Alkyl-3-benzyl-2-piperidinones (δ-Valerolactams) and Hexahydro-2*H*-azepin-2-ones (ϵ-Caprolactams)

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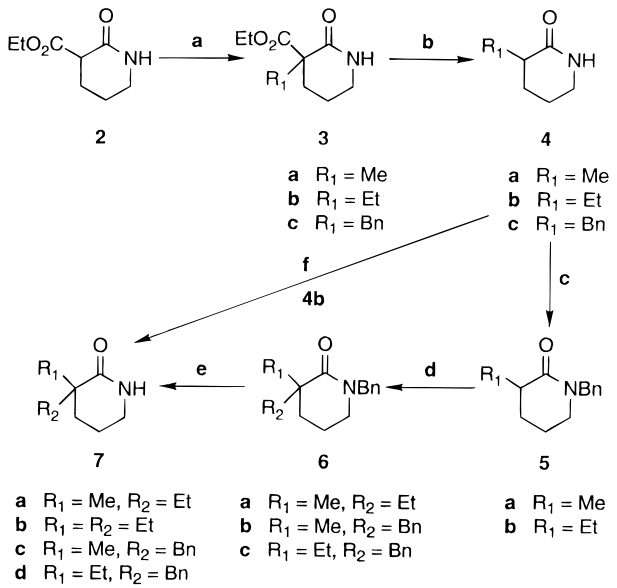
A series of 3-substituted 2-piperidinone (δ-valerolactam) and hexahydro-2*H*-azepin-2-one (ϵ-caprolactam) derivatives were prepared and evaluated as anticonvulsants in mice. In the 2-piperidinone series, 3,3-diethyl compound **7b** is the most effective anticonvulsant against pentylenetetrazole-induced seizures (ED_{50}, 37 mg/kg; PI (TD_{50}/ED_{50}), 4.46), and 3-benzyl compound **4c** (ED_{50}, 41 mg/kg; PI, 7.05) is the most effective anticonvulsant against seizures induced by maximal electroshock. By contrast, none of the ϵ-caprolactams tested had anticonvulsant effects below doses causing rotorod toxicity. log *P* values were correlated with neurotoxicity and [^{35}S]TBPS displacement, but not with anticonvulsant activity. Electrophysiological evaluations of selected compounds from each series indicated that both the δ-valerolactams and ϵ-caprolactams potentiated GABA-mediated chloride currents in rat hippocampal neurons.

A recent study from this laboratory described the anticonvulsant activities of a series of 2-pyrrolidinones (γ-butyrolactams) containing alkyl and/or phenylmethyl (benzyl) substituents at C-3.[1] Overall, it was found that 3,3-disubstituted 2-pyrrolidinones had anticonvulsant activities against seizures induced either by pentylenetetrazole (PTZ) or by maximal electroshock (MES) which were superior to those reported for the previously studied congeneric α,α-dialkyl-substituted γ-butyrolactones (GBLs) and γ-thiobutyrolactones (TBLs).[2] Within this context, to further define the structure−activity relationships of anticonvulsant lactams, we have investigated the effect of ring size on pharmacological activity. A series of 3,3-disubstituted 2-piperidinone (δ-valerolactam) and hexahydro-2*H*-azepin-2-one (ϵ-caprolactam) derivatives has been prepared, and their anticonvusant activities against PTZ- and MES-induced seizures has been studied. The effect of the compounds on [^{35}S]-*tert*-butylbicyclophosphorothionate ([^{35}S]TBPS) binding to the picrotoxin site on $GABA_A$ receptors was examined, and the effects of selected compounds on $GABA_A$ receptor function were measured using electrophysiological methods.

Chemistry

Monosubstituted 2-piperidinones **4a**−**c** were prepared from 3-(ethoxycarbonyl)-2-piperidinone (**2**) by reported procedures[3] as summarized in Scheme 1. Attempted C-alkylation of lactams **4a** and **4b** with benzyl bromide in the presence of 2 equiv of *n*-butyllithium in THF at 0 °C as described in the preparation of 3,3-dialkyl-2-piperidinones[7] led only to small amounts of the corresponding products **7c** and **7d**, respectively. Hence, an alternative approach, in which *N*-benzyl lactams **5a**,**b** (prepared from **4a**,**b** under phase-transfer conditions[8]) were initially alkylated[9,10] with appropriate alkyl halides in the presence of lithium diisopropylamide (LDA) in THF−HMPA at −78 °C, followed by removal of the *N*-benzyl group from resulting **6a**−**c** with lithium in liquid ammonia,[9,11] was used to prepare lactams **7a**, **7c**, and **7d** (Scheme 1). The diethyl lactam **7b**[12] was prepared in a slightly different manner. Thus, lactam **4b** was reacted with Me_3SiCl in the presence of excess Et_3N in benzene to afford the corresponding *N*-silyl lactam, which was treated with LDA at −23 °C in THF to form the enolate and then alkylated with ethyl iodide at −78 °C to provide lactam **7b** after aqueous desilyla-

Scheme 1[a]



[a] (a) R_1X, NaOEt; (b) (i) NaOH, (ii) heat; (c) $PhCH_2Br$, KOH, Bu_4NHSO_4; (d) R_2X, LDA; (e) Li, NH_3; (f) (i) Me_3SiCl, Et_3N, (ii) EtI, LDA.

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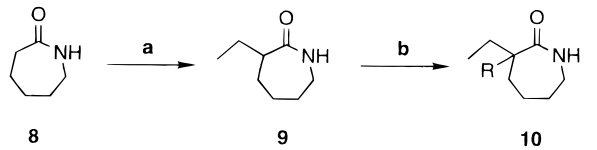
Scheme 2[a]



8 9 10

a R = Et
b R = Bn

[a] (a) (i) Me_3SiCl, Et_3N, (ii) EtI, LDA; (b) (i) Me_3SiCl, Et_3N, (ii) RX, LDA.

tion.[13] As summarized in Scheme 2, ϵ-caprolactams **9**, **10a**, and **10b** were prepared from ϵ-caprolactam (**8**) by a similar silylation, alkylation, and desilylation route.

Results and Discussion

The anticonvulsant potencies (ED_{50}) against PTZ- and MES-induced seizures in mice, neurotoxicity (TD_{50}) as evaluated by a rotorod test, and protective indices (PI = TD_{50}/ED_{50}) for the 2-piperidinone and ϵ-caprolactam derivatives are summarized in Table 1. For comparison, earlier results[1,14,15] from studies which utilized identical methods to obtain these values for 3-(phenylmethyl)-2-pyrrolidinone (**11a**), 3,3-diethyl-2-pyrrolidinone (**11b**), and antiepileptic drugs ethosuximide, phenobarbital, and valproic acid are also included in Table 1.

Among the 2-piperidinone derivatives, the unsubstituted lactam **1**, which was reported previously to produce mild sedation in mice at a dose of 750 mg/kg,[16] has neither anticonvulsant activity nor neurotoxicity at doses up to 600 mg/kg. The 3-methyl lactam **4a** is a very weak anticonvulsant, and the corresponding 3-ethyl compound **4b** displays both greater anticonvulsant activity and neurotoxicity. The 3-benzyl lactam **4c** has an anticonvulsant activity which is significantly higher than that found for compounds **4a** and **4b**. The dialkyl lactams **7a** and **7b** have better anticonvulsant activity than monoalkyl-substituted lactams **4a** and **4b**, with diethyl compound **7b** being a significantly more potent anticonvulsant than compound **7a** in the two seizure models examined. An additional 3-alkyl substituent along with the 3-benzyl group (compare compound **4c** with compounds **7c** and **7d**) causes an increase in rotorod toxicity, but does not significantly alter anticonvulsant activity. For comparison, anticonvulsant activity also has been reported for 3-methoxy-3-phenyl-2-piperidinone (ED_{50} = 50 mg/kg against subcutaneous Metrazol and 121 mg/kg against MES; rotorod TD_{50} = 239 mg/kg).[17]

Overall, the structure−activity relationships of the 2-piperidinone derivatives investigated are very similar to those reported earlier for the corresponding 2-pyrrolidinone derivatives.[1] In each series, the compounds with the best anticonvulsant profiles have either the 3-benzyl (compounds **4c** and **11a**) or 3,3-diethyl (compounds **7b** and **11b**) substituents. Compounds **7b** and **11b** are equally potent and superior to all but phenobarbital in anti-PTZ activity. Compounds **4c** and **11a** exhibit similar anticonvulsant potency in the MES test, but compound **11a** is about twice as neurotoxic as **4c**. The lower neurotoxicity of **4c** gives a PI value of 7.05 against MES, which is greater than the PI value of phenobarbital. With regard to the PI value for anti-PTZ activity, **7b** (PI = 4.46) ranked ahead of phenobarbital and second only to the five-membered ring analogue **11b**.

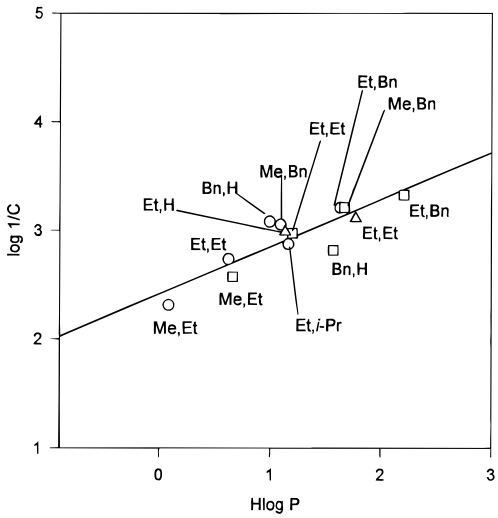


Figure 1. Plot of log 1/*C* against Hlog *P*, where *C* is TD_{50} expressed in moles per kilogram mouse: γ-butyrolactams (circles), δ-valerolactams (squares), ϵ-caprolactams (triangles). The substituents on the 3-position in each lactam are indicated next to the data points.

In contrast to the lack of behavioral effects produced by unsubstituted 2-piperidinone **1**, unsubstituted ϵ-caprolactam **8** caused a nonsedating toxicity in five out of six mice at a dose of 300 mg/kg in the PTZ screen. At a dose of 500 mg/kg, compound **8** produced clonic, but not tonic seizures in four out of six mice. These results are in general agreement with results from an earlier study in which lactam **8** was found to cause slight sedation at 300 mg/kg and Straub tail and clonic and tonic convulsions at 500 mg/kg when injected intraperitonially into mice.[16]

The favorable effects (enhancement of anticonvulsant activity relative to neurotoxicity) of C-3 substitution for compounds in the 2-piperidinone series were not observed in the ϵ-caprolactam series. Compounds **9** and **10a** had anticonvulsant activity only at doses which caused rotorod neurotoxicity. Compound **10b**, which was very insoluble, had no neuroactivity at the highest dose that could be evaluated. Hence, whereas the structure−activity relationships for C-3 alkyl and benzyl substituents and anticonvulsant activity are similar in the 2-pyrrolidinone and 2-piperidinone series, these relationships are clearly different in the ϵ-caprolactam series. Most notably, the high anticonvulsant activities found for compounds **7b** and **11b** are not found for compound **10a**.

Other investigators have also failed to find any substitution patterns which produce useful anticonvulsant ϵ-caprolactams. The convulsant activity of lactam **8** was found to be enhanced significantly by introduction of alkyl groups at C-4 and C-6 of the lactam ring. By contrast, ϵ-caprolactams substituted at C-5 were inactive, while some with bulky substituents at C-7 were reported to be depressants.[18,19]

The interactions of the lactams with the picrotoxin binding site of the $GABA_A$ receptors found in rat brain membranes were assessed by determining IC_{50} values for [^{35}S]TBPS displacement and are provided in Table 1. The best anticonvulsant lactams studied display weak interactions with the picrotoxin site on the $GABA_A$ receptor, and there is clearly no correlation between anticonvulsant activity and IC_{50} values for TBPS dis-

Table 1. Anticonvulsant Activity, Neurotoxicity, [^{35}S]TBPS Binding Data, and Protective Index Values for 2-Piperidinones (**1**−**7d**), Hexahydro-2*H*-azepin-2-ones (**8**−**10b**), 2-Pyrrolidinones (**11a**,**b**), Ethosuximide, Phenobarbital, and Valproic Acid

	C-3 substituents		anticonvulsant potency ED_{50}[a] (mg/kg)		rotorod toxicity TD_{50}[b] (mg/kg)	protective index (PI) TD_{50}/ED_{50}		[^{35}S]TBPS displacement IC_{50}[c] (mM)
compd	R_1	R_2	PTZ	MES		PTZ	MES	
1	H	H	>600 (0/6)[d]	>600 (0/6)	>600 (0/6)			197 ± 4.5
4a	Me	H	>600 (1/6)	>600 (0/6)	>600 (2/6)			27.7 ± 0.8
4b	Et	H	297 [196−449][e]	550 [462−654]	>325 {325,450}[f]	>1.09	>0.59	8.78 ± 0.24
4c	Bn	H	82 [61−109]	41 [31−55]	289 [175−478]	3.52	7.05	1.44 ± 0.04
7a	Me	Et	168 [143−197]	199 [175−227]	378 [339−422]	2.25	1.90	4.41 ± 0.11
7b	Et	Et	37 [25−56]	54 [33−87]	165 [89−307]	4.46	3.06	1.31 ± 0.06
7c	Me	Bn	56 [36−89]	50 [41−60]	125 [100−155]	2.23	2.50	0.73 ± 0.01
7d	Et	Bn	61 [38−99]	70 [28−175]	103 [70−152]	1.69	1.47	0.27 ± 0.00
8	H	H	>300[g] (0/6)	>300 (0/6)	<300 (9/12)	<1	<1	17.4 ± 0.24
9	Et	H	210 [172−257]	249 [186−333]	145 [106−198]	0.69	0.58	3.20 ± 0.07
10a	Et	Et	226 [180−285]	178 [99−320]	131 [82−208]	0.58	0.74	0.38 ± 0.02
10b	Et	Bn	>100 (0/6)	>100 (0/6)	>100 (0/6)			0.09 ± 0.01
11a[h]	Bn	H	71 [43−101]	41 [20−63]	144 [125−168]	2.03	3.51	2.44 ± 0.17
11b[h]	Et	Et	46 [30−63]	174 [133−229]	260 [219−320]	5.65	1.49	5.81 ± 0.12
ethosuximide[i]			161 [137−189]	>562	378 [320−436]	2.35	<0.67	
phenobarbital[j]			22 [17−28]	17 [14−23]	88 [71−112]	4.00	5.18	
valproic acid[i]			133 [109−154]	206 [176−247]	282 [258−315]	2.12	1.37	

[a] Dose at which 50% of the mice were protected from clonic seizures induced by pentylenetetrazole (85 mg/kg) or tonic hindlimb seizures induced by maximal electroshock. A minimum of four doses of each compound dissolved in 30% polyethylene glycol was administered through intraperitonial injections (0.01 mL/g of body weight). A group of six animals was used at each dose tested. [b] Dose at which 50% of the mice failed the rotorod toxicity test. [c] Binding data are presented as the mean and range from duplicate experiments performed in triplicate. Values reported for **8**, **9**, **10a**, and **10b** are the mean ± SEM of three experiments performed in triplicate. [d] 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. [e] Numbers in brackets are the 95% fiducial limits. [f] Numbers in braces are the highest 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. [g] Caused toxicity in five out of six mice at a dose of 300 mg/kg, but the animals were not notably sedated. At a dose of 500 mg/kg, only clonic but not tonic seizures were observed in four out of six mice. [h] Data is from ref 1. [i] Data is from ref 14. [j] Data is from ref 15.

placement in the binding experiments (e.g., compare the results shown for compounds **7b**, **7d**, and **10a** in Table 1). Additionally, no correlation between the calculated log *P* values, Hlog *P*,[20] and the anticonvulsant activity (r^2 = 0.208 for PTZ) of substituted 2-pyrrolidinones, 2-piperidinones, and ϵ-caprolactams described in this and our previous paper[1] was observed. By contrast, a plot of log 1/*C* (where *C* is the TD_{50} value in moles per kilogram) against Hlog *P* of the same lactams (Figure 1) shows that there is a reasonably high degree of correlation between the neurotoxicity and lipophilic character of the lactams (r^2 = 0.759). Similar correlations have been observed previously for other congeneric series of CNS active compounds.[21] Lastly, a correlation (r^2 = 0.698) was observed between lipophilicity and the ability of these lactams to displace TBPS from the picrotoxin site on the $GABA_A$ receptor.

The effects of compounds **7b**, **7d**, **10a**, and **10b** on GABA receptor function were determined using electrophysiological methods. All four compounds enhanced 3 μM GABA-induced chloride currents in cultured rat hippocampal neurons (Figure 2), and the actions of the compounds were blocked by the picrotoxin antagonist[22] α-isopropyl-α-methyl-γ-butyrolactone (Table 2). The potencies are comparable to those reported previously for the corresponding 2-pyrrolidinones (for example, 1 mM of compound **11b** gives a response of 137 ± 6% relative to 3 μM GABA control = 100%), indicating that increasing ring size by one or two carbons has little effect on this response. The results obtained with ϵ-caprolactam **10a** in this assay would suggest that this compound should be an effective anticonvulsant, but this was not found to be the case. Previously, the modulatory actions of another ϵ-caprolactam, hexahydro-3,3-diallyl-6,6-dimethyl-2*H*-azepin-2,4-dione, at $GABA_A$ receptors also was found not to correlate with the compound's in vivo activity. This compound, which at a concentration of 1 mM enhances GABA-mediated chloride current (114% of control) in mouse spinal cord neurons,[23] was found to be a potent convulsant in mice (CD_{50} = 40 mg/kg).[24]

In summary, the structure−activity relationships for anticonvulsant lactams has been extended to 3-alkyl-substituted 2-piperidinones and ϵ-caprolactams. The anticonvulsant profiles of the 2-piperidinones and earlier studied 2-pyrrolidinones are similar, whereas the

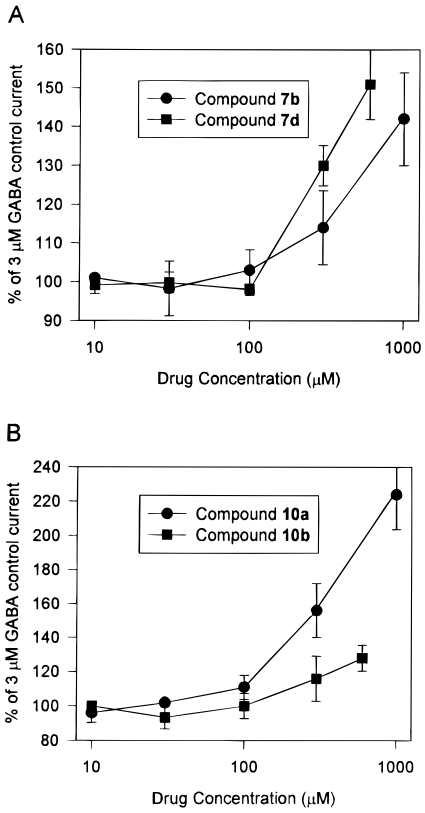


Figure 2. Concentration−response curves for the potentiation of 3 μM GABA-mediated chloride currents in cultured hippocampal neurons by compounds **7b** and **7d** (panel A) and **10a** and **10b** (panel B). Data points are the mean ± SEM for at least four cells at each concentration tested.

ϵ-caprolactams are much weaker anticonvulsants. In particular, compounds **4c** and **7b** exhibit an anticonvulsant profile resembling that of phenobarbital. Additional studies to elucidate the interactions of these compounds with $GABA_A$ receptors and to identify the role of other receptors in the anticonvulsant actions of these compounds are in progress.

Experimental Section

General Methods. 2-Piperidinone (**1**), 3-(ethoxycarbonyl)-2-piperidinone (**2**), and hexahydro-2*H*-azepin-2-one (**8**) were obtained from Aldrich Chemical Co. (Milwaukee, WI). 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. Solvents used for extractions were dried over $MgSO_4$, filtered, and removed on a rotary evaporator. Elemental analyses were performed at M-H-W Laboratories in Phoenix, AZ. NMR spectra, IR spectra, melting points, and chromatographic separations were obtained by methods described previously.[1]

3-Methyl-2-piperidinone (4a): mp 55−56 °C (lit.[4] mp 46 °C; lit.[25] mp 53−55 °C).

3-Ethyl-2-piperidinone (4b): mp 67−68 °C (lit.[5] mp 66−68 °C); IR 3279−3072 (NH), 1657 (C═O) cm^{-1}; ^1H NMR δ 7.36 (br, 1, NH), 3.36−3.22 (m, 2, H-6), 2.26−2.15 (m, 1, H-3), 2.00−1.46 (m, 6, CH_3CH_2, H-4, H-5), 0.95 (t, 3, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR δ 175.33, 42.05, 42.02, 25.23, 24.23, 21.08, 11.15.

3-(Phenylmethyl)-2-piperidinone (4c): mp 119−121 °C (lit.[6] mp 115−116 °C); IR 3251−3026 (NH), 1661 (C═O), 1605 (C═C) cm^{-1}; ^{13}C NMR δ 174.30, 139.85, 129.25, 128.36, 126.14, 42.87, 42.45, 37.43, 25.42, 21.24. Anal. ($C_{12}H_{15}NO$) C, H, N.

3-Methyl-1-(phenylmethyl)-2-piperidinone (5a): A well-stirred mixture of the lactam **4a** (4.52 g, 40.0 mmol), benzyl bromide (8.21 g, 48.0 mmol), and Bu_4NHSO_4 (2.72 g, 8.00 mmol) in THF (200 mL) was treated with powdered 85% KOH (2.9 g, 44 mmol) at 0 °C in a N_2 atmosphere. The reaction mixture was stirred at room temperature for 24 h, poured into saturated NH_4Cl (60 mL), and extracted with ether (3 × 50 mL), and the combined organic extract was washed with brine (50 mL). Solvent removal gave a yellow oil, which was flash chromatographed over silica gel (hexanes−$CHCl_3$−EtOAc, 7:2:1) to give 7.33 g (90%) of *N*-benzyl lactam **5a** as a colorless oil, with spectroscopic characteristics identical to those reported earlier.[26]

5b was similarly prepared.

3-Ethyl-1-(phenylmethyl)-2-piperidinone (5b). Lactam **5b**[27] (2.03 g, 89%) was prepared from **4b** (1.33 g, 10.5 mmol) as a colorless oil: ^{13}C NMR δ 172.79, 137.48, 128.52, 127.93, 127.22, 50.29, 47.44, 42.90, 25.74, 24.91, 21.59, 11.47. Anal. ($C_{14}H_{19}NO$) C, H, N.

3-Ethyl-3-methyl-1-(phenylmethyl)-2-piperidinone (6a). A solution of lactam **5a** (3.25 g, 16.0 mmol) in THF (5 mL) was added slowly (*ca*. 5 min) to a solution of LDA [prepared from diisopropylamine (2.42 g, 24.0 mmol) and *n*-butyllithium in hexanes (2.5 M, 9.2 mL, 23 mmol)] in THF (30 mL) at 0 °C in a N_2 atmosphere, and the mixture was stirred for 45 min. The temperature was then reduced to −78 °C, and a solution of iodoethane (3.92 g, 25.1 mmol) in THF (5 mL) and HMPA (2.4 mL, 13.8 mmol) was added over a period of 10 min. Stirring was continued for 2 h at −78 °C, and the reaction was quenched by addition of saturated NH_4Cl (50 mL). The layers were separated, the aqueous phase was further extracted with ether (3 × 50 mL), and the combined organic extract was washed with brine (50 mL). Solvent removal gave 5.90 g of a pale yellow liquid, which upon column chromatography over silica gel (hexanes−EtOAc, 9:1) followed by bulb-to-bulb distillation [pot temperature 110−115 °C (1 mmHg)] afforded lactam **6a** (2.52 g, 68%) as a colorless viscous liquid: IR 1635 (C═O), 1595 (C═C) cm^{-1}; ^1H NMR δ 7.34−7.22 (m, 5, PhH), 4.66 (d, 1, J = 14.6 Hz, diastereotopic H of CH_2Ph), 4.49 (d, 1, J = 14.6 Hz, diastereotopic H of CH_2Ph), 3.24−3.14 (m, 2, H-6), 1.89−1.68 (m, 4, H-4, H-5), 1.59−1.48 (m, 2, CH_3CH_2), 1.23 (s, 3, CH_3), 0.88 (t, 3, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR δ 175.43, 137.56, 128.33, 127.73, 126.98, 50.18, 47.66, 41.72, 32.42, 31.84, 25.65, 19.30, 8.47. Anal. ($C_{15}H_{21}NO$) C, H, N.

Similarly prepared were the following.

3-Methyl-1,3-bis(phenylmethyl)-2-piperidinone (6b). Lactam **6b** (3.72 g, 71%) was prepared from **5a** (3.65 g, 18.0 mmol) as a colorless oil: IR 1635 (C═O), 1605 (C═C) cm^{-1}; ^1H NMR δ 7.30−7.12 (m, 10, PhH), 4.74 (d, 1, J = 14.6 Hz, diastereotopic H of NCH_2), 4.39 (d, 1, J = 14.6 Hz, diastereotopic H of NCH_2), 3.33 (d, 1, J = 13.2 Hz, diastereotopic H of CH_2Ph), 3.11−2.95 (m, 2, H-6), 2.65 (d, 1, J = 13.2 Hz, diastereotopic H of CH_2Ph), 1.84−1.44 (m, 4, H-4, H-5), 1.31

Table 2. Antagonism of 2-Piperidinone and Hexahydro-2*H*-azepin-2-one Derivative Induced Potentiation of 3 μM 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]
7b (1 mM)	142 ± 10[c]	6
7b (1 mM) + α-IMGBL (3 mM)	102 ± 6*	6
7d (300 μM)	138 ± 8	6
7d (300 μM) + α-IMGBL (3 mM)	93 ± 4*	5
10a (200 μM)	117 ± 4	6
10a (200 μM) + α-IMGBL (3 mM)	105 ± 2**	5
10b (600 μM)	128 ± 8	9
10b (600 μM) + α-IMGBL (3 mM)	107 ± 3**	14

[a] To calculate the percentage response, the magnitude of the peak current produced by 3 μM GABA plus compound(s) was normalized with respect to the peak current produced by 3 μM GABA alone on the same cell. A percentage response of 100% reflects no change in the current compared to 3 μM GABA alone. [b] N = Number of cells examined. [c] Values are the mean ± SEM. *p < 0.01 by Student's t test. **p < 0.05 by Student's t test. Statistical significance calculated for test compound alone vs test compound and α-IMGBL.

(s, 3, CH_3); ^{13}C NMR δ 174.64, 138.06, 137.20, 130.69, 128.31, 127.78, 127.75, 126.99, 126.09, 50.43, 47.70, 45.49, 43.04, 31.91, 26.86, 19.20. Anal. ($C_{20}H_{23}NO$) C, H, N.

3-Ethyl-1,3-bis(phenylmethyl)-2-piperidinone (6c). Lactam **6c** (3.10 g, 84%) was prepared from **5b** (2.60 g, 12.0 mmol)- as a colorless solid: mp 88−90 °C (from CH_2Cl_2−hexane); IR 1625 (C═O), 1595 (C═C) cm^{-1}; ^1H NMR δ 7.32−7.17 (m, 10, PhH), 4.67 (d, 1, J = 14.5 Hz, diastereotopic H of NCH_2), 4.50 (d, 1, J = 14.5 Hz, diastereotopic H of NCH_2), 3.34 (d, 1, J = 13.0 Hz, diastereotopic H of CH_2Ph), 3.11−3.03 (m, 1, diastereotopic H of H-6), 2.96−2.89 (m, 1, diastereotopic H of H-6), 2.59 (d, 1, J = 13.0 Hz, diastereotopic H of CH_2Ph), 1.99−1.90 (m, 1, diastereotopic H of CH_3CH_2), 1.71−1.26 (m, 5, H-4, H-5, diastereotopic H of CH_3CH_2), 0.92 (t, 3, J = 7.4 Hz, CH_3CH_2); ^{13}C NMR δ 174.08, 138.43, 137.37, 130.59, 128.34, 127.96, 127.86, 127.05, 126.15, 50.54, 47.57, 46.88, 44.63, 32.70, 28.24, 19.74, 8.79. Anal. ($C_{21}H_{25}NO$) C, H, N.

3-Ethyl-3-methyl-2-piperidinone (7a). To a well-stirred solution of lactam **6a** (2.08 g, 9.00 mmol) in THF (27 mL) and liquid NH_3 (180 mL) was added Li metal (0.63 g, 90 mmol) at −78 °C slowly over a period of 5 min. The cooling bath was removed and the reaction mixture stirred for 1 h at refluxing NH_3. Then it was heated for 10−15 min at 60 °C to evaporate NH_3, the white residue was treated carefully with water (50 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extract was washed with brine (50 mL). Removal of the solvent gave 1.81 g of a colorless viscous residue, which upon flash chromatography over silica gel (1% MeOH in $CHCl_3$−EtOAc, 1:1) afforded the lactam **7a** (1.10 g, 87%) as a colorless solid: mp 67−69 °C (from CH_2Cl_2−hexane); IR 3285−3064 (NH), 1646 (C═O) cm^{-1}; ^1H NMR δ 6.20 (br, 1, NH), 3.34−3.22 (m, 2, H-6), 1.87−1.68 (m, 4, H-4, diastereotopic H of CH_3CH_2 and H-5), 1.59−1.43 (m, 2, diastereotopic H of CH_3CH_2 and H-5), 1.19 (s, 3, CH_3), 0.88 (t, 3, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR δ 178.43, 42.68, 41.33, 32.08, 31.86, 25.36, 19.42, 8.47. Anal. ($C_8H_{15}NO$) C, H, N.

Similarly prepared were the following.

3-Methyl-3-(phenylmethyl)-2-piperidinone (7c). Lactam **7c** (1.75 g, 86%) was prepared from **6b** (2.93 g, 10.0 mmol) as a colorless solid: mp 76−78 °C (from ether−hexane); IR 3210−3028 (NH), 1657 (C═O), 1600 (C═C) cm^{-1}; ^1H NMR δ 7.30−7.18 (m, 5, PhH), 5.69 (br, 1, NH), 3.23 (d, 1, J = 13.3 Hz, diastereotopic H of CH_2Ph), 3.16−3.08 (m, 2, H-6), 2.67 (d, 1, J = 13.3 Hz, diastereotopic H of CH_2Ph), 1.81−1.63 (m, 3, H-4, diastereotopic H of H-5), 1.52−1.41 (m, 1, diastereotopic H of H-5), 1.26 (s, 3, CH_3); ^{13}C NMR δ 177.57, 137.85, 130.46, 127.83, 126.15, 44.77, 42.54, 42.30, 31.68, 26.07, 19.81. Anal. ($C_{13}H_{17}NO$) C, H, N.

3-Ethyl-3-(phenylmethyl)-2-piperidinone (7d). Lactam **7d** (1.43 g, 73%) was prepared from **6c** (2.76 g, 9.00 mmol) as a colorless solid: mp 101−102 °C (from CH_2Cl_2−hexane); IR 3203−3028 (NH), 1656 (C═O), 1595 (C═C) cm^{-1}; ^1H NMR δ 7.29−7.18 (m, 5, PhH), 6.06 (br, 1, NH), 3.25 (d, 1, J = 13.2 Hz, diastereotopic H of CH_2Ph), 3.22−3.01 (m, 2, H-6), 2.59 (d, 1, J = 13.2 Hz, diastereotopic H of CH_2Ph), 1.95−1.84 (m, 1, diastereotopic H of CH_3CH_2), 1.69−1.59 (m, 3, H-4, diastereotopic H of H-5), 1.51−1.36 (m, 2, diastereotopic H of CH_3CH_2 and H-5), 0.93 (t, 3, J = 7.4, CH_3CH_2); ^{13}C NMR δ 176.70, 138.19, 130.41, 127.91, 126.18, 46.35, 44.20, 42.47, 32.07, 27.94, 19.74, 8.71. Anal. ($C_{14}H_{19}NO$) C, H, N.

3,3-Diethyl-2-piperidinone (7b). To a solution of lactam **4b** (1.27 g, 10.0 mmol) and triethylamine (10.1 g, 100 mmol) in benzene (30 mL) was added chlorotrimethylsilane (4.36 g, 40.0 mmol) with stirring in an atmosphere of N_2. The resulting suspension was stirred at room temperature for 12 h, diluted with benzene (30 mL), and filtered through a sintered glass funnel. The filtrate was concentrated and the residue bulb-to-bulb distilled [pot temperature 70 °C (0.7 mmHg)] to give 3-ethyl-1-(trimethylsilyl)-2-piperidinone (1.51 g, 76%) as a colorless liquid: IR 1657 (C═O) cm^{-1}; ^1H NMR δ 3.24−3.11 (m, 2, H-6), 2.30−2.15 (m, 1, H-3), 2.01−1.39 (m, 6, H-4, H-5, CH_3CH_2), 0.92 (t, 3, J = 7.5 Hz, CH_3CH_2), 0.25 (s, 9, $Si(CH_3)_3$).

A solution of the above *N*-trimethylsilyl lactam (1.49 g, 7.50 mmol) in THF (10 mL) was added slowly (*ca*. 5 min) to LDA [prepared from diisopropylamine (0.95 g, 9.4 mmol) and *n*-butyllithium (2.5 M, 3.8 mL, 9.5 mmol)] in THF (10 mL) at −78 °C with stirring in an atmosphere of N_2. The resulting solution was kept at −23 °C for 1 h and recooled to −78 °C, and iodoethane (1.76 g, 11.3 mmol) was added to it in one portion. The reaction mixture was allowed to warm to room temperature (*ca*. 3 h), and stirring was continued for another 2 h period. Water (25 mL) was added, the layers were separated, the aqueous phase was extracted with ether (3 × 30 mL), and the combined organic extract was washed with brine (30 mL). Removal of the solvent gave 1.39 g of viscous oil, which upon flash chromatography over silica gel (hexanes−acetone−EtOAc, 2:1:1) afforded the pure lactam **7b** (0.93 g, 80%) as a colorless solid: mp 62−63 °C (from hexanes at −5 °C) (lit.[12] mp 61−64 °C); IR 3284−3090 (NH), 1654 (C═O) cm^{-1}; ^1H NMR δ 5.90 (br, 1, NH), 3.30−3.25 (m, 2, H-6), 1.86−1.66 (m, 6, H-4, H-5, 2 × diastereotopic H of CH_3CH_2), 1.56−1.44 (m, 2, 2 × diastereotopic H of CH_3CH_2), 0.88 (t, 6, J = 7.4 Hz, 2 × CH_3CH_2); ^{13}C NMR δ 177.51, 44.78, 42.37, 30.75, 28.25, 19.81, 8.58. Anal. ($C_9H_{17}NO$) C, H, N.

Hexahydro-3-ethyl-2*H*-azepin-2-one (9). A solution of the known hexahydro-1-(trimethylsilyl)-2*H*-azepin-2-one (9.25 g, 50.0 mmol)[28] in THF (25 mL) was added slowly (*ca*. 15 min) to LDA [(prepared from diisopropylamine (5.05 g, 50.0 mmol) and *n*-butyllithium 2.5 M, 20 mL, 50 mmol)] in THF (25 mL) at −78 °C with stirring in an atmosphere of N_2. After 45 min, this was transferred (by cannula) over a 10 min period to a −78 °C solution of iodoethane (7.02 g, 45.0 mmol) in THF (50 mL). The reaction mixture was allowed to warm to room temperature (*ca*. 3 h), and stirring was continued for another 2 h period. Water (50 mL) was added, the layers were separated, the aqueous phase was extracted with ether (3 × 50 mL), and the combined organic extract was washed with brine (50 mL). Removal of the solvent gave 6.51 g of colorless solid, which upon recrystallization from CH_2Cl_2−hexanes afforded the lactam **9** (5.54 g, 79%) as colorless needles: mp 97−99 °C; IR 3302−3078 (NH), 1656 (C═O) cm^{-1}; ^1H NMR δ 6.18 (br, 1, NH), 3.34−3.12 (m, 2, H-7), 2.33−2.25 (m, 1, H-3), 2.03−1.27 (m, 8, H-4, H-5, H-6, CH_3CH_2), 0.95 (t, 3, J = 7.4 Hz, CH_3CH_2); ^{13}C NMR δ 180.17, 45.36, 41.79, 29.47, 29.42, 24.34, 12.14. Anal. ($C_8H_{15}NO$) C, H, N.

Similarly prepared by the procedure described in **7b** via the intermediate hexahydro-3-ethyl-1-(trimethylsilyl)-2*H*-azepin-2-one [colorless liquid: IR 1640 (C═O) cm^{-1}; ^1H NMR δ 3.33−3.17 (m, 2, H-7), 2.47−2.38 (m, 1, H-3), 1.93−1.21 (m, 8, H-4, H-5, H-6, CH_3CH_2), 0.91 (t, 3, J = 7.3 Hz, CH_3CH_2), 0.24 (s, 9, $Si(CH_3)_3$)] were the following.

Hexahydro-3,3-diethyl-2*H*-azepin-2-one (10a). Lactam **10a** (0.85 g, 67%) was a colorless solid: mp 77−78 °C (from hexanes at −5 °C); IR 3278−3069 (NH), 1645 (C═O) cm^{-1}; ^1H NMR δ 5.89 (br, 1, NH), 3.24−3.19 (m, 2, H-7), 1.84−1.55 (m, 10, H-4, H-5, H-6, 2 × CH_3CH_2), 0.87 (t, 6, J = 7.5 Hz, 2 × CH_3CH_2); ^{13}C NMR δ 180.39, 47.99, 42.10, 31.62, 29.06, 27.85, 23.63, 8.39. Anal. ($C_{10}H_{19}NO$) C, H, N.

Hexahydro-3-ethyl-3-(phenylmethyl)-2*H*-azepin-2-one (10b). Lactam **10b** (1.92 g, 69%) was a colorless solid: mp 100−102 °C (from EtOAc−hexanes at −5 °C); IR 3287−3062 (NH), 1647 (C═O) cm^{-1}; ^1H NMR δ 7.28−7.16 (m, 5, PhH), 6.02 (br, 1, NH), 3.27−3.04 (m, 2, H-7), 3.05 (d, 1, J = 13.5 Hz, diastereotopic H of CH_2Ph), 2.87 (d, 1, J = 13.5 Hz, diastereotopic H of CH_2Ph), 1.79−1.48 (m, 8, H-4, H-5, H-6, CH_3CH_2), 0.99 (t, 3, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR δ 179.75, 138.40, 130.74, 127.69, 125.96, 49.60, 42.14, 41.42, 31.18, 28.47, 28.40, 23.04, 8.71. Anal. ($C_{15}H_{21}NO$) C, H, N.

Neurological Evaluations, ^{35}[S]TBPS Binding, and Electrophysiology. The methods used have been described previously.[1,29] Fiducial limits were analyzed by the method of Litchfield and Wilcoxon[30] using the computer program reported by Tallarida and Murray.[31]

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