79514-45-7; 7, 83476-82-8; 7a, 71555-47-0; 8, 83476-83-9; 8a, 79514-43-5; 9, 83476-84-0; 9a, 71555-54-9; 10, 83476-85-1; 10a, 71555-52-7; 11, 83476-86-2; 11a, 71555-34-5; 12, 83476-87-3; 12a, 71555-19-6; IX, 83476-90-8; X, 83476-91-9; XI, 75488-62-9; XII, 83476-92-0; XIII, 2302-93-4; XIV, 21198-20-9; XV, 26151-76-8; XVI, 83476-88-4; hexahydro-1H-azepine, 111-49-9; 3-azabicyclo-[3.2.2]nonane, 283-24-9; 1-(2-pyridinyl)piperazine, 34803-66-2; methyl 3-(1-phenylethylidene)thiocarbohydrazide, 83476-89-5; 2-acetylpyridine, 1122-62-9; methylhydrazine, 60-34-4; phenyl isothiocyanate, 103-72-0.

Bicyclic Lactones Derived from Kainic Acid as Novel Selective Antagonists of Neuroexcitatory Amino Acids[1]

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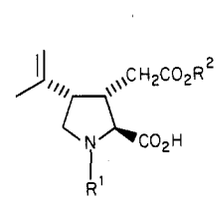
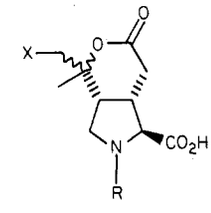
The bicyclic [2S-(2α,3β,4β)]-2-carboxy-4-(1-hydroxy-1-methylethyl)-3-pyrrolidineacetic acid δ-lactone (4), as well as its 4-[1-hydroxy-1-(iodomethyl)ethyl], 4-[1-hydroxy-1-(hydroxymethyl)ethyl], and 4-[1-hydroxy-1-[(phenylthio)methyl]ethyl] analogues, 6, 7, and 9, respectively, were designed and synthesized as potential selective antagonists of neuroexcitatory amino acids. When applied to rat brain slices, these lactones, which are chemically derived from kainic acid, inhibit the stimulation of Na^+ fluxes induced by the neuroexcitants kainic acid and *N*-methyl-D-aspartic acid. Lactone 4 and the hydroxy lactone 7 block preferentially the response to *N*-methyl-D-aspartic acid, while the iodo lactone 6 and the phenylthio lactone 9 are mainly kainic acid antagonists. Total inhibitions can be obtained, half of the maximal effect being observed at lactone concentrations in the range of 0.2–3 mM.

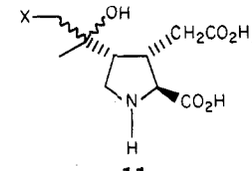
Glutamic and aspartic acids are powerful excitants of neuronal cells in the mammalian central nervous system, where they have been suggested to function as natural excitatory neurotransmitters.[2-4] They are also suspected of being involved in the etiology of neurological disorders like the epilepsies and Huntington's chorea.[5,6] Studies of the effects of glutamic acid and other acidic amino acids on neuronal excitability have led to the recognition of different classes of excitatory amino acid receptor sites.[7,8] The pharmacological characterization of these receptors involved the use of compounds such as 2-amino-5-phosphonovaleric acid,[9] D-α-aminoadipic acid,[10] D-α-aminosuberic acid,[10] γ-D-glutamylglycine,[11] and diethyl glutamate,[12] which are capable of inhibiting the effects of some excitatory amino acids. However, the scarcity of available antagonists, as well as their relatively poor selectivity and receptor affinity, call for the elaboration of a larger variety of specific antagonists. In addition to their utility in research, such compounds may provide a basis for the development of drugs for the therapy of brain disorders resulting from excessive excitation. As part of an effort toward this aim, chemical modifications of the well-known neuroexcitant kainic acid (1)[13] have been



1, $R^1 = R^2 = H$
2, $R^1 = H$; $R^2 = Me$
3, $R^1 = CO_2Bu^t$; $R^2 = H$



4, X = R = H
5, X = I; R = CO_2Bu^t
6, X = I; R = H
7, X = OH; R = H
8, X = SPh; R = CO_2Bu^t
9, X = SPh; R = H
10, X = OH; R = CO_2Bu^t



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carried out. This unsaturated dicarboxylic amino acid was converted into the bicyclic lactones 4, 6, 7, and 9 by cyclization of the γ-carboxy function onto the double bond of the isopropenyl group. The design and synthesis of these compounds as potential antagonists were prompted by the knowledge that esterification of an excitatory amino acid may lead to a product which, while devoid of agonist properties, displays antagonist activity. This is true for

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diethyl glutamate,[12] as well as for γ-methyl kainate (2).[1] Accordingly, it seemed reasonable to expect that compounds 4, 6, 7, and 9, in which the γ-carboxyl group of kainic acid (1) is blocked as an intramolecular ester, would be capable of inhibiting the effects of excitatory amino acids. It was also anticipated that by virtue of the conformational rigidity of their bicyclic structure, these lactones would act as receptor-selective ligands.

Chemistry. The lactones 4, 6, 7, and 9 were prepared with the commercially available kainic acid (1) as starting material. Two isomers, designated A and B, of each of the compounds 6, 7, and 9 were obtained.

Lactone 4 was prepared by heating a solution of kainic acid (1) in 10% sulfuric acid. For the preparation of iodo lactone 6, the disodium salt of 1 reacted with di-*tert*-butyl dicarbonate[14] to give 1-(*tert*-butyloxycarbonyl)kainic acid (3). Treatment of 3 with potassium triodide and sodium bicarbonate resulted in the formation of two isomers of the N-protected iodo lactone 5, which were separated by preparative TLC. Removal of the *tert*-butyloxycarbonyl protecting group by formic acid afforded two isomers of the iodo lactone 6.

In order to ease the separation of the isomers of the N-protected iodo lactone 5, their mixture was esterified with diazomethane. Treatment of each of the isomers of the methyl ester of 5 with sodium hydroxide in aqueous acetone caused, in addition to hydrolysis of the ester group, substitution of iodide by hydroxide to give, after removal of the N-protecting group, the respective isomers of the hydroxy lactone 7.

A mixture of the isomers of 7 was obtained by direct hydroylactonization of kainic acid (1) with hydrogen peroxide in aqueous acetic acid.

For the preparation of phenylthio lactone 9, 1-(*tert*-butyloxycarbonyl)kainic acid (3) was treated consecutively with triethylamine and benzenesulfenyl chloride[15] to furnish the N-protected phenylthio lactone 8 as a mixture of two isomers. Following chromatographic separation, each of the isomers of 8 was converted into the corresponding isomer of the phenylthio lactone 9 by treatment with formic acid.

On paper electrophoresis, at 3000 V and pH 6.5, the lactones 4, 6, 7, and 9 migrate to the negative pole with R_f's similar to that of proline. Treatment of these lactones with NaOH brings about their conversion into species that, like kainic acid (1), migrate to the positive pole. These are probably the hydrolysis products of the lactones, namely, the corresponding hydroxy acids 11,[16] which upon acidification are reconverted into the respective lactones.

Biological Results and Discussion

The assay used to evaluate the antagonist activity of the lactones is based on the ability of excitatory amino acids to increase the permeability of the neuronal membrane to sodium ions. In practice, rat striatum slices are loaded with radioactive sodium ions. The increase in the efflux of radioactive sodium induced by an agonist and its inhibition by the drug tested for antagonist activity are measured. The detailed description of the method has been published.[1,8]

When applied to rat striatum slices, the lactones 4, 6, 7, and 9 failed to cause an increase in the sodium efflux rate. Only after NaOH treatment of the lactones was a weak agonist activity observed, due to the formation of the corresponding hydroxy acids 11.[17]

Table I. Percent Response to Agonists in the Presence of Antagonists[a]

	agonist			
antagonist	30 μM NMDA	0.1 mM KA	0.5 mM L-Glu	0.1 mM Quis
2 mM 4	16 ± 2* (IC_{50} = 0.3 mM)	66 ± 20 (IC_{50} = 3 mM)	96 ± 31	94 ± 5
2 mM 6A	42 ± 7*	15 ± 5*	74 ± 11	96 ± 10
2 mM 6B	49 ± 9*	8 ± 1*	79 ± 14	111 ± 27
3 mM 7[b]	36 ± 3* (IC_{50} = 2 mM)	50 ± 11* (IC_{50} = 3 mM)	106 ± 15	94 ± 12
1.5 mM 9A	10 ± 5*		84 ± 30	
1 mM 9A		16 ± 4*		76 ± 14
1 mM 9B	36 ± 13*	0* (IC_{50} = 0.2 mM)	87 ± 26	53 ± 24*
1 mM 2APV	0 ± 2*	118 ± 30	64 ± 3*	91 ± 3
1 mM γDGG	5 ± 2*	47 ± 14*	71 ± 11*	100 ± 4

[a] For the method by which the stimulation of $^{22}Na^+$ efflux from preloaded rat striatum slices was measured, see ref 1. One-hundred percent response is the increase in $^{22}Na^+$ efflux rate induced by the given concentration of the agonist in the absence of any antagonist. The data represent the mean response plus or minus standard deviation from at least triplicate experiments. The asterisk indicates the statistical significance at the level of $p < 0.01$ of the difference from control as calculated by variance analysis. IC_{50} represents the concentration at which the antagonist inhibits half of the response of the agonist and was determined from dose–response curves (see text). [b] Almost identical results were obtained from 7A and 7B. The results given here were obtained with a 1:1 mixture of the isomers.

The lactones were then tested for their ability to antagonize the action of *N*-methyl-D-aspartic acid (NMDA), kainic acid (1, KA), L-glutamic acid (L-Glu), and quisqualic acid (Quis), the most selective agonists of the four classes of excitatory amino acid receptors.[8] The results are shown in Table I, which also includes the inhibition data for two standard antagonists, 2-amino-5-phosphonovaleric acid (2APV) and γ-D-glutamylglycine (γDGG).[8] The four lactones were found to block to varying extents the responses to NMDA and KA. With the exception of a moderate inhibition of the effects of Quis by the phenylthio lactones **9A** and **9B**, no significant antagonism of L-Glu and Quis was observed. Thus, some degree of receptor selectivity has been achieved. Although structurally related to kainic acid, the lactones 4, 6, 7, and 9 do not interact exclusively with the "KA receptor". In fact, the lactone 4 and the hydroxy lactones **7A,B** inhibit better the response to NMDA than that to KA, the first lactone being the most selective NMDA antagonist among the tested kainic acid derivatives. Preference for the KA receptor is displayed by the iodo lactones **6A,B** and even more by the phenylthio lactones **9A,B**. Thus, the selectivity pattern of the lactones is determined by the nature of their side-chain substituent X.

Dose–response curves were carried out for the inhibition of the effects of 30 μM NMDA and 0.1 mM KA by varying concentrations of lactones 4, 7, and **9B**. In all cases, a total inhibition of the response to the agonist could be observed. Using these curves, we determined the concentrations at

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(15) K. C. Nicolaou, S. P. Seitz, W. J. Sipio, and J. F. Blount, *J. Am. Chem. Soc.*, **101**, 3884 (1979).
(16) Base treatment of the iodo lactone 6 gives a mixture of the iodohydroxy acid (11, X = I) and the dihydroxy acid (11, X = OH) as detected by paper electrophoresis and TLC.
(17) V. I. Teichberg, O. Goldberg, and A. Luini, *Mol. Cell. Biochem.*, **39**, 281 (1981).

which the lactones produce 50% inhibition of the effects of the agonists (IC_{50}) (see Table I). It can be seen that the IC_{50} values, which are taken as an indication of the inhibitory potency of the lactone, depend on both the nature of the lactone and the agonist. The highest potencies are observed for the action of lactone **4** on the response to NMDA and of the phenylthio lactone **9B** on the response to KA.

The configuration of the newly formed chiral center in the lactone ring of compounds **6**, **7**, and **9** does not seem to influence the receptor selectivity of the lactone. The two isomers of the iodo lactone **6** and the hydroxy lactone **7** exhibit similar patterns of activity on the responses to the four agonists tested. Although IC_{50}'s were not calculated for the iodo lactones **6A,B**, it can be seen from Table I that at a concentration of 2 mM the potencies of the two isomers in antagonizing the response to NMDA are similar and the same is true for the response to KA. Inspection of the values obtained for the inhibitory effects of the phenylthio lactones **9A,B** reveals that also in this case the receptor selectivity pattern is very similar for both isomers. However, there is a difference in their potencies, since isomer **9B** at 1 mM produces a better inhibition of the responses to KA and Quis than isomer **9A** at the same concentration.

In conclusion, the choice of lactones derived from kainic acid as a new class of potential antagonists of excitatory amino acids has proved to be justified. Since both the selectivity and the potency of the lactones **4**, **6**, **7**, and **9** vary with their side-chain substituent X, it is reasonable to assume that further variations in X may provide compounds exhibiting antagonist properties different from those of the already available lactones.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. Mass spectra were obtained with a Varian MAT-731 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Proton NMR spectra were recorded at 270 MHz on a Bruker WH-270 instrument; chemical-shift assignments were assisted by selective decoupling experiments. Organic solutions were dried over anhydrous $MgSO_4$.

1,1-Dimethylethyl Hydrogen [2*S*-(2α,3β,4β)]-3-(Carboxymethyl)-4-(1-methylethenyl)-1,2-pyrrolidinedicarboxylate (3). To a stirred solution of 2.13 g (10 mmol) of kainic acid (**1**) and 0.8 g (20 mmol) of NaOH in 4 mL of water and 8 mL of *tert*-butyl alcohol was added 2.4 g (11 mmol) of di-*tert*-butyl dicarbonate[14] during 1 h, followed by 8 mL of *tert*-butyl alcohol. The mixture was stirred overnight, diluted with 10 mL of water, and extracted with pentane. The aqueous solution was acidified with $KHSO_4$, at 0 °C, to pH 2 and extracted with ethyl acetate. The organic solution was dried and evaporated to give 2.98 g (95%) of the N-protected derivative **3**: mp 149–150 °C dec (colorless needles from hexane–ethyl acetate); $[\alpha]^{22}_D$ −26.4° (*c* 1, MeOH). Anal. ($C_{15}H_{23}NO_6$) C, H, N.

[2*S*-(2α,3β,4β)]-2-Carboxy-4-(1-hydroxy-1-methylethyl)-3-pyrrolidineacetic Acid δ-Lactone (4). A solution of 213 mg (1 mmol) of kainic acid (**1**) in 8 mL of 10% H_2SO_4 was heated under reflux during 24 h, cooled to 0 °C, and neutralized with aqueous $Ba(OH)_2$. The $BaSO_4$ was filtered off, and the solution was evaporated. The residue was recrystallized from aqueous acetone to yield 128 mg (60%) of the lactone **4**:[18] ^1H NMR (D_2O) δ 1.42 (s, CH_3), 1.50 (s, CH_3), 2.60 (dd, *J* = 9 and 23 Hz, one of CH_2CO), 2.82 (ddd, *J* = 8, 8, and 12 Hz, H_4), 3.1–3.4 (m, H_3, one of H_5 and one of CH_2CO), 3.76 (dd, *J* = 8 and 12 Hz, one of H_5), 3.98 (d, *J* = 3.5 Hz, H_2).

[2*S*-(2α,3β,4β)]-2-Carboxy-4-[1-hydroxy-1-(iodomethyl)ethyl]-3-pyrrolidineacetic Acid δ-Lactone (6). To a stirred suspension of the *tert*-butyloxycarbonyl derivative **3** in 4 mL of water was added, at 0 °C, 210 mg (2.5 mmol) of $NaHCO_3$, followed by a solution of 254 mg (1 mmol) of I_2 and 365 mg (2.2 mmol) of KI in 6 mL of water. The resulting solution was kept overnight at 0 °C and then acidified to pH 2 with $KHSO_4$ and extracted with chloroform. The organic solution was washed consecutively with 10% aqueous Na_2SO_3 and water, dried, and evaporated to give 420 mg of the N-protected iodo lactone **5** as a mixture of two isomers (by TLC). Preparative TLC on silica gel plates (hexane–ethyl acetate–acetic acid, 50:50:1, v/v) gave in the upper band 121 mg of isomer A of **5**[19] and in the lower band 145 mg of isomer B of **5**.[19] Compound **5A** was treated with 98% formic acid during 5 h to give, after evaporation and trituration with ether, 84 mg (25% from **3**) of **isomer A** of the **iodo lactone 6**: mp 208–209 °C dec (colorless prisms from water); $[\alpha]^{22}_D$ 5° (*c* 0.1, H_2O); ^1H NMR (D_2O) δ 1.55 (s, CH_3), 2.62 (dd, *J* = 5.1 and 17.6 Hz, one of CH_2CO), 3.1–3.3 (m, H_3, H_4, and one of CH_2CO), 3.36 (t, *J* = 11.8, one of H_5), 3.61 (AB q, *J* = 11.6 Hz, CH_2I), 3.82 (dd, *J* = 8 and 11.8 Hz, one of H_5), 4.03 (d, *J* = 3.6 Hz, H_2). Anal. ($C_{10}H_{14}INO_4$) C, H, I, N. A similar treatment of the isomer **5B** yielded 102 mg (30% from **3**) of **isomer B** of the **iodo lactone 6** as colorless prisms: mp 207 °C dec; $[\alpha]^{22}_D$ −16° (*c* 0.1, H_2O); ^1H NMR (D_2O) δ 1.66 (s, CH_3), 2.60 (dd, *J* = 3.4 and 17.3 Hz, one of CH_2CO), 3.0–3.1 (m, H_4), 3.18–3.33 (m, H_3, one of H_5 and one of CH_2CO), 3.50 (AB q, *J* = 11 Hz, CH_2I), 3.32 (dd, *J* = 7.8 and 12 Hz, one of H_5), 4.03 (d, *J* = 3.4 Hz, H_2). Anal. ($C_{10}H_{14}INO_4$) C, H, I, N.

[2*S*-(2α,3β,4β)]-2-Carboxy-4-[1-hydroxy-1-(hydroxymethyl)ethyl]-3-pyrrolidineacetic Acid δ-Lactone (7). (a) Iodolactonization of 470 mg (1.5 mmol) of the *tert*-butyloxycarbonyl derivative **3** as described above for the preparation of **6** gave 630 mg of a mixture of the two isomers of the N-protected iodo lactone **5**. Treatment with ethereal diazomethane at 0 °C, followed by chromatography of the product on silica gel plates (hexane–ethyl acetate, 2:1, v/v), afforded in the less polar band 260 mg of the methyl ester of **5A**. High-resolution MS Calcd for $C_{14}H_{21}INO_4$ [$(M - CO_2Me)^+$]: *m/e* 394.0514. Found: *m/e* 394.0530. The more polar band consisted of 316 mg of the methyl ester of **5B**. High-resolution MS Calcd for $C_{14}H_{21}INO_4$ [$(M - CO_2Me)^+$]: *m/e* 394.0514. Found: *m/e* 394.0532. The ester of **5A** was dissolved in 1.5 mL of acetone and 1.8 mL of 1 N NaOH. After 90 min, the solution was cooled to 0 °C and acidified to pH 2 with 1 N HCl. The acetone was evaporated, and the aqueous solution was extracted with ethyl acetate. The organic solution was washed with water, dried, and evaporated. A solution of the residue (which probably consisted of isomer A of the N-protected hydroxy lactone **10**) in 5 mL of acetic acid and 1.5 mL of water was kept at 100 °C during 3 h and then evaporated to give, after trituration of the residue with ether, 109 mg (32% from **3**) of **isomer A** of the **hydroxy lactone 7**: mp 245–246 °C dec (colorless needles from aqueous acetone); $[\alpha]^{22}_D$ −17.2° (*c* 1, H_2O); ^1H NMR (D_2O) δ 1.50 (s, CH_3), 2.61 (dd, *J* = 4 and 17 Hz, one of CH_2CO), 2.80 (ddd, *J* = 8, 8 and 12 Hz, H_4), 3.2–3.4 (m, H_3, one of H_5 and one of CH_2CO), 3.68 (s, CH_2OH), 3.80 (dd, *J* = 8 and 13 Hz, one of H_5), 4.01 (d, *J* = 3 Hz, H_2). Anal. ($C_{10}H_{15}NO_5$) C, H, N. A similar treatment of the methyl ester of **5B** yielded 134 mg (39% from **3**) of **isomer B** of the **hydroxy lactone 7**: mp 248–249 °C (colorless prisms from aqueous acetone); $[\alpha]^{22}_D$ 9.8° (*c* 1, H_2O); ^1H NMR (D_2O) δ 1.37 (s, CH_3), 2.51 (dd, *J* = 8 and 18.5 Hz, one of CH_2CO), 2.80 (ddd, *J* = 8, 8, and 12 Hz, H_4), 3.11 (dd, *J* = 9 and 18.5 Hz, one of CH_2CO), 3.27 (m, H_3), 3.38 (t, *J* = 12 Hz, one of H_5), 3.66 (AB q, *J* = 12.5 Hz, CH_2OH), 3.82 (dd, *J* = 8 and 12 Hz, one of H_5), 4.06 (d, *J* = 3.2 Hz, H_2). Anal. ($C_{10}H_{15}NO_5$) C, H, N.

(b) To a solution of 0.5 g (2.35 mmol) of a kainic acid (**1**) in 50 mL of acetic acid was added 30 mL of 30% H_2O_2. After 48 h, the solution was evaporated (at 1 torr), and the residue was triturated with ether to give 0.53 g of a colorless solid consisting (by ^1H NMR) of 85% of the hydroxy lactone **7** as an approximately 1.3:1 mixture of isomers A and B. Purification and partial separation of the isomers were achieved by crystallization from aqueous acetone.

[2*S*-(2α,3β,4β)]-2-Carboxy-4-[1-hydroxy-1-[(phenylthio)methyl]ethyl]-3-pyrrolidineacetic Acid δ-Lactone (9). To a

(18) H. Morimoto, *J. Pharm. Soc. Jpn.*, **75**, 916 (1955).

(19) For high-resolution MS of the methyl ester of this compound, see the preparation of **7**.

stirred suspension of 313 mg (1 mmol) of the *tert*-butyloxycarbonyl derivative **3** in 6 mL of dry methylene chloride was added, under an argon atmosphere, 3 mL (2.15 mmol) of triethylamine. To the resulting solution was added, at −78 °C, a solution of 0.2 g (1.4 mmol) of benzenesulfenyl chloride in 2 mL of methylene chloride during 15 min. After being allowed to reach room temperature, the solution was evaporated, and the residue was taken up in a mixture of ethyl acetate and water. The stirred mixture was acidified to pH 2 with 1 N HCl. The aqueous phase was extracted with more ethyl acetate, and the combined organic extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel plates (hexane–ethyl acetate–acetic acid, 50:50:1, v/v) to give in the upper band 215 mg of isomer A of the N-protected phenylthio lactone **8**. High-resolution MS Calcd for $C_{21}H_{27}NO_6S$ (M^+): *m/e* 421.1559. Found: *m/e* 421.1513. From the lower band, 89 mg of the isomer **8B** was obtained. High-resolution MS Calcd for $C_{21}H_{27}NO_6S$ (M^+): *m/e* 421.1559. Found: *m/e* 421.1521. Treatment of **8A** with 5 mL of 98% formic acid during 5 h, evaporation, and trituration of the residue with ether furnished 154 mg (42% from **3**) of **isomer A** of the **phenylthio lactone 9·HCO$_2$H**: mp 236–237 °C dec (colorless powder from water); $[\alpha]^{22}_D$ 13.5° (*c* 0.5, AcOH); ^{1}H NMR (CD_3CO_2D) δ 1.48 (s, CH_3), 2.59 (dd, *J* = 6 and 18 Hz, one of CH_2CO), 3.0–3.1 (m, H_4 and one of CH_2CO), 3.2–3.35 (m, H_3), 3.36 (AB q, *J* = 14.5 Hz, CH_2S), 3.35–3.5 (m, one of H_5), 3.84 (dd, *J* = 8 and 12 Hz, one of H_5), 4.29 (s, H_2), 7.2–7.3 (m, 3 Ar H), 7.4–7.5 (m, 2 Ar H). Anal. ($C_{17}H_{21}NO_6S$) C, H, N, S. A similar treatment of **8B** afforded 64 mg (17% from **3**) of **isomer B** of the **phenylthio lactone 9·HCO$_2$H**: mp 266–267 °C dec (colorless powder from water); $[\alpha]^{22}_D$ −20° (*c* 0.5, AcOH); ^{1}H NMR (CD_3CO_2D) δ 1.59 (s, CH_3), 2.64 (dd, *J* = 5.4 and 20.2 Hz, one of CH_2CO), 3.03 (ddd, *J* = 8, 8 and 12 Hz, H_4), 3.1–3.25 (m, one of CH_2CO), 3.24 (AB q, *J* = 13.7 Hz, CH_2S), 3.25–3.5 (m, H_3 and one of H_5), 3.67 (dd, *J* = 8 and 12 Hz, one of H_5), 4.34 (s, H_2), 7.2–7.4 (m, 3 Ar H), 7.4–7.5 (m, 2 Ar H). Anal. ($C_{17}H_{21}NO_6S$) C, H, N, S.

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Registry No. 1, 487-79-6; 3, 75466-86-3; 4, 78166-25-3; 5 (isomer 1), 83220-92-2; 5 (isomer 2), 83289-36-5; 5 methyl ester (isomer 1), 83220-93-3; 5 methyl ester (isomer 2), 83289-39-8; 6 (isomer 1), 83289-37-6; 6 (isomer 2), 83289-38-7; 7 (isomer 1), 83289-40-1; 7 (isomer 2), 83289-41-2; 8 (isomer 1), 83220-94-4; 8 (isomer 2), 83289-42-3; 9 (isomer 1), 83289-43-4; 9 (isomer 2), 83289-44-5; 11 (X = I), 83220-95-5; 11 (X = OH), 83220-96-6; NMDA, 6384-92-5; L-Glu, 56-86-0; Quis, 52809-07-1.

Synthesis and Pharmacological Studies of 4,4-Disubstituted Piperidines: A New Class of Compounds with Potent Analgesic Properties

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A series of 4,4-disubstituted piperidines has been synthesized and evaluated for analgesic activity. Several of these analogues show analgesic potency comparable to morphine in the mouse writhing and tail-flick tests. A number of compounds exhibit high affinity for [^{3}H]naloxone binding sites in rat brain membranes. Among the most potent derivatives are compounds **15** and **48**. Although opiate-like, attempts to modify this activity with various substituents have failed to produce antagonistic properties. A few of these analogues also show marked long-lasting serotonin antagonism in the guinea pig serotonin toxicity test and the DL-5-hydroxytryptophan induced head-twitch model in the mouse.

The search for a potent, nonaddictive analgesic with emphasis upon agonist–antagonist activity has been in progress for many years. Due to the interesting analgesic properties of 4-substituted piperidines, such as meperidine,[1-3] ketobemidone,[4,5] and fentanyl,[6-8] attempts were made to find long-acting, strong analgesics that do not cause respiratory depression or physical dependence. Although significant dissociation of analgesic and dependence liability has not been attained for this type of compound, previous work by Küehnis and co-workers[9] on 1-substituted 4-(1-acetylalkyl)-4-hydroxypiperidines stimulated our research interest. We describe here the synthesis and biological activities of a similar class of 4,4-disubstituted piperidines,[10] whose substituents are illustrated in Table I.

In order to convert potent narcotic agonists into antagonists, it has been generally considered necessary to use allyl, propyl, or cyclopropylmethyl groups[11-14] at the basic nitrogen. Although this type of substitution has failed to produce antagonistic properties in the piperidine series, e.g., when the *N*-methyl group of meperidine[15-17] was replaced with an allyl side chain, it was thought of interest to investigate whether similar effects would result following

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