with $CHCl_3$. The organic solution was dried (Na_2CO_3) and evaporated to dryness to give **18** (8.2 g, 98%): mp 121 °C. Anal. ($C_{16}H_{12}N_2O$) C, H, N.

β-Methyl-2-phenyl-6-benzoxazoleethylamine Hemisuccinate (19). Compound **18** was reduced as described for **10a** and the hemisuccinate derivative was prepared. This was crystallized from EtOH–DMF to give pure **19** (4.9 g, 39%): mp 205 °C. Anal. ($C_{18}H_{19}N_2O_3$) C, H, N.

4-Amino-3-bromo-α-methylbenzeneacetonitrile (21). 2,4,4,6-Tetrabromo-2,5-cyclohexadienone[7] (103 g, 0.31 mol) was slowly added to a stirred solution of 4-aminophenyl-α-methylacetonitrile[8] (**20**) (36.5 g, 0.25 mol) in CH_2Cl_2 (650 mL) at −30 °C. When the addition was complete the mixture was stirred for a further 1 h at −20 °C. When the solution reached ambient temperature, it was washed with cold 2 N NaOH, dried (Na_2CO_3), and evaporated to give **21** (51.5 g, 92%) as an oil: NMR (aryl) δ 6.65 (d, 5-H), 7.00 (dd, 6-H), 7.29 (d, 2-H). Anal. ($C_9H_9BrN_2$) C, H, Br, N.

3-Bromo-α-methyl-4-nitrobenzeneacetonitrile (22). Trifluoroacetic anhydride (78 mL) was added to a stirred suspension of 90% H_2O_2 (12.3 mL, 0.3 mol) in CH_2Cl_2 (300 mL) at 0 °C, and the stirred mixture was cooled in Drykold–acetone. After 5 min, a solution of **21** (22.5 g, 0.1 mol) in CH_2Cl_2 (30 mL) was slowly added so that gentle reflux conditions were maintained. The solution was then heated under reflux for 1 h, cooled, and washed with ice–H_2O and an aqueous solution of Na_2CO_3. The dried (Na_2CO_3) solution was evaporated to give **22** (24 g, 94%) as a yellow oil: NMR (aryl) δ 7.55 (dd, 6-H), 7.79 (d, 2-H), 7.90 (d, 5-H). Anal. ($C_9H_7BrN_2O_2$) C, H, Br, N.

Diethyl 4-Amino-α-methylphenylmalonate (27). The reaction of 4-fluoronitrobenzene (**25**) with the anion of diethyl methylmalonate was carried out as described for the preparation of **32a**. Impure **26** was isolated as an oil (about 80% pure by NMR analysis). A solution of this material in EtOH (100 mL) containing 10% Pd/C (1 g) was hydrogenated at 60 psi for 4 h at room temperature. The solution was filtered and the solvent was removed in vacuo. The residual oil was distilled in vacuo to yield the amine **27** (88.3 g, 32% over two stages), bp 156–161 °C (0.3 mm), as a yellow oil. The amine was characterized as its acetyl derivative in the following way. Acetyl chloride (3.87 g) was added to a stirred mixture of some of the amine (13.05 g) and $KHCO_3$ (4.95 g) in toluene (50 mL). The mixture was stirred under reflux for 1.5 h and filtered. Evaporation of the filtrate gave an oil which solidified on standing. This was pure diethyl 4-acetylamino-α-methylphenylmalonate (14.8 g, 98%): mp 74–75 °C. Anal. ($C_{16}H_{21}NO_5$) C, H, N.

Diethyl 3-Bromo-α-methyl-4-nitrophenylmalonate (29). 2,4,4,6-Tetrabromo-2,5-cyclohexadienone[7] (31 g, 0.094 mol) was slowly added to a stirred solution of **27** (20 g, 0.08 mol) in CH_2Cl_2 (300 mL) at room temperature. After being stirred for 2 h, the solution was washed with 2 N NaOH and H_2O, dried (Na_2CO_3), and evaporated to give slightly impure **28** (22.6 g, 86%). A solution of this product (3 g) in CH_2Cl_2 (3 mL) was added in one portion to a stirred solution of 30% H_2O_2 (8 mL), 0.2 mol) in trifluoracetic anhydride (55 mL). The solution was stirred for 3 h, washed with H_2O and 2 N NaOH, dried (Na_2CO_3), and evaporated to dryness to give **29** as an oil (2.2 g, 68%): NMR (aryl) δ 7.48 (dd, 6-H), 7.77 (d, 2-H), 7.83 (d, 5-H). Anal. ($C_{14}H_{16}BrNO_6$) C, H, Br, N.

Attempted Preparation of Compounds 24 and 32. Attempted displacements of halogen from compounds **22**, **23** (slightly impure by NMR analysis, prepared from **22** by hydrolysis as for **9**), **29**, and **30**[9] were unsuccessful under the following conditions: (i) reaction of the compounds with hot or cold solutions of NaOH in H_2O and also in the presence of DMF; (ii) with NaOAc in AcOH and H_2O; (iii) with NaOMe and NaOEt in MeOH, EtOH, Me_2SO, and HMPT at various temperatures and concentrations; (iv) with KO-*t*-Bu in *t*-BuOH.

Acknowledgment. We wish to thank our colleagues in the Biology and Physical Organic Departments of the Lilly Research Centre for providing the biological and spectral data.

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3,4-Methylenedioxyphenyl-, Isopropylidenedioxyphenyl-, and Benzyl-Substituted Chiral 2-Aminosuccinimides and 3-Aminopyrrolidines. Stereoselective Investigations of Potential Anti-Parkinsonian, Antipsychotic, and Anticonvulsant Activities[1]

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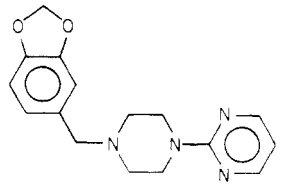
The chiral title compounds **2**–**11** were assessed for their potential anti-Parkinsonian, antipsychotic, and anticonvulsant properties. The most striking differences in the biological activity of enantiomeric pairs were noted for D-(*R*)-2-amino-*N*-(3,4-methylenedioxyphenyl)succinimide hydrochloride (**2**) vs. L-(*S*)-**3** and D-(*R*)-2-amino-*N*-(3,4-isopropylidenedioxyphenyl)succinimide (**4**) vs. L-(*S*)-**5**. D-(*R*)-**2** partially attenuated amphetamine-induced stereotyped behavior, whereas D-(*R*)-**4** antagonized oxotremorine-induced tremors. Their respective enantiomorphs were inactive in these tests. No differences in anticonvulsant potency of enantiomeric pairs were observed. The stereoselective actions of D-(*R*)-**2** and **4** were rationalized on the basis of the presence or absence of *gem*-dimethyl functions in isopropylidenedioxy vs. methylenedioxy groups; the data seem to indicate that these methyl groups influence selective receptor site interaction in the D-(*R*) series.

Piribedil (**1**), like apomorphine, is thought to act by direct stimulation of central dopaminergic receptors but possesses a more prolonged duration of action.[2,3] Whereas this compound exhibits anti-Parkinsonian activity, it is less

effective clinically for the treatment of this disease than L-Dopa.[4-6] Piribedil and apomorphine do not possess full agonistic activity at dopamine receptors; it seems likely that their potential antagonistic properties reduce their clinical utility in the treatment of Parkinson's disease.[6] Hence, there exists the need to develop pure dopaminergic agonists devoid of antagonist activity. This report describes the synthesis and biological properties of mainly basic amino-substituted chiral succinimides (**2–9**) and pyrrolidines (**10, 11**) having phenyl, methylenedioxyphenyl, or isopropylidinedioxyphenyl groups. Piribedil contains the methylenedioxyphenyl function bonded to a basic heterocyclic side chain. Therefore, we investigated analogues **2–11** for their potential anti-Parkinsonian activity in order to provide leads for the development of new heterocycles exhibiting such important properties. Further, compounds **2–11** are readily synthesized from aspartic acid of known absolute configuration thereby permitting pharmacological evaluation of enantiomers which may be selective in their action. In order to explore their selective activity, these compounds were also assessed for their anticonvulsant and neuroleptic properties. Owing to their structural relationship to the previously reported chiral succinimide and glutarimide anticonvulsants[7,8] and the potentially neuroleptic chiral pyrrolidino-substituted 10,11-dihydrodibenzo[b,f]thiepins,[9] such activities might also be anticipated for some of these compounds.



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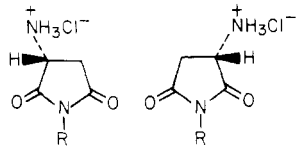
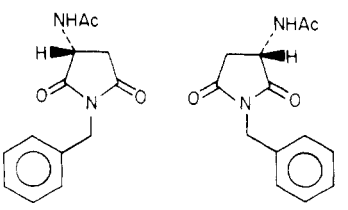
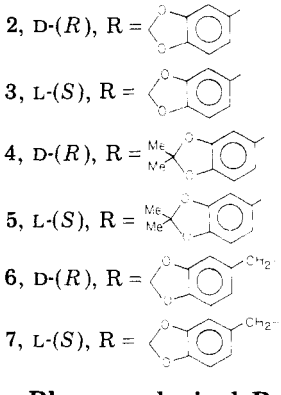


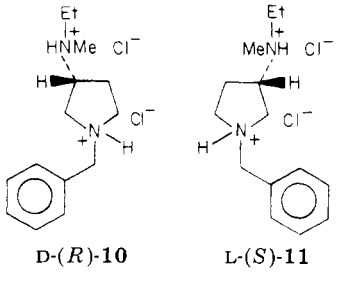
D-(*R*) L-(*S*)



D-(*R*)-8 L-(*S*)-9



2, D-(*R*), R =
3, L-(*S*), R =
4, D-(*R*), R =
5, L-(*S*), R =
6, D-(*R*), R =
7, L-(*S*), R =



D-(*R*)-10 L-(*S*)-11

Pharmacological Results. In general the median neurotoxic dose (TD_{50}) and time of peak activity, as measured by impairment of rotarod performance, were similar for the various enantiomorphic compounds, although in all cases, the D series was more active (Table I). For enantiomorphs D-(*R*)-**2** and L-(*S*)-**3**, at doses of 3.70–5.55 mmol/kg, ataxia, increased excitability, clonic seizure-like activity, and death were observed in about 60% of the animals. For enantiomorphs D-(*R*)-**4** and L-(*S*)-**5** at doses of 2.68 mmol/kg and greater, there was sedation, loss of righting reflex, and finally death, following a clonic seizure-like activity. At doses up to 2.81 mmol/kg, enantiomorphs D-(*R*)-**6** and L-(*S*)-**7** exhibited no gross behavioral effects. At toxic doses (6.1 mmol/kg and greater), enantiomorphs D-(*R*)-**8** and L-(*S*)-**9** produced twitching, increased excitability to touch, occasional clonic seizure-like movements, and loss of righting reflex lasting for 2–4 h. For enantiomorphs D-(*R*)-**10** and L-(*S*)-**11** at doses of 0.60–0.69 mmol/kg, respiratory depression, clonic seizure-like activity, ataxia, twitching, loss of righting reflex, and death were noted in 15–20 min; lower doses failed to impair rotarod performance.

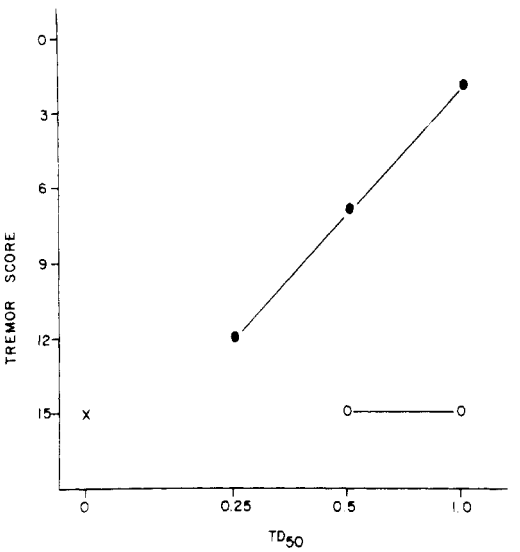


Figure 1. Effects of **4** and **5** on oxotremorine-induced tremors in mice. Animals were pretreated ip with saline (0) or test compounds (0.25–1 TD_{50}) 30 min prior to oxotremorine (1 mg/kg ip). The intensity of tremors was scored with 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The values represent the total score for five animals in each test group. × = saline; ● = 4; ○ = 5.

In studies designed to assess the anticonvulsant properties of these compounds, analogues **4–9** were effective against maximal electroshock seizures (MES); analogues D-(*R*)-**8** and L-(*S*)-**9**, having the *N*-benzyl substituent, were most potent. Employing a 0.5 TD_{50} dose, analogues **4–6** conferred protection against pentylenetetrazole-induced minimal (clonic) and maximal (tonic-clonic) seizures with L-(*S*)-**7** and D-(*R*)-**8** active against minimal seizures. Analogue D-(*R*)-**10** lowered the maximal seizure threshold to pentylenetetrazole by 56% (Table I).

In experiments evaluating the potential anti-Parkinsonian activity of these compounds, D-(*R*)-**2** and L-(*S*)-**3** antagonized oxotremorine-induced diarrhea and salivation by 40–60% but did not alter tremors at their respective TD_{50} doses; D-(*R*)-**4** and L-(*S*)-**5**, by contrast, did not reduce diarrhea and salivation, yet exhibited marked differences in their ability to antagonize tremors. Whereas L-(*S*)-**5** was inactive at doses up to the TD_{50} dose, its enantiomorph **4** reduced the severity of tremors in a dose-dependent manner (Figure 1).

Compounds were tested at the TD_{50} dose for their ability to antagonize (+)-amphetamine-induced stereotyped behavior, a measure of potential antipsychotic activity. With the exception of D-(*R*)-**2** (Figure 2), all other compounds were inactive in this test.

Discussion

The most striking difference in the activity of stereoisomers was observed for the chiral isopropylidenedioxyphenylsuccinimides D-(*R*)-**4** and L-(*S*)-**5** with regard to their potential anti-Parkinsonian activity. Whereas **5** failed

Table I. Anticonvulsant Activity of Chiral 2-Aminosuccinimides and 3-Aminopyrrolidine Derivatives

Compd	Time of peak effect, min	TD_{50},[a] mmol/kg[b]	Maximal electroshock seizures (MES)			Seizure (iv pentylenetetrazole), threshold ratio	
			ED_{50}, mmol/kg[b]	PT = TD_{50}/ED_{50}[b,c]	Dose	Minimal[b]	Maximal[b]
Diphenylhydantoin sodium salt	45	0.22 (0.18-0.26)	0.022 (0.017-0.028)	10.00 (7.46-13.40)	$0.5TD_{50}$	1.07 (0.90-1.26)	2.08 (1.85-2.33)
Trimethadione	5	3.98 (3.16-5.01)	3.72 (3.29-4.20)	1.07 (0.78-1.43)	$0.5TD_{50}$	2.05 (1.72-2.44)	2.25 (2.00-2.53)
Ethosuximide	5	2.32 (1.99-2.72)	Ineffective to 2.32	c	$0.5TD_{50}$	1.34 (1.18-1.54)	1.71 (1.41-2.03)
D-(*R*)-2	45-60	3.33 (2.81-3.96)	Ineffective to 3.33	c	$0.5TD_{50}$	1.03 (0.89-1.20)	0.75 (0.59-0.98)
L-(*S*)-3	45-60	5.04 (4.20-6.03)	Ineffective to 5.04	c	$0.5TD_{50}$	1.08 (0.93-1.24)	0.92 (0.73-1.21)
D-(*R*)-4	15-30	0.96 (0.91-1.00)	0.57 (0.43-0.75)	1.68	$0.5TD_{50}$	1.28 (1.13-1.45)	1.66 (1.27-2.20)
L-(*S*)-5	30-45	1.22 (1.12-1.33)	0.84 (0.62-1.12)	1.45	$0.5TD_{50}$	1.36 (1.14-1.60)	1.34 (1.05-1.83)
D-(*R*)-6	15-30	1.83 (1.63-2.05)	0.72 (0.57-0.90)	2.54	$0.5TD_{50}$	1.61 (1.45-1.79)	1.18 (1.02-1.39)
L-(*S*)-7	15-30	2.00 (1.45-2.69)	0.70 (0.57-0.87)	2.85	$0.5TD_{50}$	1.54 (1.31-1.79)	1.09 (0.96-1.26)
D-(*R*)-8	30-45	4.76 (3.84-5.89)	1.46 (1.28-1.67)	3.25	$0.5TD_{50}$	1.36 (1.16-1.58)	0.85 (0.71-1.01)
L-(*S*)-9	30-45	5.28 (4.71-5.93)	1.20 (0.87-1.66)	4.41	$0.5TD_{50}$	1.06 (0.90-1.23)	1.11 (0.90-1.36)
D-(*R*)-10	15	d	Ineffective to 0.34	c	0.34 mmol/kg	0.96 (0.88-1.05)	0.44 (0.37-0.54)
L-(*S*)-11	15	d	Ineffective to 0.34	c	0.34 mmol/kg	0.87 (0.79-0.97)	0.77 (0.57-1.03)

[a] Median, neurotoxic dose, as determined by impairment of rotarod performance. All compounds were administered intraperitoneally to 6-12 CD-1 male mice. [b] Numbers in parentheses refer to 95% confidence limits as calculated by the method of Litchfield and Wilcoxon.[26] [c] PI (protective index) could not be calculated because drug was insufficiently active to provide 50% protection (ED_{50}). [d] The LD_{40} and LD_{80} were 0.60 and 0.69 mmol/kg, respectively, with death occurring within 15-20 min; no neurotoxicity, as measured by impairment of rotarod performance, was observed.

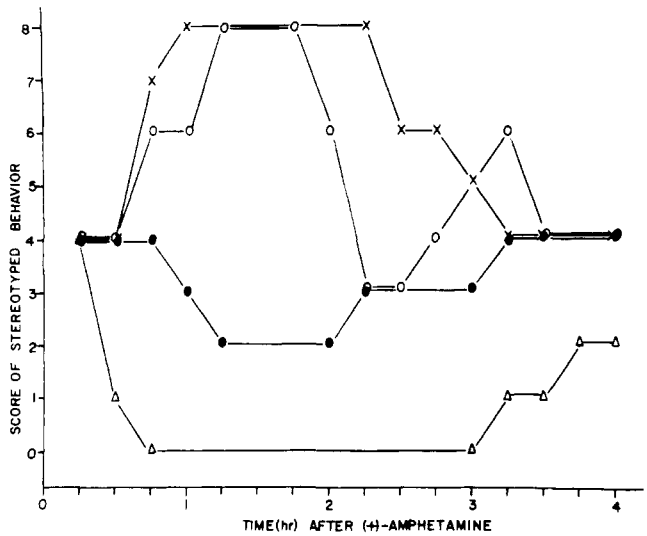
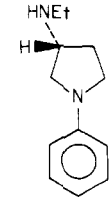


Figure 2. Effects of 2 and 3 on (+)-amphetamine-induced stereotyped behavior in rats. Animals were injected with (+)-amphetamine (10 mg/kg) and administered saline, chlorpromazine (7.5 mg/kg), or test compounds (1 TD_{50}) 15 min later. The intensity of stereotyped behavior was scored with 0 = absent, 1 = hyperactive, 2 = stereotyped behavior as defined in the Experimental Section. The values represent the total score for four animals in each test group. × = saline; Δ = chlorpromazine; ● = 2; ○ = 3.

to antagonize oxotremorine-induced tremors at doses up to the TD_{50} dose, its enantiomorph 4 showed a dose-dependent reduction in tremors at doses of 0.125–1 TD_{50}. It is unlikely that this effect is due to anticholinergic activity; doses of 4 up to the TD_{50} dose failed to reduce oxotremorine-induced salivation and diarrhea. Invoking an anticholinergic mechanism is also not warranted on structural grounds. Analogues containing only one aromatic ring separated from a basic amino group by three to four atoms, such as D-(*R*)-3-ethylamino-1-phenylpyrrolidine (12), are weak (pA_2 = 3.5–4.0) antagonists for acetylcholine in vitro.[10,11] Potent anticholinergic drugs have tertiary or quaternary amino functions generally separated by two to three carbons from diaryl-substituted acetates, related tricyclic groups, arylhydroxymethyl acetates, or arylcycloalkyl-substituted acetates.[12] Related diaryl- or tricyclic antihistamines also are more potent than 12 as cholinergic blocking agents.[13] Analogues 2–11 are more closely related to 12 and, therefore, should be expected to have only weak anticholinergic activity. The fact that 4, and none of the other analogues, antagonizes oxotremorine-induced tremors suggests that this compound is exerting its action by mechanisms independent of its predictably weak anticholinergic properties.



D-(*R*)-12

From this limited series it would appear that the *gem*-dimethyl groups of the isopropylidenedioxy function have a marked effect on stereoselective antagonism of oxotremorine-induced tremors; i.e., whereas D-(*R*)-4 was active in this test, the related demethyl isomer, D-(*R*)-2, was inactive. Most recent results with piribedil do not support the hypothesis that dopaminergic stimulation induced by this drug is due to the formation and accumulation of its catechol metabolite in the striatum.[14] By

analogy, it might also be inferred that the stereoselective activity of D-(*R*)-**4** is likely not due to the preferential stereoselective metabolism of the D-(*R*) enantiomorph affording an active metabolite, but further work is necessary to substantiate this hypothesis. It seems more likely that the *gem*-dimethyl functions are involved in receptor site interaction; invoking the hypothesis that the *gem*-dimethyl groups increase lipophilicity, thereby allowing for greater CNS penetration is not warranted, because the demethyl isomer, D-(*R*)-**2**, which is inactive in this test, must enter the CNS where it decreases amphetamine-induced stereotyped behavior. The lack of activity observed for other basic (**6**, **7**, **10**, **11**) and neutral (**8**,**9**) analogues lends further support to the hypothesis that *gem*-dimethyl functions influence receptor interaction of D-(*R*)-**4**.

The only evidence for a stereoselective difference in potential antipsychotic activity was observed between enantiomorphs D-(*R*)-**2** and L-(*S*)-**3**. Whereas **3** was devoid of activity in its ability to antagonize amphetamine-induced stereotyped behavior, enantiomorph **2** partially attenuated these effects. Although the potency of **2** did not compare favorably with that of chlorpromazine, the stereoselective differences in activity observed suggest that **2** may serve as a lead compound for future drug design, especially when analyzed in light of the stereoselective properties of butaclamol,[15,16] octoclothepin,[17] and the four chiral isomers [3′*S*, 10*S*; 3′*R*, 10*R*; 3′*S*, 10*R*; 3′*R*, 10*S*] of 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[*b*,*f*]thiepin.[18]

Of particular interest is the observation that insertion of *gem*-dimethyl groups into D-(*R*)-**2** affords D-(*R*)-**4** with loss of activity in this test of potential antipsychotic activity. Additionally, insertion of a methylene function between the methylenedioxyphenyl ring and the imide nitrogen yields an inactive compound [D-(*R*)-**6**]. Insertion of methyl and methylene groups is expected to increase lipophilicity, but there is no correlation with activity in this regard. Rather, it would appear that the presence or absence of the *gem*-dimethyl functions in this series markedly influences binding to different receptors in the CNS. The lack of activity for enantiomorphs **3**–**11** in this test further supports the selective properties of D-(*R*)-**2** in this model psychosis.[19,20] In 1956 Pfeiffer[21] noted that high ratios for the activities of stereoisomers are found for highly active drugs and low ratios for weakly active compounds. This rule was modified by Ariens[22] who pointed out that small ratios may be found in highly active compounds if the center of asymmetry is located in a less essential part of the molecule. Although D-(*R*)-**2** and D-(*R*)-**4** cannot be construed as being "highly active", the potency differences between these isomers and their respective enantiomers L-(*S*)-**3** and L-(*S*)-**5** are marked. These data suggest that the chiral center is located in an essential part of the structure and that selective pharmacological activity in this series may be altered by the presence (or absence) of *gem*-dimethyl functions far removed from the chiral center. Since the *gem*-dimethyl functions lie in a plane perpendicular to the plane of the benzodioxole ring, steric influences on analogue–receptor site interaction may be responsible for modification of their selective and stereochemically dependent pharmacological activities.

On the basis of general neurotoxicity studies, D-(*R*) isomers were generally more active than their L-(*S*) enantiomorphs, but no consistent pattern was observed regarding the relative activity of these enantiomorphs in the anticonvulsant studies (Table I). D-(*R*)-**2** lowered the maximal seizure threshold but had no effect on minimal seizure threshold; D-(*R*)-**4** raised both minimal and maximal seizure threshold, but neither D-(*R*)-**2** nor **4** was particularly efficacious in these anticonvulsant tests. Although no stereoselective differences in anticonvulsant activity were observed for neutral enantiomorphic imides D-(*R*)-**8** and L-(*S*)-**9**, both compounds blocked MES, a measure of potential anticonvulsant agents effective in the treatment of grand mal epilepsy. These data are consistent with previous reports from this laboratory, showing that related D-(*R*)-imides were generally more potent than or equipotent to the L-(*S*) isomer in activity when assessed for their anticonvulsant properties.[7,8]

Experimental Section

Chemistry. Melting points were determined using a calibrated Thomas-Hoover melting point apparatus. IR spectra were determined, utilizing a Perkin-Elmer 257 spectrophotometer. Optical rotations were taken on a Perkin-Elmer Model 241 digital polarimeter. NMR spectra were recorded, using the Varian A-60A spectrometer. Although spectral data are only listed for selected compounds, IR and NMR spectra were consistent with all assigned structures. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

General Method for the Synthesis of D-(*R*)- and L-(*S*)-2-Amino-*N*-(3,4-methylenedioxy- and 3,4-isopropylidenedioxyphenyl)succinimide Hydrochlorides (2–5). D-(*R*)- or L-(*S*)-*N*-*tert*-butyloxycarbonylaspartic acid (2.32 g, 0.01 mol), prepared according to the method of Grzonka and Lammek,[23] was stirred with 150 mL of Ac_2O until all solids were dissolved (ca. 1 h) and the mixture was subsequently concentrated under reduced pressure. Dry toluene (100 mL) was added, and the residual HOAc and Ac_2O were removed by azeotropic distillation on a rotary evaportor. Azeotropic distillation was repeated two additional times, and the resulting aspartic anhydride was dissolved in 150 mL of dry THF. To this solution was added either 3,4-isopropylidenedioxyaniline (1.65 g, 0.01 mol) or 3,4-methylenedioxyaniline (1.37 g, 0.01 mol) and the solution was stirred at room temperature overnight. The THF was removed under reduced pressure and 150 mL of Ac_2O was added to the residual anilide. The slurry was heated on a steam bath under a stream of dry N_2 until all solids dissolved. The AcOH and Ac_2O were removed under reduced pressure, and trace amounts of AcOH and Ac_2O were removed by azeotropic distillation as previously described. The residual imide was dissolved in THF (150 mL) and the solution was saturated with gaseous HCl. Stirring overnight at room temperature resulted in Boc cleavage; the crude imide hydrochloride salt was isolated by solvent removal under reduced pressure. Recrystallization from 1:4 MeOH–dioxane afforded the pure HCl salts (**2**–**5**) in yields which ranged between 71 and 94%. D-(*R*)-**2**: mp 243–245 °C; $[\alpha]^{25}_{578}$ +24.8°. L-(*S*)-**3**: mp 240–241 °C; $[\alpha]^{25}_{578}$ −25.6°. Anal. ($C_{11}H_{11}N_2O_4Cl$) C, H, N. D-(*R*)-**4**: mp 232–233 °C; $[\alpha]^{25}_{578}$ +23.1°. L-(*S*)-**5**: mp 232–233 °C; $[\alpha]^{25}_{578}$ −21.1°. Anal. ($C_{13}H_{15}N_2O_4Cl$) C, H, N.

D-(*R*)- and L-(*S*)-2-Amino-*N*-piperonylsuccinimide Hydrochlorides (6 and 7). The synthesis for D-(*R*)-**6** and L-(*S*)-**7** was identical with the preparation of **2**–**5** except that piperonylamine was employed and the crude imide HCl product was washed with absolute EtOH and recrystallized from 1:4 MeOH–Et_2O or 1:10 EtOH–EtOAc affording yields of approximately 50%. Specific rotations were too small to be accurately determined. D-(*R*)-**6**: mp 227–228 °C. L-(*S*)-**7**: mp 228–229 °C. Anal. ($C_{12}H_{13}N_2O_4Cl$) C, H, N.

D-(*R*)- and L-(*S*)-*N*-acetyl-2-amino-*N*-benzylsuccinimides (8 and 9) were prepared according to a modification of the method of Witiak et al.[7] in which benzylamine (2.85 g, 0.03 mol) and D-(*R*)- or L-(*S*)-*N*-acetylaspartic anhydride (4.7 g, 0.03 mol) and absolute EtOH (200 mL) were stirred overnight, while being protected from moisture. The solvent was removed under reduced pressure and the residue was dried for 2 h at room temperature under reduced pressure. The residue was dissolved in 200 mL of Ac_2O and heated on a steam bath for 4 h, while being protected from moisture. The AcOH–Ac_2O were removed under reduced pressure followed by azeotropic distillation with toluene. The residue was crystallized from MeOH–Et_2O affording 4.4 g (60%) of either D-(*R*)-**8** (mp 171–175 °C; $[\alpha]^{25}_{365}$ +3.8°) or L-(*S*)-**9** [mp 171–175 °C; $[\alpha]^{25}_{365}$

4.0°. Anal. ($C_{13}H_{14}N_2O_3$) C, H, N].

Conversion of D-(*R*)- and L-(*S*)-Imides (8 and 9) to Their Corresponding Secondary Amines [D-(*R*)- and L-(*S*)-*N*-Benzyl-3-ethylaminopyrrolidines], Precursors to D-(*R*)-10 and L-(*S*)-11, Respectively. Imides D-(*R*)-8 or L-(*S*)-9 (10.0 g, 0.041 mol) were suspended in dry THF (150 mL). To the stirred suspension, protected from moisture, was added slowly 4.65 g (1.23 mol) of $LiAlH_4$ in 100 mL of dry THF. After the addition was completed (ca. 0.5 h) the solution was heated under reflux overnight, cooled, and treated successively with 10 mL of 5% NaOH solution and 15 mL of H_2O. The resulting precipitate was filtered and washed with THF. The combined filtrates were concentrated under reduced pressure, and the residue was dissolved in 100 mL of Et_2O. The Et_2O solution was washed with two portions of saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a yellow oil. Distillation afforded 7.2 g (85.4%) of the respective isomer: bp 83–85 °C (0.01 mm); NMR ($CDCl_3$) δ 1.06 (t, 3, J = 7 Hz, CH_2CH_3), 1.25–2.95 (m, 9, pyrrolidine H's + CH_2CH_3), 3.05–3.45 (m, 1, NH), 3.58 (s, 2, CH_2Ph), 7.26 (s, 5, ArH). Rotations were too small to measure.

D-(*R*)- and L-(*S*)-*N*-Benzyl-3-ethylmethylaminopyrrolidines (10 and 11, Respectively). The D-(*R*)-10 and L-(*S*)-11 isomers were prepared from their respective secondary amines (5.0 g, 0.245 mol) by dissolving in MeCN (75 mL) followed by addition of 9.5 g of 36% formalin solution. After stirring for 5 min, $NaBH_3CN$ (2.42 g, 0.385 mol) was added in a single portion. An exothermic reaction took place and an oil separated. HOAc was added after stirring for 2 h; the solution remained acidic (pH 5–6). The solvent was removed under reduced pressure, and 50 mL of 5% NaOH solution was added to the residue. The aqueous mixture was extracted with three portions of Et_2O (25 mL). The combined Et_2O layers were washed with two portions of saturated NaCl solution (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Distillation afforded 4.4 g (82%) of a yellow oil, bp 92–96 °C (0.04 mm), for each isomer. The dihydrochloride salts were prepared and recrystallized from MeOH–Me_2CO exhibiting mp 189–194 °C (hygroscopic). Rotations were too small to measure. NMR ($CDCl_3$) δ 1.01 (t, 3, J = 7 Hz, CH_2CH_3), 2.16 (s, 3, NCH_3), 1.48–3.30 (m, 9, pyrrolidine H's + CH_2CH_3), 3.56 (s, 2, CH_2Ph), 7.25 (s, 5, ArH). Anal. [$C_{14}H_{24}N_2Cl_2$, L-(*S*)-11 isomer] C, H, N.

Pharmacology. Male albino CD-1 mice (20–25 g) and Sprague–Dawley rats (200–250 g) were used in these studies. All test compounds except 8 and 9 were administered in aqueous solutions in a constant volume of 0.1 and 1.0 mL/100 g of body weight to rats and mice, respectively. Imides 8 and 9 were utilized in suspension as previously reported.[7,8]

The time of maximal central activity and the median neurotoxic dose (TD_{50} calculated as described below) were determined, employing the rotarod.[24] The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the mouse to remain on a horizontal rod rotating at 6 rpm for 1 min. All seizure studies were carried out at the time of peak activity.

Drugs were evaluated for their ability to prevent the hindlimb-extensor component of MES evoked by a supramaximal current (50-mA ac, 0.2-s stimulus duration) employing corneal electrodes. The ability of saline or the 0.5 TD_{50} dose of test compounds to modify minimal (clonic) and maximal (tonic–clonic) seizure threshold was determined using a timed iv infusion of pentylenetetrazole (0.5%, 0.51 mL/min, iv). The threshold ratio was calculated as the mean mg/kg of pentylenetetrazole required to produce seizures in drug-treated mice divided by the mg/kg of this convulsant required in saline-treated animals. Threshold ratios with corresponding 95% confidence intervals greater than 1.00 denote a significant increase in seizure threshold or a protective (anticonvulsant) effect.[25]

For the determination of the ED_{50} or TD_{50}, groups of 6–12 mice were given a range of doses of the test compounds until at least three points were established in the range of 10–90% seizure protection or minimal neurotoxicity. From a plot of the data, the respective ED_{50}, TD_{50}, 95% confidence intervals, and protective indices (PI = TD_{50}/ED_{50}) were calculated by the method of Litchfield and Wilcoxon.[26] The PI was not calculated for compounds providing less than 50% protection.

The ability of test compounds to antagonize oxotremorine (1.0 mg/kg) induced tremors, diarrhea, and salivation was conducted in groups of five mice to assess potential anti-Parkinsonian activity.[27]

Test compounds were evaluated for their ability to antagonize amphetamine-induced stereotyped behavior, a measure of potential antipsychotic activity.[28] Groups of four rats were injected with (+)-amphetamine (10 mg/kg, ip) and administered test compounds, chlorpromazine (7.5 mg/kg), or saline 15 min later. Observations were made at 15-min intervals for 4 h after amphetamine injection, and the stereotypic behavior of the animals was scored on a scale of 0–2:[16,28] score 0, normal behavior, characterized by occasional exploration of test cages, sniffing, grooming, and sleeping; score 1, excitation, characterized by constant sniffing and movement, with head elevated; score 2, stereotyped behavior, characterized by head down, gnawing and/or licking of the wires of the cage, forward motion absent, with occasional retropulsion. Values are expressed as the total score for four animals in each test group.

References and Notes

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