ture, such interactions could result in substantial neuronal damage. This aspect of DOQ activity has been suggested previously.[3]

Nucleophilic interactions of the *o*-quinone of [^{3}H]-NE, with macromolecules as proposed by Maguire et al. (see Figure 14, ref 4), are completely consonant with the present findings. Furthermore, the quantitative data herein suggest that interaction of the *o*-quinone with particulate bound sulfhydryl functions constitutes the principal reaction.

All of the competitive reactions discussed herein are concentration dependent. The relative concentrations of reducing agents and nucleophiles have wide variations in brain regions and are not accurately known, especially at the microenvironmental level (i.e., nerve endings, etc.). Nevertheless, the comparative rates measured here provide useful guidelines for predicting the fate of any DOQ produced in vivo. It is pertinent in this respect to note that rat whole brain levels for ascorbic acid and glutathione are approximately equal when expressed on a molar basis (AA, 2.6 μmol/g;[8] GSH, 3.3 μmol/g[9]).

Finally, it should be noted that enzymatically promoted hydroxylations or oxidative condensations to melanin-like products in certain discrete CNS regions are not precluded by the arguments presented here.

Acknowledgment. The support of this work via NSF Grant 32846X is gratefully acknowledged. The computer electrochemistry equipment was purchased through NIH Grant 5 RO1 NS 10042. R. L. McCreery acknowledges the support he received as a National Science Foundation Graduate Fellow. We are also indebted to Dr. R. Mark Wightman and Mr. Willie Chey for independent experimental verification of some of the rate measurements.

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8-Chloro-(*S*)- and -(*R*)-10-[(*S*)- and -(*R*)-3'-methylethylaminopyrrolidino]-10,11-dihydrodibenzo[*b*,*f*]thiepins. Synthesis and Pharmacological Studies[1]

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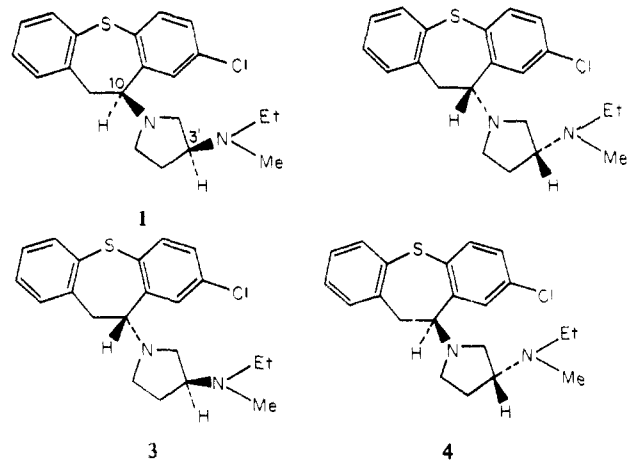
The synthesis for 8-chloro-(*S*)- and -(*R*)-10-[(*S*)- and -(*R*)-3'-methylethylaminopyrrolidino]-10,11-dihydrodibenzo[*b*,*f*]thiepins is presented. The absolute configuration at position 3' of the aminopyrrolidino side chain is known from synthesis and corresponds to the asymmetric carbon atom in (*S*)- or (*R*)-aspartic acid. The absolute configuration at C-10 of the dihydrodibenzo[*b*,*f*]thiepin ring system was deduced from ORD–CD analysis coupled with degradation of partially resolved (+)-8-chloro-10-amino-10,11-dihydrodibenzo[*b*,*f*]thiepin to (+)-(*S*)-1,2-diphenylethylamine. The four isomers were studied in mice for their ability to block conditioned avoidance responding, antagonize oxotremorine, and act as analgetics and anticonvulsants. These compounds were found to be nonselective antagonists of histamine, acetylcholine, and $BaCl_2$ in vitro. The compounds exerted effects similar to those of chlorpromazine. Stereoselective differences in activity between diastereoisomers, rather than between enantiomorphs, were generally observed.

Previous reports from this laboratory have considered the stereoselective biological properties of a number of enantiomorphic compounds synthesized from amino acids of known absolute configuration.[2-4] Among various D-(*R*)- and L-(*S*)-3-ethylaminopyrrolidino-substituted dihydrodibenzo[*b*,*f*]- and -[*b*,*e*]thiepins, xanthenes, and diphenylmethanes, the dihydrodibenzo[*b*,*f*]thiepin system seemed to warrant additional study for its potential antipsychotic activity.[4] To further explore stereostructure–activity relationships in a variety of biological systems we synthesized the four chiral isomers [3'*S*,10*S* (**1**); 3'*R*,10*R* (**2**); 3'*S*,10*R* (**3**); 3'*R*,10*S* (**4**)] of 8-chloro-10-(3'-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[*b*,*f*]thiepin. The absolute configuration at position 3' of the aminopyrrolidino function corresponds to the asymmetric carbon atom in (*S*)- or (*R*)-aspartic acid; i.e., (*S*)-aspartic acid served as a precursor for **1** and **3** while (*R*)-aspartic acid served as a precursor for **2** and **4**. Studies leading to the assignment of absolute configuration at position 10 in each of the four isomers (**1**–**4**) are described in this article. The evaluation of these isomers as potential drugs for the treatment of psychotic disorders, depression, Parkinson's disease, convulsive disorders, and pain was carried out. It was of particular interest to us to determine whether diastereoisomeric and/or enantiomorphic differences in activity existed.



1 **2** **3** **4**

Synthesis. Tricyclic ketone **5**[5] served as starting

† This paper is dedicated to my major professor, Dr. Edward Smissman. Professor Smissman was an inspiring teacher and a very close friend; he gave to me considerably more than a scientific education.

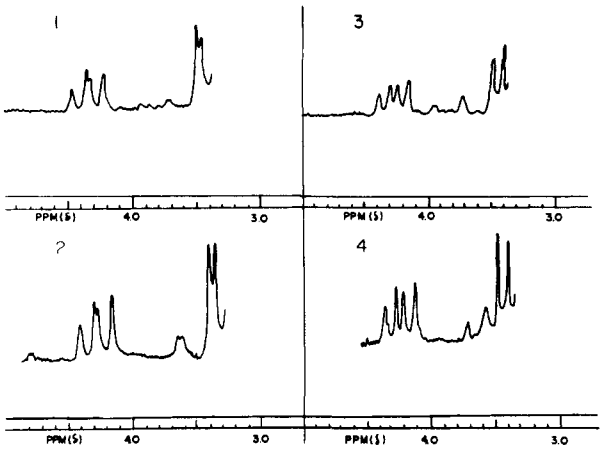


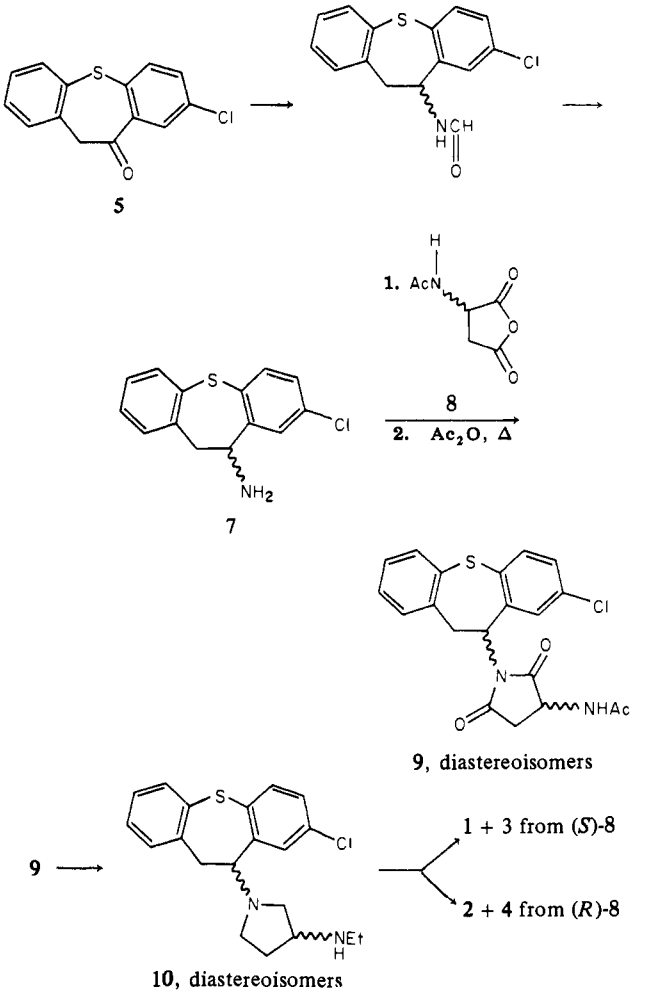
Figure 1. NMR spectra of the C-10 proton centered at approximately δ 4.2–4.3 for the four 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[b,f]thiepin isomers (1–4) in $CDCl_3$: 1 = 3′S,10S isomer; 2 = 3′R,10R isomer; 3 = 3′S,10R isomer, 4 = 3′R,10S isomer.

Table 1. Comparative Toxicological and Neuropsychopharmacological Activities of Dihydrodibenzo[b,f]thiepin Isomers 1–4[a]

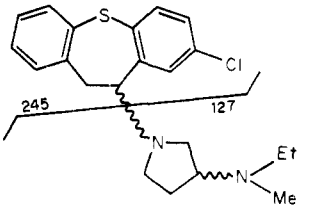
Compd	LD_{50}[b]	TD_{50}[c]	ED_{50}[d]
1	175 (158–194)	6.2 (4.2–9.1)	6.8 (4.1–11.3)
2	217 (200–236)	6.4 (4.5–9.1)	6.4 (3.9–10.4)
3	177 (166–189)	12.5 (10.7–14.6)	12.0 (8.8–16.3)
4	186 (160–216)	13.6 (10.8–17.2)	12.0 (7.3–19.8)

[a] All drugs were administered ip. Values represent the mean (95% confidence limits) as calculated by the method of Litchfield and Wilcoxon.[37] [b] Lethality was determined in groups of eight mice 24 hr after a single dose. [c] The neurotoxic dose was determined in groups of five mice at the time of peak effect utilizing a rotarod apparatus. [d] Median dose required to impair conditioned avoidance responding in groups of ten mice at the time of peak effect.

material and was converted to the formamido derivative **6** in 56% yield using the Wallach–Leuckart reaction.[6] Hydrolysis (concentrated HCl) followed by neutralization (NH_4OH) afforded racemic tricyclic amine **7** in 50% yield. Condensation of *dl*-**7** with *N*-acetyl-L-(*S*)- or -D-(*R*)-aspartic anhydride (**8**)[7] in absolute EtOH yielded a crude mixture of amides which was not purified but immediately converted to the diastereoisomeric mixture of imides (**9**) by heating in Ac_2O on a steam bath. Removal of the solvent followed by chromatography on silica gel afforded the diastereoisomeric mixture of imides **9** in 60% yield. Isomeric components of mixture **9** could not be separated as could not the diastereoisomeric amines **10** resulting from $LiAlH_4$ reduction of the imide mixture. The diastereoisomeric nature of mixture **10** was confirmed by NMR analysis after chromatography of the reaction mixture on silica gel by elution with EtOAc–MeOH–NH_4OH (90:8:2); the methyl proton resonance signals for **10** derived from either (*S*)-**8** or (*R*)-**8** existed as two triplets accounting for equal amounts of two diastereoisomers. Methylation of mixture **10** utilizing HCHO and $NaBH_3CN$[8] afforded the desired diastereoisomeric tertiary amines [**1** and **3** from (*S*)-**8**; **2** and **4** from (*R*)-**8**]. TLC [silica gel, EtOAc–MeOH–NH_4OH (90:9:1)] of the two mixtures of diastereoisomeric amines derived from either (*S*)-**8** or (*R*)-**8** afforded two distinct spots of nearly equal intensity and nearly identical R_f values. The two isomers, **1** and **3** [from (*S*)-**8**] or **2** and **4** [from (*R*)-**8**], of each mixture were separated by repeated column chromatography on silica gel using EtOAc–MeOH–NH_4OH (90:9:1) as the eluting solvent. The less polar isomers, **1** and **2**, of each mixture were proven to be enantiomorphic. As expected, the melting points of the HCl salts of **1** and **2** were identical as were the melting points of the hydrochloride salts of enantiomorphs **3** and **4**.



Structure Proof for Isomers 1–4. The mass spectra of the HCl salts of **1–4** were virtually identical and showed molecular ions at *m/e* 372. All four spectra exhibited major peaks attributable to ion fragments arising from cleavage of the pyrrolidino side chain (*m/e* 245 and 127).



The relative stereochemical relationship between isomers **1–4** was established by NMR and ORD–CD analysis. The NMR spectra for **1** and **2** were superimposable as were the spectra for **3** and **4**. Notable differences in the H-10 proton resonance signal for the **1–2** pair vs. the **3–4** pair were observed and are found in Figure 1. The resonance signal centered at δ 4.25 assigned to H-10 of **1** or **2** was split into a pair of doublets with apparent coupling constants of 8 and 6.5 Hz. For **3** or **4** the H-10 resonance signal was similarly split, but now the apparent couplings were 9 and 5.5 Hz. These data, coupled with ORD and CD analysis, confirmed the enantiomorphic nature of **1** and **2** and their diastereoisomeric relationships to enantiomorphs **3** and **4**: $[\alpha]^{22}D$ 5.6° for **1** and −4.6° for **2**; $[\alpha]^{22}D$ −2.36° for **3** and 4.8° for **4**.

The uv absorption spectra for isomers **1–4** were similar.

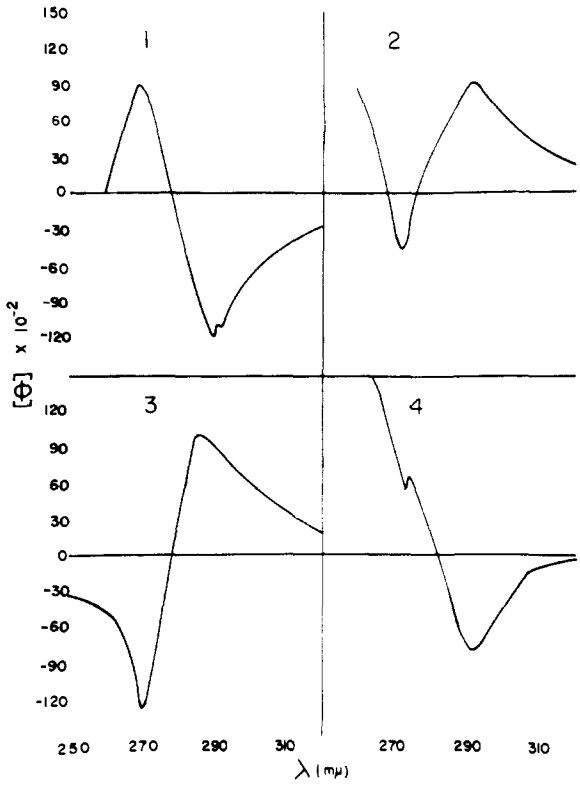


Figure 2. CD spectra in MeOH of the HCl salts for the four 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[*b*,*f*]thiepin isomers (1–4): 1 = 3′*S*,10*S* isomer (*c* 1.43); 2 = 3′*R*,10*R* isomer (*c* 1.417); 3 = 3′*S*,10*R* isomer (*c* 1.316); 4 = 3′*R*,10*S* isomer (*c* 1.323).

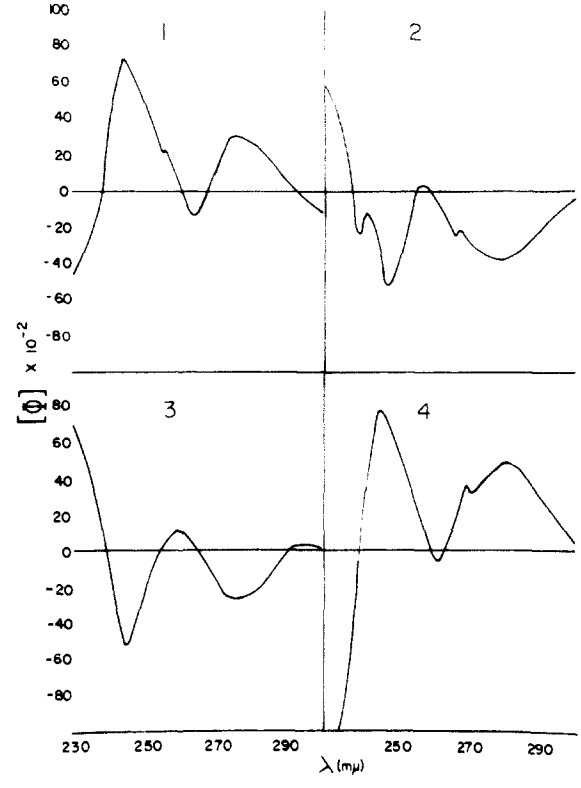
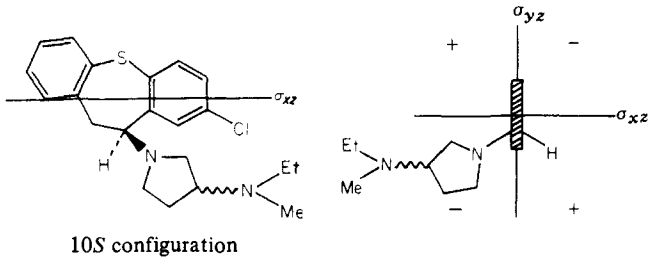


Figure 3. ORD spectra in MeOH of the HCl salts for the four 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[*b*,*f*]thiepin isomers (1–4): 1 = 3′*S*,10*S* isomer (*c* 1.43); 2 = 3′*R*,10*R* isomer (*c* 1.417); 3 = 3′*S*,10*R* isomer (*c* 1.316); 4 = 3′*R*,10*S* isomer (*c* 1.323).

Enantiomorphs **1** and **2** exhibited λ_{max} at 295, 274, and 257 nm. Enantiomorphs **3** and **4** exhibited λ_{max} at 295, 277, and 258.5 nm. The four isomers each exhibited two Cotton effects with CD maxima between 285–293 and 270–275 nm (Figure 2) which reflect the absolute configuration of the asymmetric aromatic chromophore at C-10. Owing to overlapping Cotton effects in the ORD (Figure 3), the CD spectra were found to be more useful for determining the absolute configurations at the C-10 position of isomers **1–4**. The quadrant sector rule,[9] which applies to the longer wavelength (^1L_b) Cotton effect (285–293 nm) for the chlorophenyl ring bonded directly to C-10, predicts that those isomers (**1** and **4**) having a negative ^1L_b Cotton curve should have the *S* absolute configuration; i.e., with σ_{xz} and σ_{yz} being the planes defined by the indicated σ_{xz} axis and by the plane of the chlorophenyl ring, the 10-(*S*)-aminopyrrolidino group lies in the negative quadrant. Conversely, the absolute configuration at C-10 for **2** and **3** is predicted to be *R*.



10*S* configuration

Although the quadrant sector rule has often been of value for predicting the absolute configuration of simple aromatic amines, the sign of the ^1L_b band is known to be influenced by the nature of the ring substituents.[10] Since we did not know how the Cl and S functions influenced the sign and magnitude of the ^1L_b band in these compounds, independent evidence correlating the sign of this band with the absolute configuration at C-10 was sought. Accordingly, tricyclic amine **7** was resolved using di-*p*-toluoyl-*d*-tartaric acid. The isolated (+) enantiomorph exhibited λ_{max} 270 and 254 nm and $[\alpha]^{22}D$ 15°. The ORD and CD spectra for (+)-**7** are shown in Figure 4; the high wavelength ^1L_b transition of the chlorophenyl function for (+)-**7** was optically active and gave a negative Cotton effect detectable in the CD spectrum at 280 nm. On the basis of these data we concluded that the absolute configuration at C-10 in (+)-**7** was the same as in **1** and **4**.

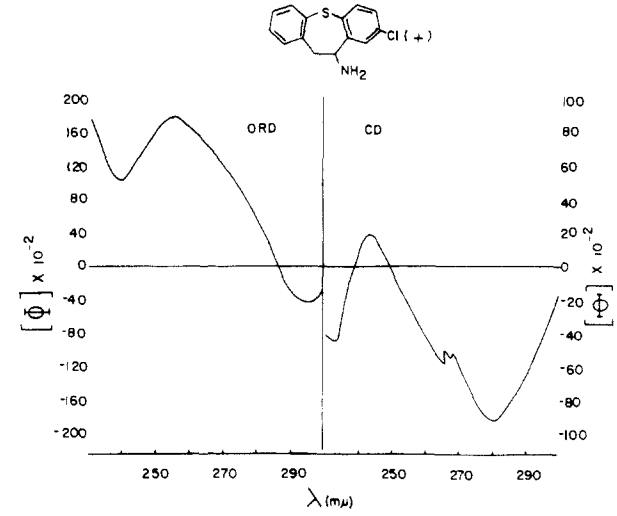
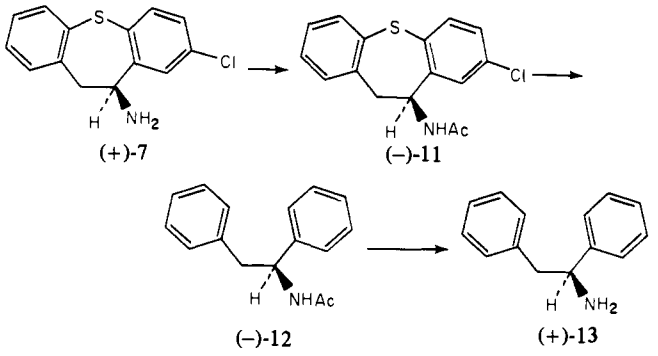


Figure 4. ORD (left) and CD (right) curves in MeOH (*c* 0.196) for (+)-(*S*)-8-chloro-10-amino-10,11-dihydrodibenzo[*b*,*f*]thiepin (**7**).

That (+)-**7** has the *S* absolute configuration was confirmed by degradation to optically active 1,2-diphenylethylamine [(+)-**13**]. The absolute configuration of

(−)-(*R*)-1,2-diphenylethylamine had previously been established by degradation to (*R*)-aspartic acid.[11] Although attempted conversion of (+)-**7** to (+)-**13** by concomitant Raney nickel (W-2) desulfurization and dechlorination failed, conversion of acetyl derivative (−)-**11** to (−)-**12** under these conditions proved successful. Mass spectrometric analysis of the products of attempted Raney nickel desulfurization of (+)-**7** revealed formation of deschloro products under mild conditions (room temperature overnight); under severe conditions (refluxing overnight), dechlorination and aromatic ring saturation occurred, but there was no evidence that desulfurization took place. On the other hand, (−)-(*S*)-acetyl derivative **11** ($[\alpha]^{22}D$ −33°), prepared from (+)-**7** in 77% yield utilizing Ac_2O, was cleanly converted to (−)-(*S*)-acetyl derivative **12** in 49% yield with Raney nickel. Hydrolysis of (−)-**12** [$[\alpha]^{22}D$ −10° (lit.[11] $[\alpha]^{18}D$ for (+)-**12** +35.7°)] in boiling H_2SO_4 followed by isolation of (+)-**13** as the HCl salt confirmed the *S* absolute configuration for these compounds. Amine (+)-**13** HCl exhibited mp 259–260° with $[\alpha]^{22}D$ +32°; optically pure (+)-(*S*)-1,2-diphenylethylamine hydrochloride,[12] mp 259–260°, exhibited $[\alpha]^{20}D$ +128°. The optical purity for (+)-**13** and, hence, (+)-**7** was approximately 25%. The absolute configuration for compounds (+)-**7**, (−)-**11**, (−)-**12**, (+)-**13**, **1**, and **4** at C-10 must be *S*. From ORD and CD analysis the absolute configuration at C-10 for **2** and **3** must therefore be *R*.



Pharmacological Results. The acute toxicities of the four isomers (**1**–**4**) in mice were similar, with acute LD_{50} values ranging from 175 to 217 mg/kg ip (Table I). The LD_{50} of isomer **2** (217 mg/kg) was observed to be higher than **1** or **3** (175–177 mg/kg) or **4** (186 mg/kg). The toxic effects observed at these and higher doses were common to all test compounds. Mice showed a marked reduction in spontaneous motor activity and muscle tone and exhibited ataxia, loss of righting reflex, jumping, twitching, tremors, clonic–tonic seizures of the body and limbs, and respiratory depression. Death usually occurred within 2–3 hr after the administration of toxic doses of these compounds.

The neurotoxicity (TD_{50}), measured by rotarod performance, of enantiomorphs **1** and **2** was twice that of their respective diastereoisomers. Enantiomorphs **1** and **2** possessed the same potency on rotarod performance; similarly, enantiomorphs **3** and **4** exhibited almost identical potencies (Table I). The four isomers exhibited a time of peak activity of 60–90 min in this test. Spontaneous motor activity was depressed in a dose-related manner when tested at 5–20 mg/kg. In these limited studies, enantiomorphs **1** and **2** were noted to cause a more profound reduction in activity than their respective diastereoisomers **3** and **4**.

When the isomeric dihydrodibenzo[*b*,*f*]thiepins were tested for their ability to impair conditioned avoidance responding, enantiomorphs **1** and **2** were observed to be

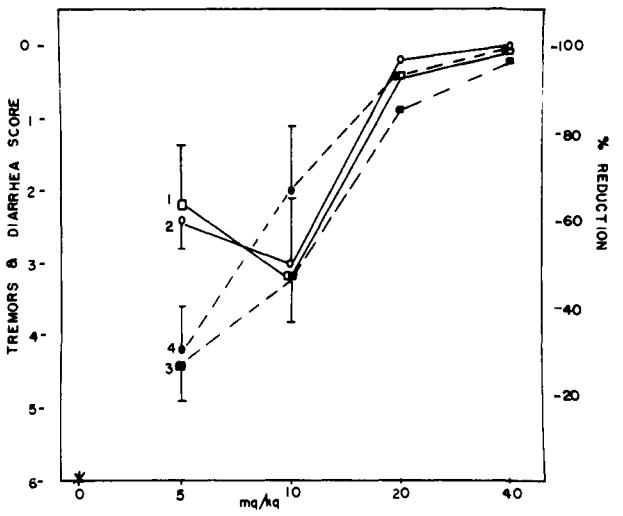


Figure 5. The effects of the four 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrobenzo[*b*,*f*]thiepin isomers (**1**–**4**) on oxotremorine-induced tremors and diarrhea. Groups of five mice were pretreated with saline or test compounds 60–90 min prior to oxotremorine (1.0 mg/kg ip). The intensity of tremors and diarrhea was evaluated for 30 min and scored as described in the Experimental Section. Values represent the mean score ± SEM. All doses of all compounds significantly ($p < 0.05$) reduced the intensity of these symptoms. Statistically significant differences between **2** vs. **4** ($p < 0.025$) and **1** vs. **3** ($p < 0.05$) at 5 mg/kg: *, tremors and diarrhea score in the absence of any isomer (**1**-**4**); □, **1** (3′*S*,10*S* isomer); ○, **2** (3′*R*,10*R* isomer); ■, **3** (3′*S*,10*R* isomer); ●, **4** (3′*R*,10*S* isomer).

1.8–1.9 times as potent as their respective diastereoisomers **3** and **4** (Table I). While the median effective dose for each compound in this test was virtually identical to its TD_{50}, only avoidance responding was disrupted; upon initiation of shock, all test animals readily and rapidly escaped the shock.

At the time of peak activity these compounds (40 mg/kg) reduced mouse rectal temperature 5.1–6.7°. At doses up to 40 mg/kg, these test compounds failed to antagonize reserpine (4 mg/kg) induced hypothermia, sedation, or ptosis or potentiate the excitatory effects of L-Dopa (100 mg/kg).

A selective antagonism of some of the effects of oxotremorine (1.0 mg/kg) was noted. The severity of oxotremorine-induced diarrhea and tremors was reduced with increasing doses (5–40 mg/kg) (Figure 5). Enantiomorphs **1** and **2** exhibited virtually identical dose–response antagonism; enantiomorphs **3** and **4** were also found to be similar to each other. At 5 mg/kg enantiomorphs **3** and **4** were one-half as potent as their corresponding diastereoisomers ($p < 0.005$); increasing the dose of **3** and **4** from 10 to 40 mg/kg produced the expected dose-related antagonism with **4** more active than **3** at a dose of 10–20 mg/kg. By contrast, isomers **1** and **2** exhibited biphasic antagonism, exerting greater activity at 5 mg (60–65%) than at 10 mg (45–50%); doses of 20–40 mg/kg abolished signs of tremors and diarrhea by 93–100%. While lower doses were ineffective, **2** and **3** (100 mg/kg) reduced the severity of oxotremorine-induced salivation 60 and 27%, respectively; **1** and **4** were ineffective antagonists even at this high dose. At 40 mg/kg the test compounds were incapable of antagonizing oxotremorine-induced hypothermia.

The analgetic activity was evaluated using a hot wire analgetic apparatus; the reaction times of mice pretreated with test compounds and saline were compared. All four dihydrodibenzo[*b*,*f*]thiepin isomers significantly ($p <$ 0.001) elevated reaction times to thermally induced pain

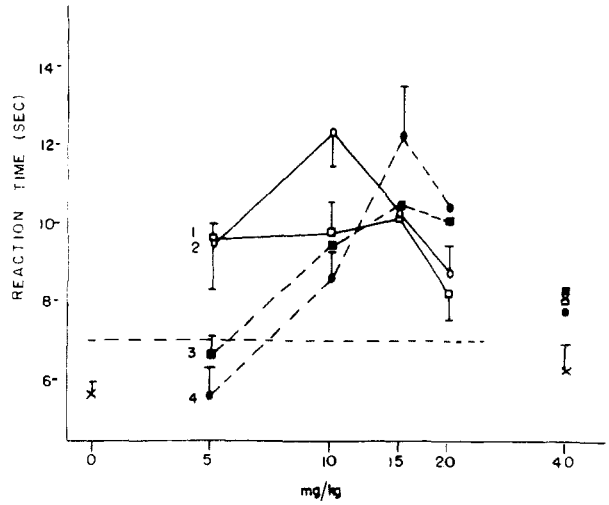


Figure 6. The effects of the four 8-chloro-10-(3'-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[b,f]thiepin isomers (1–4) on reaction times of mice subjected to thermally induced pain. X = reaction time with saline control. Two controls are indicated; one (depicted on the left) for isomer doses 5–20 mg/kg and one (depicted on the right) for 40 mg/kg of test compounds. Values represent the mean ± SEM in seconds for response to pain. Each point represents 5 experimental and 20 control animals. All experimental values higher then 7.0 sec are significantly greater ($p < 0.05$) than control values except at 40 mg/kg of test compounds. Significant differences ($p < 0.025$) between isomers: 2 vs. 4 (5 and 10 mg/kg); 1 vs. 3 (5 mg/kg). □, 1 (3'*S*,10*S* isomer); ○, 2 (3'-*R*,10*R* isomer), ■, 3 (3'*S*,10*R* isomer); ●, 4 (3'*R*,10*S* isomer).

Table II. Anticonvulsant Activity of Dihydrodibenzo[b,f]thiepin Isomers 1–4[a]

Compd	Seizure threshold ratios (95% confidence limits)	
	Minimal	Maximal
1	1.16[b] (1.00–1.35)	0.93 (0.76–1.15)
2	1.08 (0.95–1.21)	0.75[c] (0.63–0.87)
3	1.27[b] (1.08–1.50)	1.00 (0.84–1.22)
4	1.24[b] (1.09–1.40)	0.73[c] (0.66–0.80)

[a] Saline (1 ml/100 g) and all isomers (40 mg/kg) were administered ip 60–90 min prior to pentylenetetrazole in groups of 8–10 mice. Seizures were induced by iv infusion of a 0.5% solution of pentylenetetrazole.[33] [b] Elevation in minimal seizure threshold ($p < 0.05$). [c] Reduction in maximal seizure threshold ($p < 0.05$).

at doses of 10–20 mg/kg; enantiomorphs 1 and 2 were also active ($p < 0.001$) at 5 mg/kg (Figure 6). Greatest analgetic activity was observed with all compounds at 10–15 mg/kg, with reaction times 1.5–2.2-fold longer than controls. The analgetic protection was reduced at 20 mg/kg; at 40 mg/kg reaction times were only 23–29% longer than saline-pretreated mice. The dose–response curves for diastereoisomers 2 and 4 (the most active compounds) were similar with 2 being 1.5–2.0 times more potent. Differences in analgetic activity were observed between the diastereoisomers at the lowest doses tested, i.e., 2 vs. 4 and 1 vs. 3 at 5 mg/kg and 2 vs. 4 at 10 mg/kg ($p < 0.025$).

All compounds except 2 significantly reduced minimal seizure susceptibility to an intravenous infusion of pentylenetetrazole (Table II). Enantiomorphs 3 and 4 appear to be somewhat more active at 40 mg/kg than enantiomorphs 1 and 2 in reducing minimal seizure susceptibility. Conversely, the diastereoisomers 2 and 4 enhanced maximal seizure susceptibility to pentylenetetrazole; 1 and 3 were found to be inactive.

As noted previously, moderately high doses of these compounds appeared to cause muscle weakness and flaccidity. However, when evaluated for potential neuromuscular blocking activity, doses up to 20 mg/kg failed to impair the ability of mice to remain on an inclined wire mesh screen.

In preliminary experiments, conducted in vitro, employing the classical method of Magnus on the guinea pig ileum, the test compounds (10^{-8}–10^{-6} *M*) partially and nondifferentially antagonized histamine- and acetylcholine-induced contractions. In subsequent studies, all compounds (5×10^{-7} *M*) reduced $BaCl_2$ (5×10^{-7} *M*) spasms by 40–50%, thus suggesting nonspecific antispasmodic activity. Such an action may correspond to the muscle flaccidity observed in vivo.

Discussion

Nuclear substitution with Cl and formation of the tertiary rather than secondary amine at position 3' of the pyrrolidino ring converted a pharmacologically unexciting dihydrodibenzo[b,f]thiepin[4] to a compound having relatively potent activity with potential clinical utility for the treatment of psychosis and the relief of pain. Differences in pharmacological activity between diastereoisomers (1 and 2 vs. 3 and 4) were observed in several studies, whereas few differences were noted between enantiomorphs (1 vs. 2 or 3 vs. 4).

These pharmacological results are consistent with those reported by Jilek et al.[13] who observed that both enantiomorphs of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[b,f]thiepin exhibited similar pharmacological activities. The differences in pharmacological activity observed between diastereoisomers are likely a reflection of relatively small conformational differences in the central seven-membered ring. Although differences in conformation can be detected in the NMR (Figure 1) these differences cannot easily be explained on the basis of configurational changes at the pyrrolidino 3' position.

Results obtained with diastereoisomeric dihydrodibenzo[b,f]thiepins (1–4) lead us to conclude that future drug design in this series, which is directed toward the development of isomers having major stereoselective differences in activity, should emphasize the synthesis of diastereoisomers having large structural differences; less consideration should be given to exploitation of chiral differences in drug design. Although the relative relationship of the configuration between the two asymmetric centers is most important for stereoselective activity, further work is necessary before these results can be explained on conformational grounds. Thiepin ring and infinite side-chain conformational possibilities coupled with notions of multiple modes of binding to pharmacological receptors[14,15] and allosteric[16] and macromolecular perturbation[17] phenomena are far too complex to interpret with this limited series of compounds. Further, nothing is known about stereoisomeric effects on distribution and metabolism of compounds 1–4.

Owing to the chemical similarities between isomers 1–4 and the phenothiazine tranquilizers (e.g., chlorpromazine) it is not surprising that the majority of the effects observed for these two groups of compounds are similar. The acute toxic doses for isomers 1–4 were 2–3 times higher than those reported for chlorpromazine in mice (92 mg/kg),[18] while the therapeutic index (LD_{50}/ED_{50}) for blocking conditioned avoidance responding falls in the same range for chlorpromazine (25–30 mg/kg)[18] and enantiomorphs 1 and 2. For enantiomorphs 3 and 4 the therapeutic index is somewhat lower than that reported for chlorpromazine. Like chlorpromazine these isomers are devoid of antidepressant activity as evidenced by their inability to antagonize reserpine-induced sedation, ptosis, or hypothermia and to potentiate the excitatory effects of L-Dopa. All of these isomers exhibited nonspecific anti-

spasmodic activity against $BaCl_2$ as does chlorpromazine on the guinea pig ileum in vitro. However, these isomers possess the theoretical structural requirements necessary for antihistaminic[4,19] and anticholinergic[20] activities. Similar to chlorpromazine all four isomers produced hypothermia (5.1–6.7°) in mice; the reduction in body temperature by these isomers (40 mg/kg) was of approximately the magnitude as that observed for chlorpromazine (7.6°, M. C. Gerald, unpublished observations) at 10 mg/kg.

Chlorpromazine has been shown to antagonize oxotremorine-induced temors.[21] Similar antagonism has been observed for isomers 1–4 (5–10 mg/kg) which were also found to antagonize oxotremorine-induced diarrhea. Only diastereoisomers 2 and 3 partially blocked oxotremorine-induced salivation at high doses. Thus the potential anti-Parkinson activity of these compounds is difficult to assess at this time.

It is well known that chlorpromazine potentiates the analgetic effects of morphine, meperidine, and aspirin.[22] Our compounds also exhibited analgetic activity and may be pharmacologically related to the phenothiazine tranquilizer, methotrimeprazine [(−)-2-methoxy-10-(3-dimethylamino-2-methylpropyl)phenothiazine] which acts as a potent analgetic.[23] The (−) isomer is more potent than the (+) isomer.[24] The stereochemical correlations, if any, between analgetic activity and the preferred "active conformations" of isomer 1–4, methotrimeprazine, morphine, and the analgetically active (−)-(*R*)-*N*,*N*-dimethyl-1,2-diphenylethylamine[12] [(*R*)-13] remain to be determined. The decrease and eventual loss of analgetic activity for isomers 1–4 at higher doses (Figure 6) may be due to antagonism by saturation of analgetic receptor sites. However, recent unpublished studies in our laboratories show that high doses of isomers 1–4 do not antagonize morphine-induced analgesia.

Structural analogs of the hydantoin and oxazolidinone anticonvulsants show few stereoselective differences in activity, supporting the view that the action of these compounds is nonspecific.[25,26] However, we have previously observed some marked differences in anticonvulsant activity in a series of enantiomorphic succinimide and glutarimide anticonvulsants of known absolute configuration.[3] Isomers 1–4 also exhibit stereoselective anticonvulsant activity (Table II). Enantiomorphs 3 and 4 are more effective against pentylenetetrazole-induced minimal seizures while diastereoisomer 2 was inactive. Diastereoisomers 2 and 4 potentiated pentylenetetrazole-induced maximal seizures while their respective enantiomorphs 1 and 3 were inactive. Although these stereoselective effects are not marked, it is of interest to note that diastereoisomers (2 and 4 vs. 1 and 3) behave similarly, whereas in other pharmacological tests enantiomorphic pairs (1 and 2 vs. 3 and 4) showed similar biological activity. These differences may be related to differences in receptor-site chemistry, but further work is necessary before firm conclusions can be drawn.

On the basis of the results presented in this paper it seems to us that continued evaluation of stereostructure–activity relationships as a means of increasing drug potency while concomitantly reducing toxicity remains a valid approach to the rational development of therapeutic agents. For many years this approach to the rational design of drugs was advocated by Professor Edward Smissman to whom this article is dedicated.

Experimental Section

For obtaining physical data on our compounds the following equipment was employed: melting points, calibrated Thomas-Hoover apparatus; ir spectra, Perkin-Elmer 257 spectrophotometer; uv spectra, Cary Model 15 spectrophotometer; ORD–CD spectra, Durrum-Jasco spectrometer; NMR spectra, Varian A-60A spectrophotometer with Me_4Si as an internal standard; mass spectra, Du Pont 21-491 mass spectrometer interphased with a Hewlett-Packard 2100A computer. Elemental analyses were performed by Clark Microanalytical Laboratories, Urbana, Ill.

8-Chloro-10-formamido-10,11-dihydrodibenzo[*b*,*f*]thiepin (6). To a suspension of 8-chloro-10,11-dihydrodibenzo[*b*,*f*]-thiepin-10-one (**5**,[5] 11.5 g, 0.044 mol) in 23 g (0.45 mol) of formamide was added 97% HCO_2H (5 g, 0.11 mol). The mixture was heated under reflux at 180–190° for 16 hr. After cooling, the mixture was poured into 300 ml of H_2O and allowed to stand for 3 hr. The precipitated solid was filtered, washed (H_2O), and air-dried. Recrystallization from benzene afforded 7.18 g (56%) of white crystals, mp 195–197°. Anal. ($C_{14}H_{12}NSCl$) C, H, N.

8-Chloro-10-amino-10,11-dihydrodibenzo[*b*,*f*]thiepin (7). Compound **6** (6.8 g, 0.024 mol) was added to 250 ml of concentrated HCl and heated at reflux for 6 hr. Most of the solid dissolved and the amine hydrochloride precipitated upon cooling to room temperature. The mixture was further cooled in an ice bath and the solid was filtered. The crystalline solid was suspended in 20 ml of H_2O and neutralized with excess NH_4OH solution. After standing for 1 hr at room temperature, the solid was extracted into benzene. The organic layer was washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure affording a light yellow oil. Crystallization from hexane (containing a trace of EtOH) afforded 3.2 g (50%) of **7** as cream-colored needles, mp 73–77°. Anal. ($C_{13}H_{10}SNCl$) C, H, N, Cl.

Preparation of *SR* and *SS* Imides (9) from *N*-Acetyl-L-(*S*)-aspartic Anhydride (8) and Racemic Amine (7). To a solution of **7** (6.55 g, 0.025 mol) in 200 ml of absolute EtOH was added *N*-acetyl-L-(*S*)-aspartic anhydride (**8**, 3.93 g, 0.025 mol). The mixture was stirred at room temperature for 20 hr with protection from moisture. EtOH was removed under reduced pressure, and the remaining solid was washed with 100 ml of Et_2O and dried under reduced pressure for 3 hr. The solid material (9.9 g) containing the *SR* and *SS* amides was used without further purification for the preparation of the diastereoisomeric imide mixture.

Impure amides (9.9 g) were dissolved in 250 ml of Ac_2O and heated on a steam bath for 4 hr while protected from moisture. The Ac_2O was removed under reduced pressure and the residual traces were removed with the aid of toluene. The resulting solid (9.5 g) showed one major spot and several minor spots on TLC (silica gel, EtOAc). The solid was dissolved in a small quantity of EtOAc–$CHCl_3$ and chromatographed on silica gel (100 g) using EtOAc as the eluting solvent. The fractions containing the desired material (by TLC) were combined and concentrated under reduced pressure yielding 6 g (ca. 60%) of a crude mixture (TLC pure) of *RS* and *SS* imides **9**.

A small amount of the imides **9** was crystallized from EtOAc–Et_2O to give a white crystalline solid: mp 186° dec; $[\alpha]^{22}D$ 11.6° (*c* 0.43, MeOH); NMR ($CDCl_3$) δ 7–7.7 (7, c, aromatic), 6.5 [1, d, $-NHC(=O)CH_3$], 5.66 (1, d of d, H-10, J = 11 and 4 Hz), 4.35 (1, d of d, H-11, J = 13 and 11 Hz), 4–4.4 (1, m, side-chain methine), 3.2 (1, d of d, H-11, J = 13 and 4 Hz), 2.88 (2, m, side-chain methylene), 2.00 ppm [3, s, $NHC(=O)CH_3$].

8-Chloro-(*S*)- and -(*R*)-10-[(*S*)-3'-ethylaminopyrrolidino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (10). To a slurry of $LiAlH_4$ (9.5 g, 0.25 mol) in 500 ml of dry Et_2O was added slowly the solid diastereoisomeric mixture of **9** (10 g, 0.025 mol). After the addition was complete, the reaction mixture was refluxed for 16 hr with constant stirring. The reaction mixture was cooled to room temperature and the excess $LiAlH_4$ was decomposed by dropwise addition of 10 ml of H_2O, followed by 10 ml of 15% aqueous NaOH solution and finally 30 ml of H_2O. The resulting white granular precipitate was filtered and washed with excess Et_2O. The combined filtrates were concentrated to 200 ml, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure to give 8 g of yellow gum. TLC of this residue showed one major spot with several minor spots (silica gel, EtOAc–MeOH–NH_4OH 90:8:2). The product was purified by chromatography on silica gel to give 5.3 g of oily diastereoisomers which could not be separated. This oil was employed in the subsequent reaction.

8-Chloro-(S)- and -(R)-10-[(S)-3'-methylethylamino-pyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin (1 and 3). The mixture of diastereoisomeric secondary amines (5.00 g, 0.014 mol) was dissolved in 100 ml of MeCN; 4.5 ml of 37% aqueous HCHO solution was added and stirred for 25 min at room temperature. Solid $NaBH_3CN$ (2.64 g, 0.042 mol) was added and stirring was continued for 16 hr. The mixture was concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was separated and extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure affording 4.5 g of a light brown viscous oil. TLC of this oil showed two major spots (silica gel, EtOAc–MeOH–NH_4OH 90:9:1). Repeated chromatography on silica gel by elution with the above solvent system afforded fractions containing 1 and 3. Fractions containing 1 (less polar on TLC) were combined and evaporated affording 1.3 g of light yellow gum. Similarly, fractions containing 3 (more polar on TLC) were combined and evaporated affording 1.25 g of light yellow gum. The combined yield of 1 and 3 was 2.55 g (50%).

NMR ($CDCl_3$) of 1 showed δ 6.95–7.6 (7, c, aromatic), 4.35 (1, d of d, H-10, J = 8 and 6.5 Hz), 1.8–4.0 (9, c, methylene + methine protons), 2.2 (3, s, NMe), 1.07 ppm (3, t, NCH_2CH_3, J = 7 Hz). The di-HCl salt prepared in MeOH–gaseous HCl was crystallized from MeOH–Et_2O affording a white solid: mp 238–242° dec; $[\alpha]^{22}D$ 5.6° (c 1.4, MeOH); uv spectrum (MeOH) λ_{max} 295 nm (log ϵ 4.05), 274 (4.25), 257 (4.20); CD (Figure 2); ORD (Figure 3); mass spectrum (70 eV) m/e 372. Anal. ($C_{21}H_{27}SN_2Cl_3$) C, H, N.

NMR ($CDCl_3$) of 3 showed δ 6.9–7.6 (7, c, aromatic), 4.25 (1, d of d, H-10, J = 9 and 5.5 Hz), 1.9–3.5 (9, c, methylene + methine protons), 2.15 (3, s, NMe), and 1.03 ppm (3, t, NCH_2CH_3, J = 7 Hz). The di-HCl salt prepared in MeOH–gaseous HCl was crystallized from MeOH–Et_2O affording a white solid: mp 230° dec (softening at 160°); $[\alpha]^{22}D$ –2.36° (c 1.3, MeOH); uv spectrum (MeOH) λ_{max} 295 nm (log ϵ 4.10), 277 (4.22), 258 (4.15); CD (Figure 2); ORD (Figure 3); mass spectrum (70 eV) m/e 372. Anal. ($C_{21}H_{27}SN_2Cl_3$) (analysis fit is based on the presence of 20% monohydrochloride in this sample) C, H, N, S, Cl.

8-Chloro-(S)- and -(R)-10-[(R)-3'-methylethylamino-pyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin (2 and 4). Diastereoisomeric tertiary amines 2 and 4 were prepared from N-acetyl-D-(R)-aspartic anhydride (8) and racemic 5 according to the methods described for the preparation of 1 and 3.

NMR ($CDCl_3$) of 2 (less polar on TLC) showed δ 6.95–7.6 (7, c, aromatic), 4.35 (1, d of d, H-10, J = 8 and 6.5 Hz), 1.8–4.0 (9, c, methylene + methine protons), 2.2 (3, s, NMe), 1.07 ppm (3, t, NCH_2CH_3, J = 7 Hz). The di-HCl salt of 2 prepared in MeOH–gaseous HCl was crystallized from MeOH–Et_2O affording a white crystalline solid: mp 238–240° dec; $[\alpha]^{22}D$ –4.6° (c 1.4, MeOH); uv spectrum (MeOH) λ_{max} 295 nm (log ϵ 4.11), 274 (4.32), 257 (4.27); CD (Figure 2); ORD (Figure 3); mass spectrum (70 eV) m/e 372. Anal. ($C_{21}H_{27}SN_2Cl_3$) C, H, N.

NMR ($CDCl_3$) of 4 (more polar on TLC) showed δ 6.9–7.6 (7, c, aromatic), 4.25 (1, d of d, H-10, J = 9 and 5.5 Hz), 1.9–3.5 (9, c, methylene + methine protons), 2.15 (3, s, NMe), and 1.03 ppm (3, t, NCH_2CH_3, J = 7 Hz). The di-HCl salt of 4 prepared in MeOH–gaseous HCl was crystallized from MeOH–Et_2O affording a white solid: mp 230° dec (softening at 160°); $[\alpha]^{22}D$ 4.8° (c 1.32, MeOH); uv spectrum (MeOH) λ_{max} 295 nm (log ϵ 4.09), 277 (4.21), 259 (4.14); CD (Figure 2); ORD (Figure 3); mass spectrum (70 eV) m/e 372. Anal. ($C_{21}H_{27}SN_2Cl_3$) C, H, N.

Resolution of Racemic Amine (7) with Di-p-toluoyl-d-tartaric Acid. A solution of 3.86 g (0.01 mol) of di-p-toluoyl-d-tartaric acid in 50 ml of MeOH was added to a solution of 2.61 g (0.01 mol) of racemic amine in 50 ml of EtOAc. The solution formed was left for 12 hr at room temperature. A total of 4.2 g of the salt precipitated. Recrystallization from MeOH afforded 2.3 g of the salt, mp 204–205°. Repeated crystallizations did not change the melting point. Decomposition of this salt with aqueous K_2CO_3 and extraction with EtOAc afforded 0.9 g of the crude amine. Repeated crystallization from hexane afforded 0.225 g of (+) amine: mp 73–83°; $[\alpha]^{22}D$ 14.3° (c 2.0, MeOH); uv spectrum (MeOH) λ_{max} 270 nm (log ϵ 3.94), 254 (3.84); ORD and CD (Figure 4).

(–)-(S)-10-Acetamido-8-chloro-10,11-dihydrodibenzo-[b,f]thiepin (11). To a sample of partially resolved (+)-7 ($[\alpha]^{22}D$ 8°, 450 mg, 1.72 mmol) in 20 ml of dry Et_2O was added 2 ml of Ac_2O. The solution was allowed to stand for 1 hr at room temperature. The crystalline precipitate was removed by filtration, washed with Et_2O (20 ml), and dried. Recrystallization from EtOH afforded 400 mg (77%) of pure acetamide: mp 195–200°; $[\alpha]^{22}D$ –33° (c 2.0, $CHCl_3$). Anal. ($C_{16}H_{14}ONSCl$) C, H, N.

Conversion of (–)-(S)-11 to (–)-(S)-N-Acetyl-1,2-diphenylethylamine [(–)-(S)-12]. To (–)-(S)-11 ($[\alpha]^{22}D$ –33°, 180 mg, 0.59 mmol) in 50 ml of absolute EtOH was added a slurry of 3.0 g of W-2 Raney nickel[27] in 50 ml of EtOH. The mixture was stirred at room temperature for 18 hr. The solids were removed by filtration and washed with excess hot EtOH, and the combined filtrates were concentrated under reduced pressure. The white crystalline residue (0.11 g) was chromatographed on silica gel. Elution with $CHCl_3$ afforded a crystalline fraction (70 mg) homogeneous on TLC ($CHCl_3$–5% MeOH). The R_f value was found to be identical with the N-acetyl derivative (dl-12) prepared from a commercial sample of 1,2-diphenylethylamine. Recrystallization from EtOH gave colorless needles (30 mg): mp 151–153°; dl-12 prepared in our laboratories had mp 151–153° (lit.[11] mp 164–165°). $[\alpha]^{22}D$ –10.6° (c 1.5, EtOH) for (–)-(S)-12. The NMR and ir spectra for (–)-12 and dl-12 were superimposable and their mixture melting point was not depressed.

Conversion of (–)-(S)-12 to (+)-(S)-1,2-Diphenylethylamine [(+)-(S)-13]. To a mixture of (–)-12 ($[\alpha]^{22}D$ –10.6°, 30 mg, 0.12 mmol) in 10 ml of 2 N H_2SO_4 sufficient MeOH (ca. 5 ml) was added to make the solution homogeneous. The mixture was refluxed overnight, cooled in an ice bath, neutralized (excess NH_4OH), and concentrated under reduced pressure. The residue was partitioned between Et_2O and H_2O and the organic layer was extracted with 10% HCl solution. The aqueous extract was neutralized (NH_4OH) and extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated under reduced pressure affording an oil (10 mg). The oil was dissolved in 2 ml of EtOH and 1 ml of concentrated HCl was added. The precipitated HCl salt was removed by filtration and recrystallized from MeOH–Et_2O affording colorless needles: mp 259–260° (lit.[12] mp 259–260°); $[\alpha]^{22}D$ 32° (c 0.25, EtOH) (lit.[12] $[\alpha]^{20}D$ 128°).

Pharmacology. The animals used in the pharmacological evaluation of the dihydrodibenzo[b,f]thiepins 1–4 were male albino CD-1 mice (18–25 g) and guinea pigs of both sexes. All test compounds were administered to mice dissolved in distilled H_2O. Acute toxicity was evaluated in groups of eight mice 24 hr after a single ip injection. The time of maximal central activity on the rotarod (see below) was determined to be 60–90 min for all test compounds. All pharmacological studies were carried out at this time unless otherwise stated. Animals were observed for 3 hr after drug administration for gross behavioral changes.

The median neurotoxic dose (TD_{50}) was determined employing the rotarod. The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the animal to remain on a horizontal rod rotating at 6 rpm for 1 min. This test was also employed to determine the time of peak activity for each compound.

The effect of these compounds on spontaneous motor activity was monitored in an actophotometer at 15-min intervals for 2 hr. Drug-induced impairment of conditioned avoidance responding in a shuttle box, a measure of potential antipsychotic activity, was evaluated in groups of ten trained mice immediately prior to and 60–90 min after drug administration. Compounds were screened for antidepressant activity, as evidenced by their ability to prevent or antagonize reserpine (4 mg/kg ip) induced hypothermia,[28] sedation,[28] and ptosis.[29] Rectal temperatures of mice were recorded with a YS-1 Tele-thermometer (Yellow Springs Instrument Co.) equipped with a small animal probe. The ability of test compounds to potentiate L-Dopa (100 mg/kg ip) stimulation was utilized to study both antidepressant and anti-Parkinson activities.[30] Antagonism of oxotremorine (1.0 mg/kg ip) induced hypothermia, salivation, diarrhea, and tremors was an additional test conducted for anti-Parkinson activity.[31] Groups of five mice were pretreated with saline or test compounds 60–90 min prior to oxotremorine. The intensity of tremors and diarrhea was evaluated for 30 min and assigned the following arbitrary scores: 0 = none, 1 = mild; 2 = moderate, 3 = severe. The sum of these two scores was computed for each animal and the mean score calculated for each treatment group. All saline pretreated mice experienced severe tremors and diarrhea and, hence, were

assigned a score of 6. Analgetic activity was evaluated employing a hot wire analgetic apparatus at 50°.[32] Antagonism of pentylenetetrazole (iv infusion of 0.5% solution) induced minimal (clonic) and maximal (tonic) seizures was utilized as a test for anticonvulsant activity.[33] Neuromuscular blocking activity was tested using an inclined wire mesh screen at a 60° angle.[34]

Antihistaminic, anticholinergic, and nonselective antispasmodic activities in vitro were determined utilizing the guinea pig ileum, suspended in Krebs' solution at 37 ± 0.5° and bubbled with 95% O_2–5% CO_2.[2b,35] The LD_{50} and ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[36] Statistical comparisons of test compounds vs. vehicle-treated control animals were carried out employing an analysis of variance followed by a t test or a Mann–Whitney U test.[37] Values are expressed as the mean (95% confidence limits) or mean ± SEM.

References and Notes

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Novel Analogs of Tricyclic Psychopharmacological Agents†

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The synthesis of several novel analogs of amitriptyline and chlorprothixene, in a number of which the position of the side-chain nitrogen atom is rigidly fixed with respect to the tricyclic nucleus, is described. The compounds were evaluated for antidepressant-like activity in the Dopa and serotonin interaction tests and for potential antipsychotic activity in the methamphetamine interaction test. 5-(3-Dimethylaminocyclohex-1-enyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**12**) was about equipotent with imipramine in the Dopa and methamphetamine tests, and 3-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-spiro-6'-3'-methyl-3'-azabicyclo[3.1.0]hexane (**23**) also displayed marked activity in the same tests. Prototype compounds for other ring systems, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)tropane (**16**) and 5-(3-dimethylaminocycloheptylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**18**), were less active.

A number of theories[1-4] have been proposed to explain the relationship between chemical structure and activity within the class of tricyclic psychopharmacological agents. The observation[5,6] that the antipsychotic activity of chlorprothixene [(*Z*)-**1**] is fifty times greater than that of (*E*)-**1** implies that such activity is critically dependent on the stereochemical relationship between an aromatic ring and the side-chain amino group. Since chlorprothixene and the antidepressant drug amitriptyline (**2**) retain considerable side-chain flexibility, it was of interest to synthesize analogs of these agents, represented by structure

† This paper is dedicated to the memory of Professor Edward E. Smissman.