

**boxylate (5e).** To a solution of 12.6 g (0.042 mol) of methyl 1,4-dihydro-7-nitro-4-oxobenzo[h]quinoline-2-carboxylate in 1 l. of methyl cellosolve was added 1 g of 10% palladium-on-charcoal catalyst and the mixture was hydrogenated at 3 atm of hydrogen. When the theoretical amount of hydrogen was absorbed then the catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. There was obtained 10.0 g (88%) of a yellow-orange solid melting at 245° dec. *Anal.* ( $C_{15}H_{12}N_2O_3$ ) H, N; C: calcd, 67.15; found, 66.18.

**Methyl 5-Amino-8-chloro-1,4-dihydro-4-oxoquinolinate (5t).** A mixture of 6.06 g (0.0214 mol) of methyl 8-chloro-1,4-dihydro-5-nitro-4-oxoquinolinate, 150 ml of methanol, and 6 g of Raney nickel catalyst was hydrogenated at 3 atm of hydrogen pressure. The catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue was recrystallized from methanol. There was obtained 2.45 g (45%) of red needles melting at 175–176°. *Anal.* ( $C_{11}H_9ClN_2O_3$ ) C, H, N.

**Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (10c)** was prepared by the method of Riegel, et al.<sup>7</sup>

**6-Chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (11g)** was prepared by the method of Tarbell.<sup>8</sup>

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and uv spectra. We also express our gratitude to Miss Christine VanHout, Mr. Charles E. Fultz, Mr. Robert L. Griffin, Mr. Nelson Major, and Mr. Arlen Taylor for providing expert technical assistance.

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## D-(R)- and L-(S)-3-Alkylaminopyrrolidino-Substituted Dihydrodibenzo[b,f]- and -[b,e]thiepins, Xanthenes, and Diphenylmethanes†

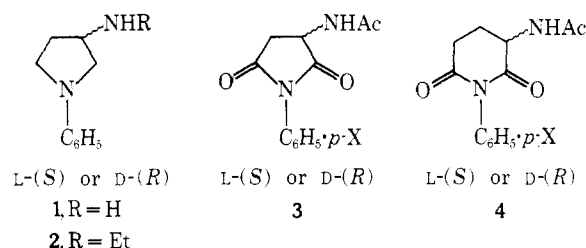
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Based upon classical structure-activity relationships, the chiral aminopyrrolidines indicated in the title may be anticipated to exhibit a variety of central and peripheral actions. For these reasons, analogs of known absolute configuration were synthesized in order to assess stereoselective differences in antipsychotic (neuroleptic), antidepressant, anti-Parkinson, antihistaminic, and anticholinergic activities. In fact, few stereoselective differences were observed. Within this series dihydrodibenzo[b,f]thiepins would appear to serve as the better lead for the future design of antipsychotic drugs. Structural requirements for  $H_1$  histamine antagonists *in vitro* are discussed.

Recent studies in this laboratory have been concerned with the synthesis and pharmacological evaluation of enantiomorphous drugs synthesized from amino acids of known absolute configuration.<sup>1-4</sup> From a theoretical point of view such compounds may serve as biological probes to study pharmacological receptor sites. For example, this laboratory reported the stereoselective synthesis<sup>1</sup> of L-(S)-3-amino-1-phenylpyrrolidine (1) from L-(S)-aspartic acid as well as the antihistaminic and anticholinergic properties of the L-(S)- and D-(R)-3-ethylamino analogs 2 determined *in vitro*.<sup>1,2</sup> While L-(S)-2 possessed ten times greater antihistaminic potency than D-(R)-2, only the latter enantiomorph had measurable anticholinergic activity. In another study having potential therapeutic significance we synthesized a series of para-substituted N-acetyl-L-(S)- and D-(R)- $\alpha$ -amino-N-phenylsuccinimides (3) and glutarimides (4) from amino acids of known absolute configuration.<sup>3</sup> Assessment of the anticonvulsant properties<sup>3,4</sup> within these two series of imides revealed that they also exhibited stereoselective biological activity with the magnitude of the activity difference between isomers a function of the para substituent on the phenyl ring.

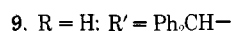
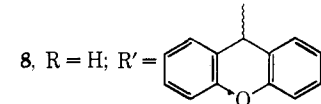
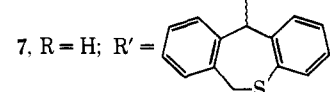
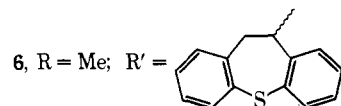
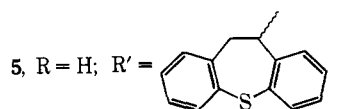
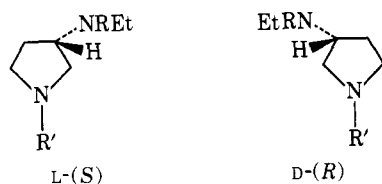
In an attempt to provide leads for the future design of



clinically useful drugs, the synthesis and pharmacological evaluation of selected tricyclic and diphenylmethane analogs (5–9) containing chiral aminopyrrolidino side chains are described in this article. Based upon classical structure-activity relationships<sup>5-7</sup> it may be anticipated that such analogs should exhibit one or more of the following actions: antipsychotic (neuroleptic), antidepressant, anti-Parkinson, antihistaminic, and anticholinergic activities. The comparative properties of these compounds are discussed in light of results obtained by others studying similar tricyclic or diphenylmethyl systems substituted with other alkylamino side chains.

**Synthetic Aspects.** D-(R)- and L-(S)-aminopyrrolidino analogs 5–9 were synthesized from N-acetyl-D-(R)- or L-(S)-aspartic anhydride (10) and the appropriate aryl amine 11–14 according to methods similar to the one reported for the preparation of D-(R)- or L-(S)-2 from D-(R)- or L-(S)-10 and aniline<sup>1</sup> (Scheme I). The dihydrodibenzo[b,f]thiepin 11, prepared according to the method of Jilek and coworkers,<sup>8</sup> served as starting material for the

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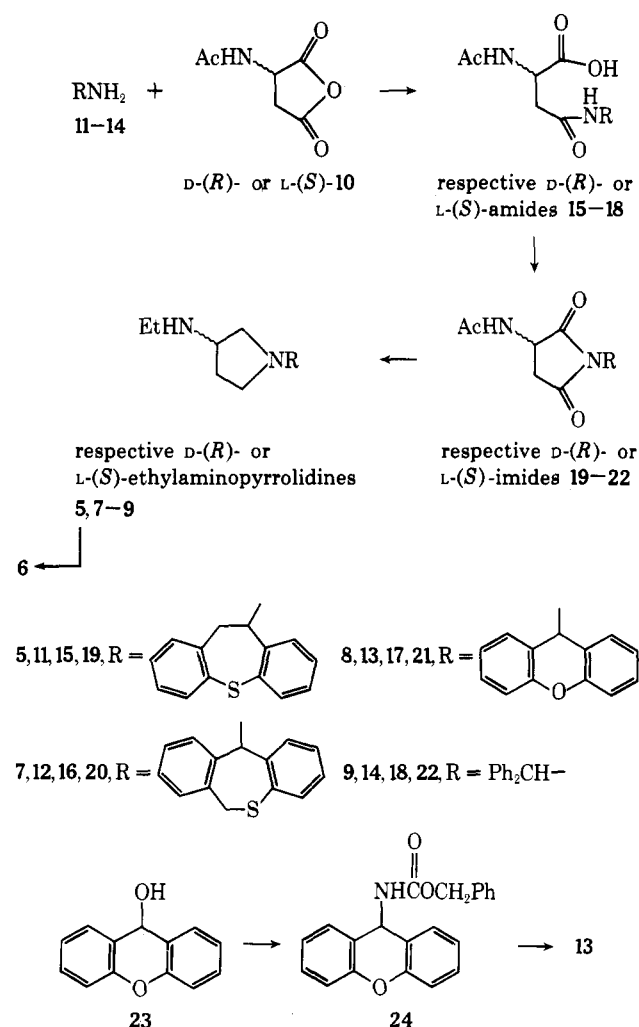


synthesis of D-(R) and L-(S) analogs 5 and 6. Similarly, the dihydrodibenzo[b,e]thiepin 12 prepared according to the method of Seidlova and coworkers<sup>9</sup> served as starting material for the preparation of D-(R)- and L-(S)-aminopyrrolidines 7. For these preliminary studies no attempt was made to separate the diastereoisomers of 5, 6, and 7. 9-Aminoxanthene (13), which served as a precursor for the preparation of D-(R)- and L-(S)-8, was prepared from xanthidrol (23). Condensation of 23 with benzyl carbamate<sup>10</sup> in acetic acid by the method of Phillips and Pitt,<sup>11</sup> who prepared a series of *N*-xanthylamides, afforded *N*-carbobenzoxy-9-aminoxanthene (24) in 74% yield. Unlike other xanthylamides, which are reported to be stable to alkaline hydrolysis,<sup>12</sup> carbamate 24 afforded 9-xanthylamine in 76% yield upon treatment with KOH in 95% EtOH. Benzhydramine (14) was prepared from benzophenone utilizing the method of Crossley and Moore<sup>13</sup> and served as starting material for the preparation of D-(R)- and L-(S)-9.

Reaction of amines 11-14 with *N*-acetyl-D-(R)- or -L-(S)-aspartic anhydride (10) yielded what is likely a mixture of  $\alpha$ - and  $\beta$ -amides in which the  $\beta$  isomers 15-18 predominate.<sup>1,3</sup> Amides 15-18 were cyclized to their respective D-(R)- and L-(S)-imides 19-22, respectively, by heating in Ac<sub>2</sub>O. LiAlH<sub>4</sub> reduction of optically active imides 19-22 afforded D-(R)- and L-(S)-ethylaminopyrrolidines 5 and 7-9, respectively, which, except for analogs 9, were shown to be optically active by ORD analysis (Experimental Section). The D-(R)- and L-(S)-imide precursors (22) to 9 exhibited detectable rotations, but the rotations for 9 were too small and fall within the experimental error of the instrument. It is known, however, that racemization does not occur when related imides are reduced with LiAlH<sub>4</sub>.<sup>1</sup> Optically active tertiary amines D-(R)- and L-(S)-6 were prepared from D-(R)- and L-(S)-5 in approximately 38% yield using the Eschweiler-Clark modification of the Leuckart reaction.<sup>14,15</sup>

Analog 5-7 were isolated as dihydrochloride salts and were found to be stable in the aqueous buffer solutions used for biological evaluation. Diphenylmethyl isomers 9 were purified by distillation of the free base. D-(R)- and L-(S)-amines 9 were dissolved in very dilute HCl; aliquots of known concentration were taken and dissolved in the

## Scheme I



appropriate buffer for pharmacological studies. Xanthene analog 8 was found to be unstable when dissolved in aqueous solutions (pH < 7.6) affording a white precipitate consisting of a mixture of xanthone, xanthene, and di-9-xanthyl ether. Salts of the parent 9-aminoxanthene (13) similarly have been reported to be unstable in aqueous solution.<sup>16</sup> For these reasons suspensions of 8 were prepared for biological studies; these analogs likely decompose to insoluble xanthyl derivatives upon injection and accordingly were found to be very toxic.

**Biological Aspects.** The acute toxicities of the secondary amines of 10,11-dihydrodibenzo[b,f]thiepin [D-(R)- and L-(S)-5] and 6,11-dihydrodibenzo[b,e]thiepin [D-(R)- and L-(S)-7] were strikingly similar, with acute LD<sub>50</sub> values in mice ranging from 145 to 160 mg/kg ip (Table I). *N*-Methylation of D-(R)- and L-(S)-5 yielded analogs D-(R)- and L-(S)-6, respectively, which significantly elevated the LD<sub>50</sub> values to 195 mg/kg (*p* < 0.05). With increasing doses, animals appeared to be sluggish, while at lethal doses all mice exhibited a reduction in spontaneous motor activity and muscle tone, with the appearance of tremors; in some instances, exophthalmos, lachrymation, and analgesia were observed. Toxic symptoms, evident only immediately prior to death, included writhing, jumping, ataxia, loss of righting reflex, tonic-clonic convulsive seizures of the body and limbs, and respiratory arrest. Death usually occurred within 10 min after the administration of D-(R)- or L-(S)-5 and their respective *N*-methylated analogs D-(R)- or L-(S)-6. Mice surviving the first hour after drug administration appeared normal at the 24-hr end point.

**Table I.** LD<sub>50</sub>'s of D-(R)- and L-(S)-Aminopyrrolidino-Substituted Aryl Analogs

Compd no.	LD <sub>50</sub> , <sup>a</sup> mg/kg ip (95% confidence limits)
D-(R)-5	160 (148-172)
L-(S)-5	155 (141-169)
D-(R)-6	195 (180-212)
L-(S)-6	195 (179-213)
D-(R)-7	145 (133-157)
L-(S)-7	160 (152-168)
D-(R)-8	Between 125-300 <sup>b</sup>
L-(S)-8	Between 125-300 <sup>b</sup>
D-(R)-9	88 (79-99)
L-(S)-9	87 (78-99)

<sup>a</sup>Test compounds were administered to groups of six mice and lethality was determined 24 hr later. <sup>b</sup>Difficult to define because of extremely poor water solubility.

The unbridged diphenyl analogs, D-(R)- and L-(S)-9, were the most toxic compounds studied in this series (Table I). Unlike the previously described dibenzothiepins, which depressed spontaneous motor activity, the isomers of the diphenyl analogs elicited stimulation within 10 min after injection. Alertness, restlessness, and increased excitability were noted at 40 mg/kg; the toxic symptoms observed at dosages approaching the LD<sub>50</sub> resembled those observed with the dibenzothiepins. The limited solubility and instability of xanthene analogs D-(R)- and L-(S)-8 precluded thorough biological evaluation of these isomers.

The general depressant effects were assessed by studying whether these test compounds were capable of prolonging barbiturate sleeping time. The results of these studies employing a fixed dose of test compound, namely 80 mg/kg, are shown in Table II. D-(R)- and L-(S)-5 and their respective N-methylated analogs [D-(R)- and L-(S)-6] enhanced phenobarbital sleeping time while the dihydro-dibenzo[b,e]thiepin isomers D-(R)- and L-(S)-7 produced a statistically nonsignificant prolongation of sleep. To permit us to differentiate whether these potentiating effects were the consequence of an impairment in phenobarbital

metabolism or a direct depression of the central nervous system, barbitol, a nonmetabolized barbiturate, was also studied. Enhancement of barbitol sleeping time was unequivocally demonstrated with D-(R)- and L-(S)-5 and their tertiary analogs D-(R)- and L-(S)-6, while the potentiation by D-(R)- and L-(S)-7 was nonsignificant. Doses of the diphenylmethyl analogs D-(R)- and L-(S)-9 approaching the LD<sub>50</sub> potentiated pentobarbital but not barbitol sleeping times. These results, and the grossly observable excitation, suggest that the diphenylmethyl derivatives inhibit the metabolism and biological inactivation of pentobarbital. Little, if any, stereoselective differences in activity were observed between the D-(R) and L-(S) isomers of the test compounds studied.

The dibenzothiepins were tested for their ability to interfere with conditioned-avoidance responding in mice. In studies employing D-(R)- and L-(S)-5 and 7 in doses as high as 130 mg/kg, animals continued to avoid a punishing shock when tested 30 min after drug administration. It was noted that a large percentage of the animals tested exhibited a sluggish rate of responding at this high dose; that is, they slowly ran down the shuttle box to the safe area. The N-methylated analogs D-(R)- and L-(S)-6, at doses of 80 mg/kg given 30 min prior to testing, significantly ( $p < 0.01$ ) impaired the ability of mice to avoid, but not escape, the shock; at this dosage level, both isomers were equally potent in this test. It should be emphasized, however, that these compounds possess relatively low potency; we have observed that chlorpromazine at doses of 3-5 mg/kg significantly disrupts conditioned-avoidance behavior.

At doses up to 80 mg/kg ip, none of the test compounds were able to antagonize the salivation, lachrymation, diarrhea, urination, and tremors produced by oxotremorine (0.5 mg/kg) in mice. D-(R)-5 (20-40 mg/kg) antagonized oxotremorine-induced hypothermia (Table III); this antagonism was of interest in view of the hypothermic actions of D-(R)-5 (see below). However, at doses of 65-130 mg/kg these analogs failed to antagonize the effects of reserpine or tryptamine and did not potentiate the stimulatory effects of L-Dopa or tryptamine. On the basis of the

**Table II.** Potentiating Effect of D-(R)- and L-(S)-Aminopyrrolidino-Substituted Analogs on Barbiturate Sleeping Time

Expt no.	Barbiturate (dose, mg/kg ip)	Compd (dose, <sup>a</sup> mg/kg ip)	Sleeping time, <sup>b</sup> min	<i>p</i> rel to control
1	Pentobarbital Na (40)	Control	134.4 ± 22.2	
		D-(R)-5 (80)	536.0 ± 38.6	0.001
		L-(S)-5 (80)	490.3 ± 36.9	0.001
2	Barbital Na (250)	Control	5.3 ± 2.4	
		D-(R)-5 (80)	232.0 ± 42.0	0.001
		L-(S)-5 (80)	262.6 ± 41.5	0.001
3	Pentobarbital Na (40)	Control	57.6 ± 11.9	
		D-(R)-7 (80)	150.2 ± 28.4	N.S.
		L-(S)-7 (80)	99.1 ± 27.9	N.S.
4	Barbital Na (250)	Control	15.4 ± 9.8	
		D-(R)-7 (80)	71.3 ± 38.3	N.S.
		L-(S)-7 (80)	55.6 ± 32.8	N.S.
5	Pentobarbital Na (40)	Control	23.2 ± 5.0	
		D-(R)-6 (80)	188.0 ± 36.1	0.001
		L-(S)-6 (80)	242.3 ± 49.7	0.001
6	Barbital Na (250)	Control	0	
		D-(R)-6 (80)	376.7 ± 71.1	0.001
		L-(S)-6 (80)	489.2 ± 156	0.001
7	Pentobarbital Na (40)	Control	14.0 ± 3.2	
		D-(R)-9 (80)	94.0 ± 10.4	0.01
		L-(S)-9 (80)	93.6 ± 10.1	0.01
8	Barbital Na (250)	Control	0	
		D-(R)-9	0	N.S.
		L-(S)-9	0	N.S.

<sup>a</sup>Each compound was injected into mice 45 min before barbiturates. <sup>b</sup>Values represent the mean of six to ten mice ± S.E.M. Sleeping time is defined as the duration of time between the loss and recovery of the righting reflex of mice.

**Table III.** Interactions of Oxotremorine and Atropine with Dihydrodibenzothiepin Analogs on Rectal Temperature in Mice

Expt	Test compd	Dose, mg/kg ip		N	Redn of rectal temp at 60 min $\pm$ S.E.M.
A <sup>a</sup>	Saline	1 ml/100 g	Oxotremorine	10	7.5 $\pm$ 0.4
	D-(R)-5	20	Oxotremorine	10	5.5 $\pm$ 0.4 <sup>b</sup>
	D-(R)-5	40	Oxotremorine	10	5.3 $\pm$ 0.4 <sup>b</sup>
B <sup>c</sup>	Saline	1 ml/100 g	Atropine	5	0.0 $\pm$ 0.2
	L-(S)-5	80	Saline	5	2.6 $\pm$ 0.7
	L-(S)-5	80	Atropine	5	4.1 $\pm$ 0.7 <sup>d</sup>

<sup>a</sup>Mice were pretreated with saline or test drugs 15 min prior to administration of oxotremorine (0.5 mg/kg ip). <sup>b</sup>Drug values significantly lower than controls ( $p < 0.01$ ). <sup>c</sup>Mice were pretreated with saline or atropine (5 mg/kg ip) 10 min prior to administration of test drugs. <sup>d</sup>Atropine nonsignificantly ( $p < 0.20$ ) potentiated L-(S)-5-induced hypothermia.

**Table IV.** Hypothermic Activity of Dihydrodibenzothiepin and Diphenylmethane Analogs in Mice<sup>a</sup>

Compd	Time of peak hypothermia, min	Redn in body temp ( $^{\circ}$ C) $\pm$ S.E.M.
Saline	160	0.2 $\pm$ 0.3 <sup>b</sup>
D-(R)-5	40	4.3 $\pm$ 0.6
L-(S)-5	40	3.2 $\pm$ 0.8
D-(R)-6	60	7.9 $\pm$ 0.8
L-(S)-6	60	8.0 $\pm$ 0.5
D-(R)-9	40	3.2 $\pm$ 0.8
L-(S)-9	40	2.0 $\pm$ 0.8

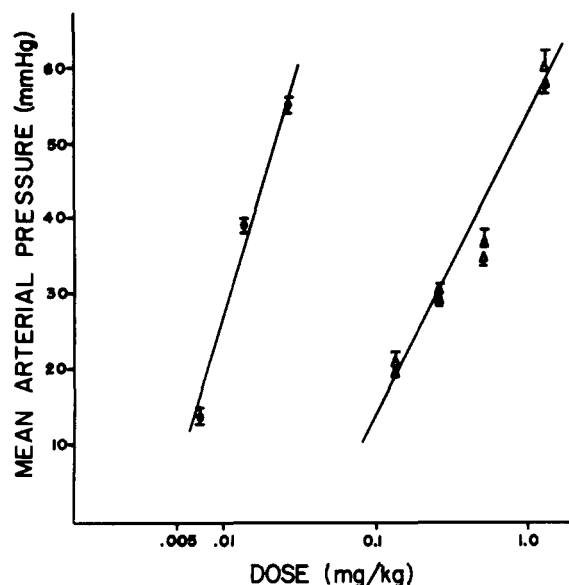
<sup>a</sup>Mice were administered saline (1 ml/100 g) or test compounds (80 mg/kg ip) and rectal temperatures monitored at 20-min intervals for 240 min. Room temperature was  $23 \pm 0.5^{\circ}$ . <sup>b</sup>Values represent the mean reduction in body temperature  $\pm$  S.E.M. for groups of five mice.

tests conducted, it was concluded that the test compounds lacked antidepressant or anti-Parkinson activities.

All test compounds produced hypothermia in mice in a dose-dependent manner, with no apparent stereoselective differences observed (Table IV). Employing a fixed dose of 80 mg/kg, the *N*-methyl analogs D-(R)- and L-(S)-6 were about twice as potent as their desmethyl analogs D-(R)- and L-(S)-5. It was of interest to determine whether atropine sulfate (5 mg/kg) was capable of blocking the hypothermic effects of the dibenzothiepins. We noted unexpectedly that atropine nonsignificantly ( $p < 0.20$ ) potentiated the reduction in body temperature elicited by L-(S)-5 1.6-fold (Table III); at this time we have no explanation for these findings.

The secondary and tertiary amines in the dihydrodibenzothiepin series (5-7) all possessed approximately equivalent hypotensive potency, with no stereoselective differences observed. The effects of D-(R)- and L-(S)-5 on mean arterial pressure in an anesthetized rat are shown in Figure 1; for comparative purposes, the hypotensive effects of acetylcholine were also studied. Acetylcholine was found to be approximately 30 times as active as the test compounds. Doses of 0.28 mg/kg iv of D-(R)- and L-(S)-7 reduced the mean arterial pressure 30-36 mm, which was equivalent to the effects observed at the same dose of their position isomers D-(R)- and L-(S)-5. The *N*-methylated analogs of 5, namely D-(R)- and L-(S)-6, also lowered blood pressure 27-35 mm. Among the compounds studied in this series the diphenylmethyl analogs, D-(R)- and L-(S)-9, were least active in their hypotensive potency; 5.6 mg/kg iv elicited only an 11-14 mm drop in pressure.

All test compounds possessed antihistaminic, anticholinergic, and antiserotonergic activities *in vitro* employing the classical method of Magnus on the guinea pig ileum. These results are depicted in Table V. D-(R)- and L-(S)-5 were approximately 6-10 times more potent than D-(R)- and L-(S)-7 in antihistaminic potency. The tertiary



**Figure 1.** The effects of D-(R)-5 ( $\blacktriangle$ ), L-(S)-5 ( $\triangle$ ), and acetylcholine ( $\bullet$ ) on mean arterial pressure in the anesthetized rat. Compounds were injected into the external jugular vein and mean arterial pressure was measured from the common carotid artery. Values represent the mean  $\pm$  S.E.M. blood pressure (mm) of three determinations.

amines, D-(R)- and L-(S)-6, were about 60 times more active in anticholinergic activity than D-(R)- and L-(S)-5, and about ten times as potent in their relative antihistaminic and antiserotonergic effects. Among the dihydrodibenzothiepin analogs, the only major stereoselective difference was observed between D-(R)- and L-(S)-7; in preliminary experiments, the latter isomer was nine times as potent in its ability to antagonize serotonin. The diphenylmethyl compounds D-(R)- and L-(S)-9 were the most active test compounds studied *in vitro* and were almost as potent as methapyrilene, atropine, and cyproheptadine in their capacity to antagonize histamine, acetylcholine, and serotonin, respectively. Limited solubility in water and their instability in aqueous buffers below pH 7 precluded testing *in vitro* of the xanthene analogs, D-(R)- and L-(S)-8.

## Discussion

Correlation of structure and biological activity of tricyclic antidepressive and antipsychotic drugs is difficult because such biological properties are influenced by seemingly minor changes in chemical composition and stereochemistry of the tricyclic ring, ring substituents, and the aminoalkyl side chain.<sup>6,7,17,18</sup> While, for example, optical isomers of 3-dimethylamino-2-methylpropyl-substituted phenothiazines exhibit significantly different potencies,<sup>19</sup> few stereoselective differences were observed in the biological activity of the D-(R)- and L-(S)-aminopyrrolidino-sub-

**Table V.** Antagonist Activity *in Vitro* for Dihydrodibenzothiepin and Diphenylmethyl Analogs against Histamine, Serotonin, and Acetylcholine

Antagonists <sup>a</sup>	ED <sub>50</sub> ± S.E.M. <sup>b</sup>		
	Histamine·2HCl (2.4 × 10 <sup>-8</sup> M)	Serotonin creatinine sulfate (5.0 × 10 <sup>-8</sup> M)	Acetylcholine Cl (2.4 × 10 <sup>-8</sup> M)
Methapyrilene HCl	(5.7 ± 1.0) × 10 <sup>-9</sup>		
Cyproheptadiene HCl		(6.3 ± 0.7) × 10 <sup>-8</sup>	
Atropine sulfate			(1.8 ± 0.0) × 10 <sup>-9</sup>
D-(R)-5	(5.9 ± 0.2) × 10 <sup>-8</sup>	2.0 × 10 <sup>-6</sup>	(5.4 ± 0.2) × 10 <sup>-6</sup>
L-(S)-5	(8.4 ± 0.2) × 10 <sup>-8</sup>	3.5 × 10 <sup>-6</sup>	(6.3 ± 0.7) × 10 <sup>-6</sup>
D-(R)-6	(4.4 ± 0.2) × 10 <sup>-8</sup>	(1.3 ± 0.3) × 10 <sup>-7</sup>	(3.1 ± 0.4) × 10 <sup>-8</sup>
L-(S)-6	(4.1 ± 0.4) × 10 <sup>-8</sup>	(1.4 ± 0.3) × 10 <sup>-7</sup>	(3.7 ± 0.5) × 10 <sup>-8</sup>
D-(R)-7	(6.2 ± 0.9) × 10 <sup>-7</sup>	1.0 × 10 <sup>-6</sup>	(3.5 ± 0.3) × 10 <sup>-6</sup>
L-(S)-7	(5.3 ± 0.3) × 10 <sup>-7</sup>	9.0 × 10 <sup>-6</sup>	(4.6 ± 0.2) × 10 <sup>-6</sup>
D-(R)-9	(8.8 ± 0.5) × 10 <sup>-9</sup>	(9.4 ± 0.4) × 10 <sup>-8</sup>	(8.5 ± 0.4) × 10 <sup>-9</sup>
L-(S)-9	(9.2 ± 0.5) × 10 <sup>-9</sup>	(9.0 ± 0.9) × 10 <sup>-8</sup>	(9.0 ± 0.5) × 10 <sup>-9</sup>

<sup>a</sup>Guinea pig ileum was pretreated with each antagonist at 37° for 2 min before an agonist was added to the bath. <sup>b</sup>Values are the results of three determinations ± S.E.M. Values without S.E.M. are the mean of two determinations.

stituted 6-7-6 tricyclic systems studied. Owing to the instability of similarly substituted 6-6-6 tricyclic systems of xanthene (8) and its thioxanthene analog, comparisons in biological activity between 6-6-6 and 6-7-6 ring systems in this series could not be carried out. As expected, the tertiary amines of D-(R)- and L-(S)-5 (*i.e.*, 6) possessed lower acute toxicity, with greater central and *in vitro* activity than the corresponding secondary amines. Moreover, while they are of relatively low potency, based upon conditioned-avoidance studies, these compounds appear to have potential antipsychotic activity; insertion of chlorine at the 2 position may enhance the activity of this series.<sup>6</sup> Stereoselective differences in biological activity of diastereoisomeric analogs also may be enhanced by such nuclear substitution.<sup>6</sup> With the exception of the lead obtained as a result of biological evaluation of D-(R)- and L-(S)-6, there is little evidence to suggest that this series of test compounds possesses potential antipsychotic, antidepressant, or anti-Parkinson activities. Apart from the diphenylmethyl analogs 9, all compounds were approximately equiactive in their hypotensive potency. For this preliminary series of compounds further efforts to define the nature of the diastereoisomeric composition of the D-(R)- and L-(S)-aminopyrrolidino-substituted dihydrodibenzothiepins for the purpose of correlating structure with biological activity are not warranted because of their low potency. From these studies it does appear, however, that structural modification of the dihydrodibenzo[b,f]thiepins, rather than the [b,e]thiepins, has the greatest potential for development of clinically useful antipsychotic drugs.

The diphenylmethyl analogs 9 were observed to be highly active, but not selective, antagonists *in vitro* of histamine, serotonin, and acetylcholine. The lack of stereoselective antihistaminic activity *in vitro* is in agreement with studies carried out by others;<sup>20-27</sup> stereoselective antihistaminic activity has only been observed when the asymmetric center was located α to the aromatic ring functions suggesting that regions adjacent to the H<sub>1</sub> histamine receptor are asymmetric.<sup>1,5</sup> Receptor affinity for aryl groups binding to extrahistamine-receptor sites is influenced by the asymmetry of the C to which they are bonded. Only the less potent and smaller 1-phenylpyrrolidine analogs 2, having an asymmetric carbon atom α to the amino group, exhibit stereoselective antihistaminic activity.<sup>1</sup> The relatively high antihistaminic activity observed for the dihydrodibenzothiepin and diphenylmethyl analogs could be predicted and is in general agreement with structural and conformational requirements described by Casy and Ison<sup>28</sup> for H<sub>1</sub>-receptor antagonists; the aromatic rings of the tricyclic analogs are at approxi-

mately right angles to one another and regardless of absolute configuration comparison of Dreiding molecular models indicates that the alkylaminopyrrolidino function may be rotated, thereby affording a juxtaposition of aromatic rings and basic amino groups similar to those found in the amino-2-butenes studied by Casy and Ison.<sup>28</sup> These data also support conclusions of Hanna and Ahmed;<sup>29</sup> there does not seem to be a strict requirement for the fully extended *trans*-N-C-C-N conformation for H<sub>1</sub>-receptor antagonists.<sup>29</sup> In fact, potent antihistamines have N to aromatic ring distances ranging from approximately 5 to 7 Å<sup>5</sup> where at least one ring is capable of assuming a position 5-6 Å from the amino N.<sup>5</sup> Conformational alteration of this distance by varying the dihedral angle in N-C-C-N falls within a 1-Å range (*i.e.*, the N to N distance in *trans*-N-C-C-N is *ca.* 2.9 Å while the N to N distance for the eclipsed conformation is *ca.* 1.9 Å); the alteration of this angle, therefore, should afford compounds having relatively small differences in antihistaminic potency.

### Experimental Section†

10-[L-(S)-3-Ethylaminopyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin dihydrochloride (5) was prepared from L-(S)-19 according to the method described for L-(S) enantiomorph 7 in 72% yield; mp 130-140°; ORD (*c* 1.47, MeOH) [φ]<sub>350</sub> +5.7°, [φ]<sub>400</sub> +2.2°, [φ]<sub>450</sub> +0.5°.

10-[D-(R)-3-Ethylaminopyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin dihydrochloride (5) was prepared from D-(R)-19 according to the method described for L-(S) enantiomorph 7 in 73% yield; mp 131-140°; ORD (*c* 1.44, MeOH) [φ]<sub>350</sub> -15.2°, [φ]<sub>400</sub> -9.1°, [φ]<sub>450</sub> -6.6°. *Anal.* (C<sub>20</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>·H<sub>2</sub>O) C, H, N.

10-[D-(R)-3-Methylethylaminopyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin dihydrochloride (6). To a mixture of 1.8 ml (0.035 mol) of 90% HCO<sub>2</sub>H and 1.2 ml (0.015 mol) of 37% H<sub>2</sub>CO was added 2.9 g (0.009 mol) of D-(R)-5. The mixture was heated on a steam bath for 16 hr. After cooling, 15 ml of 3 N HCl was added and the mixture concentrated under reduced pressure. The residue was shaken with 3 N NaOH and Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). Dry Et<sub>2</sub>O was added until the total volume was *ca.* 850 ml. Dry HCl was passed through the solution for 10 min precipitating an off-white solid. The mixture was cooled for 2 hr at -15° and filtered. The hygroscopic solid was recrystallized from MeOH-Et<sub>2</sub>O affording 1.39 g (38%) of the dihydrochloride salt which melts with decomposition at temperatures >75°; ORD (*c* 1.38, MeOH) [φ]<sub>350</sub> -28.3°, [φ]<sub>400</sub> -19.7°, [φ]<sub>450</sub> -14.6°. *Anal.* (C<sub>21</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>S) C, H, N.

10-[L-(S)-3-Methylethylaminopyrrolidino]-10,11-dihydrodibenzo[b,f]thiepin dihydrochloride (6) was prepared from L-(S)-5

†Melting points were determined using a calibrated Thomas-Hoover melting point apparatus. Compounds were characterized with the aid of a Perkin-Elmer 257 spectrophotometer and Varian A-60A nmr spectrometer. ORD spectra were recorded at 25° utilizing a Durham-Jasco ORD/CD instrument. Elemental analyses were performed by Clark Microanalytical Labs, Urbana, Ill.

according to the method described for the D-(R) isomer affording 1.55 g (42%) of dihydrochloride salt which melts with decomposition at temperatures  $>75^\circ$ : ORD ( $c$  1.49, MeOH)  $[\phi]_{350} +9.4^\circ$ ,  $[\phi]_{400} +5.5^\circ$ ,  $[\phi]_{450} +3.3^\circ$ ; mass spectrum (70 eV)  $m/e$  (rel intensity) 338 (0.6) parent, 210 (base) dibenzothiepin cation.

**11-[L-(S)-3-Ethylaminopyrrolidino]-6,11-dihydrodibenzo[b,e]thiepin Dihydrochloride (7).** To a stirred suspension of  $\text{LiAlH}_4$  (1.67 g, 0.045 mol) in dry  $\text{Et}_2\text{O}$  (200 ml) was added 4.0 g (0.011 mol) of L-(S)-20 suspended in  $\text{Et}_2\text{O}$  (100 ml). After addition, the mixture was stirred overnight and the excess  $\text{LiAlH}_4$  decomposed by dropwise addition of ice-cold 10% NaOH. The mixture was filtered and the  $\text{Et}_2\text{O}$  filtrate was washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure affording a residual oil. Passage of HCl gas through an  $\text{Et}_2\text{O}$  solution of the oil afforded the amine HCl salt. The salt was filtered and recrystallized by dissolving in a minimum amount of EtOH followed by addition of  $\text{Et}_2\text{O}$ -petroleum ether (1:1). Recrystallization afforded 3.0 g (70%) of 7: mp  $125\text{--}135^\circ$  dec; ORD ( $c$  1.52, MeOH)  $[\phi]_{350} -11.5^\circ$ ,  $[\phi]_{400} -8.3^\circ$ ,  $[\phi]_{450} -6.8^\circ$ . *Anal.* ( $\text{C}_{20}\text{H}_{26}\text{Cl}_2\text{N}_2\text{S}\cdot 2\text{H}_2\text{O}$ ) C, H, N.

**11-[D-(R)-3-Ethylaminopyrrolidino]-6,11-dihydrodibenzo[b,e]thiepin dihydrochloride (7)** was prepared from D-(R)-20 according to the method described for the L-(S) enantiomorph in 62% yield: mp  $124\text{--}133^\circ$  dec.

**1-(9'-Xanthyl)-3-L-(S)-ethylaminopyrrolidine (8).** To a slurry of 7.0 g (0.18 mol) of  $\text{LiAlH}_4$  in 250 ml of dry  $\text{Et}_2\text{O}$  was added 4.7 g (0.014 mol) of N-(9'-xanthyl)-2-L-(S)-acetylaminosuccinimide (21). The mixture was heated at reflux with constant stirring for 24 hr. After cooling, the excess  $\text{LiAlH}_4$  was decomposed by dropwise addition of 10% aqueous NaOH solution. The white salts that formed were filtered and washed with liberal portions of  $\text{Et}_2\text{O}$ . The filtrate and washings were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. The residual yellow oil was distilled affording 3.2 g (78%) of a viscous pale yellow oil: bp  $162\text{--}164^\circ$  (0.15 mm);  $[\alpha]_D +2.3^\circ$  ( $c$  2.2, MeOH). *Anal.* ( $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ ) C, H, N.

**1-(9'-Xanthyl)-3-D-(R)-ethylaminopyrrolidine (8)** was prepared from D-(R)-21 in a manner similar to the one described for L-(S)-8 affording a viscous yellow oil: bp  $166\text{--}167^\circ$  (0.30 mm);  $[\alpha]_D -2.7^\circ$  ( $c$  2.3, MeOH). *Anal.* ( $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ ) C, H, N.

**Decomposition of 1-(9'-Xanthyl)-3-ethylaminopyrrolidine (8).** Slow addition of 0.4 g of 8 to 100 ml of 3% HCl with constant stirring gave a yellow mixture with a generous precipitate. The solid material was collected and air-dried. The solid gave a very broad melting range of  $85\text{--}145^\circ$ . The solid material was shaken with 3 N NaOH and ether. Much material was insoluble in either phase and was collected. This insoluble material was recrystallized from  $\text{EtOAc}$  affording a white solid, mp  $217\text{--}220^\circ$ . This material was identified as di-9-xanthyl ether (lit.<sup>16</sup> mp  $212\text{--}214^\circ$ ) by its nmr and ir spectra.

The ether phase from the above extraction was washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The solid residue had a melting range of  $85\text{--}130^\circ$ . The nmr and ir spectra of this material showed it to be a mixture of xanthone (53%) and xanthene (47%).

**D-(R)-3-Ethylamino-1-diphenylmethylpyrrolidine (9).** To 4.36 g (0.12 mol) of  $\text{LiAlH}_4$  in 400 ml of dry  $\text{Et}_2\text{O}$  was added 3.22 g (0.01 mol) of D-(R)-22. The mixture was stirred and refluxed for 48 hr after which time the excess  $\text{LiAlH}_4$  was decomposed by addition of ice-cold 10% KOH. The salts were filtered and the  $\text{Et}_2\text{O}$  solution was dried ( $\text{CaSO}_4$ ) and concentrated under reduced pressure affording 2.6 g (93%) of a colorless oil, bp  $139\text{--}141^\circ$  (0.10–0.15 mm), which became pale yellow on exposure to air. The ORD rotation was too small to be observed.

**L-(S)-3-Ethylamino-1-diphenylmethylpyrrolidine (9)** was prepared from L-(S)-22 by the method described for the preparation of D-(R)-9 affording 2.6 g (93%) of a colorless oil, bp  $139\text{--}141^\circ$  (0.10–0.15 mm). *Anal.* ( $\text{C}_{19}\text{H}_{24}\text{N}_2$ ) C, H, N.

**N-Acetyl-D-(R)- or -L-(S)-aspartyl anhydride (10)** was prepared according to methods previously published.<sup>1,3,30</sup>

**10-Amino-10,11-dihydrodibenzo[b,f]thiepin (11)** was prepared according to the method of Jilek and coworkers:<sup>8</sup> bp  $158\text{--}161^\circ$  (0.7 mm) [lit.<sup>8</sup> bp  $162\text{--}164^\circ$  (0.8 mm)].

**11-Amino-6,11-dihydrodibenzo[b,e]thiepin (12)** was prepared according to the method of Seidlova and coworkers:<sup>9</sup> mp  $149\text{--}150^\circ$  (lit.<sup>9</sup> mp  $149\text{--}150^\circ$ ).

**9-Aminoxanthene (13).** To a solution of 70 g (1.25 mol) of KOH in 500 ml of 95% EtOH was added 15.0 g (0.045 mol) of N-carbobenzoxo-9-aminoxanthene prepared according to the method of Phillips and Pitt.<sup>11</sup> The mixture was heated at reflux for 3 days. After cooling 1.5 l. of  $\text{Et}_2\text{O}$  was added. The resulting solution was washed with  $\text{H}_2\text{O}$  until the washings were neutral. The

solution was dried ( $\text{Na}_2\text{SO}_4$ ) and the  $\text{Et}_2\text{O}$  removed under reduced pressure. The residual oil was distilled affording 6.4 g (72%) of 13, bp  $128\text{--}129^\circ$  (0.08 mm). Recrystallization from hexane afforded white needles, mp  $58\text{--}60^\circ$  (lit.<sup>12</sup> mp  $59\text{--}61^\circ$ ).

**Diphenylmethylamine (14)** was prepared in 68% yield by the method of Crossley and Moore<sup>13</sup> affording an oil: bp  $109\text{--}111^\circ$  (0.5 mm) [lit.<sup>31</sup> bp  $125\text{--}127^\circ$  (1.0 mm)].

**10-[L-(S)-3-Acetamidosuccinimido]-10,11-dihydrodibenzo[b,f]thiepin (15).** The 10-aminothiepin 11 (14 g, 0.062 mol) dissolved in 25 ml of EtOH was added to a solution of 15.7 g (0.10 mol) of L-(S)-10 in 100 ml of EtOH. After stirring at room temperature for 3 hr the solvent was removed under reduced pressure. The residual solid was dissolved in 10%  $\text{Na}_2\text{CO}_3$  and extracted with  $\text{Et}_2\text{O}$  to remove any unreacted amine. On acidification of the aqueous layer (pH 2), a flocculent precipitate of 15 separated. The precipitate was filtered, dried, and crystallized from MeOH affording 23.0 g (98%) of 15, mp  $184\text{--}188^\circ$ .

**10-[D-(R)-3-Acetamidosuccinimido]-10,11-dihydrodibenzo[b,f]thiepin (15)** was prepared from D-(R)-10 according to the method used for the preparation of the L-(S) antipode in 89% yield: mp  $183\text{--}187^\circ$ .

**11-[L-(S)-3-Acetamidosuccinimido]-6,11-dihydrodibenzo[b,e]thiepin (16).** 11-Aminothiepin (12, 3.6 g, 0.02 mol) dissolved in 10 ml of EtOH was added to a solution of 3.1 g (0.02 mol) of L-(S)-10 in 35 ml of EtOH. After stirring at room temperature for 3 hr the solvent was removed under reduced pressure. The residual solid was dissolved in 10%  $\text{Na}_2\text{CO}_3$  and extracted with  $\text{Et}_2\text{O}$  to remove any unreacted amine. On acidification of the aqueous layer (pH 2), a flocculent precipitate of 16 separated. The precipitate was filtered, dried, and crystallized from methanol affording 7.0 g (98%) of 16, mp  $199\text{--}204^\circ$  dec. *Anal.* ( $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ ) C, H, N, S.

**11-[D-(R)-3-Acetamidosuccinimido]-6,11-dihydrodibenzo[b,e]thiepin (16)** was prepared from D-(R)-10 according to the method used for the preparation of the L-(S)-16 isomer affording D-(R)-16 in 89% yield: mp  $200\text{--}206^\circ$  dec.

**D-(R)- $\alpha$ -Acetamido-N-diphenylmethylsuccinamide (18).** To a rapidly stirred solution of 36.6 g (0.2 mol) of 14 in 500 ml of absolute EtOH was added 15.7 g (0.10 mol) of D-(R)-10. The solution was stirred at room temperature for 1 hr. The reaction mixture was dissolved in 3 l. of 10%  $\text{Na}_2\text{CO}_3$  and washed with  $\text{Et}_2\text{O}$ -PhH (1:1). The carbonate solution was acidified with concentrated HCl and the white precipitate filtered. The solid was dried in a vacuum oven over  $\text{P}_2\text{O}_5$ . The resulting solid 18 (27.5 g, 81%), mp  $171\text{--}174^\circ$  (likely a mixture of  $\alpha$ - and  $\beta$ -amide isomers), was used without further purification for the preparation of D-(R)-imide 22. The L-(S) isomer 18 was similarly prepared from 14 and L-(S)-10 in approximately the same yield.

**10-[L-(S)-3-Acetamidosuccinimido]-10,11-dihydrodibenzo[b,f]thiepin (19).** Reaction of L-(S)-15 (24 g, 0.063 mol) in rapidly stirring  $\text{Ac}_2\text{O}$  (300 ml) at  $90\text{--}95^\circ$  for 1 hr afforded a yellow solution which was decolorized with charcoal, filtered, and concentrated under reduced pressure. The residue was crystallized from benzene affording 14.5 g (44%) of imide 19, mp  $182\text{--}185^\circ$ . *Anal.* ( $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ ) N, S; C: calcd, 65.56; found, 65.03; H: calcd, 4.95; found, 4.20.

**10-[D-(R)-3-Acetamidosuccinimido]-10,11-dihydrodibenzo[b,f]thiepin (19)** was prepared from D-(R)-15 according to the method used for the preparation of the L-(S) antipode 19 in 50% yield: mp  $181\text{--}184^\circ$ .

**11-[L-(S)-3-Acetamidosuccinimido]-6,11-dihydrodibenzo[b,e]thiepin (20).** Reaction of L-(S)-16 (6.0 g, 0.013 mol) in rapidly stirring  $\text{Ac}_2\text{O}$  (75 ml) at  $90\text{--}95^\circ$  for 1 hr afforded a yellow solution. This solution was decolorized with charcoal, filtered, and concentrated under reduced pressure. The residue was crystallized from PhH affording 3.6 g (44%) of imide 20, mp  $180\text{--}183^\circ$ .

**11-[D-(R)-3-Acetamidosuccinimido]-6,11-dihydrodibenzo[b,e]thiepin (20)** was prepared from D-(R)-16 according to the method described for the L-(S) isomer 20 in 41% yield: mp  $179\text{--}182^\circ$ .

**N-(9'-Xanthyl)-2-L-(S)-acetylaminosuccinimide (21).** To a solution of 30.0 g (0.152 mol) of 9-aminoxanthene (13) in 1.8 l. of absolute EtOH was added 25.0 g (0.159 mol) of finely ground L-(S)-10. The mixture was stirred at room temperature for ca. 2 hr until it became semisolid. The mixture was filtered and the solid dried at  $90^\circ$  in a vacuum oven yielding 18.0 g of a mixture of  $\alpha$ - and  $\beta$ -amides 17. The filtrate was stirred for 12 hr at room temperature after which time it again became semisolid. The solid material obtained by filtration and drying afforded an additional 13.2 g of amides 17. The final filtrate was concentrated to dryness affording an additional 20.8 g of solid 17.

The combined solids 17 (52.0 g) were heated on a steam bath in 650 ml of Ac<sub>2</sub>O with occasional shaking. After 20 min a clear solution was obtained. After heating for an additional 25 min the solvent was removed under reduced pressure. The residue obtained was dissolved in 3 l. of hot dioxane-EtOAc-EtOH (1:1:1). After cooling for 16 hr at 0–5°, crystals of L-(S)-imide 21 (6.3 g) were collected. The filtrate was concentrated to ca. 1 l. causing the precipitation of additional solid material which was recrystallized from dioxane-EtOAc-EtOH (1:2:2) affording 9.0 g of crystalline L-(S)-imide 21. The combined yield of imide, mp 272–274°, totals 15.3 g [0.046 mol, 30% based on starting 9-aminoxanthine (13)].

N-(9'-Xanthyl)-2-D-(R)-acetylaminosuccinimide (21) was prepared for essentially the same manner from 13 and D-(R)-10 as described for L-(S)-21; mp 269–272°. Anal. (C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

D-(R)-α-Acetamido-N-diphenylmethylsuccinimide (22). To 26.0 g (0.077 mol) of D-(R)-amide 18 was added 470 ml of hot Ac<sub>2</sub>O which was stirred and heated at 100° for 2 hr while the solid slowly dissolved. The solvent was removed under reduced pressure affording a viscous red oil which turned to a white powder on trituration with Et<sub>2</sub>O-PhH. Recrystallization from CHCl<sub>3</sub>-hexane afforded 11.2 g (45%) of D-(R)-22; mp 167–170°; ORD (c 2.12, MeOH) [φ]<sub>D</sub> +1.60°, [φ]<sub>500</sub> +2.81°, [φ]<sub>400</sub> +2.81°, [φ]<sub>300</sub> +6.18°. Anal. (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

L-(S)-α-Acetamido-N-diphenylmethylsuccinimide (22) was prepared from L-(S)-18 by a method identical with the preparation of D-(R)-22 in similar yield: ORD (c 2.12, MeOH) [φ]<sub>D</sub> –1.06°, [φ]<sub>500</sub> –2.97°, [φ]<sub>400</sub> –3.95°, [φ]<sub>300</sub> –9.23°.

**Pharmacology.** The animals used in the pharmacological evaluation of the test compounds were male albino ICR mice (20–25 g), male Wistar rats (250–300 g), and guinea pigs (250–350 g) of both sexes. All test compounds were dissolved or suspended in an aqueous vehicle. Acute toxicity was evaluated in mice 24 hr after a single ip injection in preliminary experiments. The time of maximal central activity was determined to be 30–45 min for all test compounds studied.

The compounds were evaluated for their general depressant activity by evaluating their ability to potentiate pentobarbital (40 mg/kg ip) and barbital (250 mg/kg ip) sleeping times in mice. Rectal temperatures of mice were recorded with a YS-1 Telethermometer (Yellow Springs Instrument Co.) equipped with a small animal probe, immediately prior to the injection of test compounds and at various time intervals up to 4 hr thereafter. Drug-induced impairment of conditioned-avoidance responding in a shuttle box, a measure of potential antipsychotic activity, was studied immediately prior to and 30 min after the administration of test compounds in groups of ten mice. Compounds were screened for antidepressant activity, as evidenced by their ability to prevent or antagonize reserpine (4 mg/kg ip) induced hypothermia,<sup>32</sup> sedation,<sup>32</sup> ptosis,<sup>33</sup> and tremors and by their ability to enhance tryptamine (35 mg/kg iv) induced tremors and convulsions.<sup>34</sup> The ability of test compounds (80 mg/kg ip) to potentiate L-Dopa (100 mg/kg ip) stimulation was utilized to study both antidepressant and anti-Parkinson activity.<sup>35</sup> Antagonism of oxotremorine (0.5 mg/kg ip) induced hypothermia, salivation, lacrimation, diarrhea, urination, and tremors was a further test conducted for anti-Parkinson activity.<sup>36</sup> The effects of the test compounds on mean arterial blood pressure were measured from the common carotid artery in rats anesthetized with sodium pentobarbital (80 mg/kg ip). Antihistaminic, anticholinergic, and antiserotonergic activities *in vitro* were determined utilizing the isolated guinea pig ileum, suspended in Kreb's solution at 37 ± 0.5° and bubbled with 95% O<sub>2</sub>–5% CO<sub>2</sub>.<sup>2,37</sup> The LD<sub>50</sub> and ED<sub>50</sub> values were calculated by the method of Litchfield and Wilcoxon.<sup>38,39</sup> Statistical comparisons of drug *vs.* control animals were carried out employing an analysis of variance followed by a *t* test.

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