A Series of Hexahydro[1,4]oxazino[3,4-*a*]isoquinolines as Potential Neuroleptics

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Received November 10, 1977

The synthesis and stereochemistry of *trans-N,N*-diethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino-[3,4-*a*]isoquinoline-3-carboxamide hydrochloride (**16**) and a series of analogues are described. **16** and its (+) isomer had neuroleptic properties in the Sidman avoidance test in gerbils. A few closely related amides of the trans series were active but cis amides were inactive as neuroleptics.

The studies reported in this paper began in 1962 when benzquinamide and tetrabenazine (Figure 1) were considered to be among the most promising nonphenothiazine neuroleptics.[1] Since *trans-N,N*-diethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide hydrochloride (**16**) has many of the structural features of these neuroleptics, its synthesis was undertaken. **16** proved to be a very interesting compound. We will describe the synthesis and configuration of **16** and its analogues and review briefly their pharmacological properties.

Chemistry. The [1,4]oxazino[3,4-*a*]isoquinoline ring system was novel when we began our synthesis (see Figure 2). More recently an aromatic analogue was described[2] and a synthesis[3] and NMR spectral analysis[4] were reported for some 3-oxo analogues. Aside from the patent literature[5,6] the only biological data reported for this class of compounds are those of the clinical studies with our most interesting compound, **16**.[7]

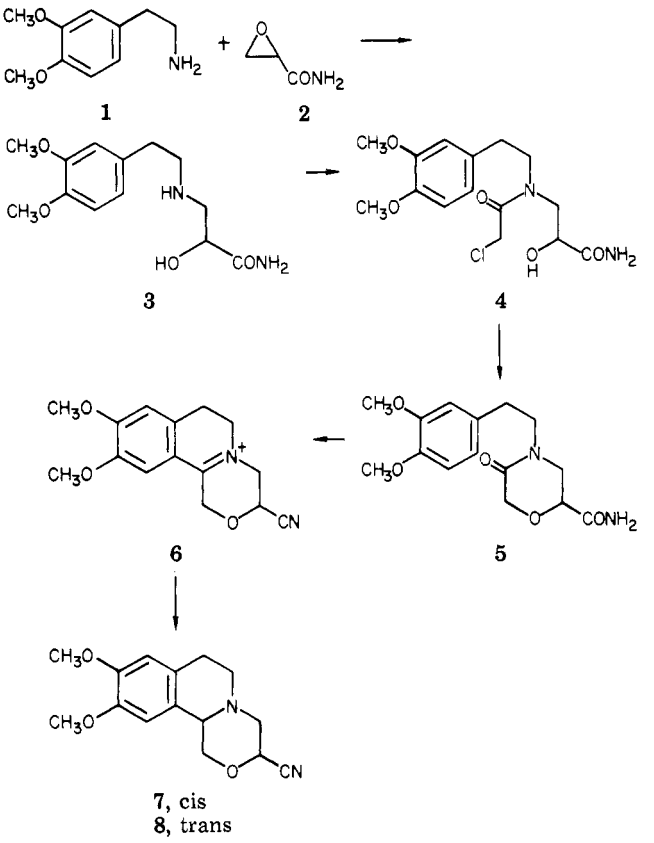
For the synthesis of **16**, homoveratrylamine (**1**) was first reacted with glycidamide (**2**) to give **3** which was acylated with chloroacetyl chloride to provide **4** (Scheme I). The latter compound was cyclized with NaOH in 2-propanol to the morpholinone carboxamide **5**. The Bischler–Napieralski cyclization of **5** to the intermediate **6** with $POCl_3$ also caused dehydration of the primary carboxamide. Compound **6** was not purified but was reduced directly with $NaBH_4$ in acetonitrile to give a mixture of cis and trans nitriles, **7** and **8**.

Hydrolysis of the mixed nitriles **7** and **8** in refluxing ethanolic KOH proceeded with isomerization at C_3 to give the trans carboxylic acid **10** (Table I). (See Figure 3 for conformation of the trans isomers.) The trans acid **10** was isolated as its hydrochloride salt and converted directly to a series of carboxamide derivatives (see Table I) via the corresponding acid chloride. The pure trans nitrile **8** was obtained from the trans acid **10** by Fischer esterification to the trans ester **13**, ammonolysis to the primary carboxamide **15**, and dehydration with $POCl_3$. Related compounds **31**–**35** were prepared analogously as described in the Experimental Section.

For analogues of the cis series, the mixture of nitriles **7** and **8** was fractionally crystallized from ethyl acetate to provide the pure cis nitrile **7**. Treatment of **7** with methanolic HCl provided the cis ester **11**, which with ammonia gave the cis primary carboxamide **14**. Hydrolysis of **7** with dilute aqueous sodium hydroxide provided the cis acid **9** which was not isolated but was converted to the cis diethylamide **18** with diethylamine via the corresponding acid chloride.

The stereochemical assignments of this series of compounds are based on the analysis of the 100-MHz NMR spectra of the cis and trans nitriles **7** and **8** (Table II) and the fact that the cis acid or nitrile is converted to the more stable trans acid on prolonged treatment with base. For an accurate interpretation of the NMR spectra, deuterium

Scheme I



was selectively placed at the 11b position by reduction of **6** with $NaBD_4$. The cis-**11b** monodeuterio derivative of **7** was separated from the trans-**11b** monodeuterio derivative of **8** by fractional crystallization. Deuterium was also placed at the 3 position of the trans nitrile **8** by hydrolysis of the mixture of **7** and **8** with KOD in refluxing EtOD and conversion of the deuterated acid to the amide and nitrile as described above for **8**. Two ABX patterns were observed in the 100-MHz NMR spectra of the nitriles **7** and **8**. One is due to the coupling of the protons on C_1 with the **11b** α proton (Figure 4, A) and the other results from the protons on C_4 coupling with the C_3 proton (Figure 4, B). Of the possible conformations that are compatible with the coupling constants of Table II, the conformation depicted in Figure 3 with ring C in a chair form and a pseudo-trans B/C ring fusion is the thermodynamically most stable one. Our conclusions are in agreement with those which Cahill and Crabb reported[4] for this ring system. Thus, the 3-substituent is equatorial in the more stable trans isomers as in Figure 3 and axial in the cis isomers.

The pharmacologically most interesting compound of this series, **17**, was resolved with optically active malic acids into its optical isomers **19** and **20** (Table I).

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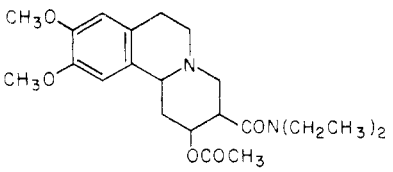
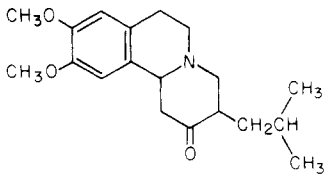
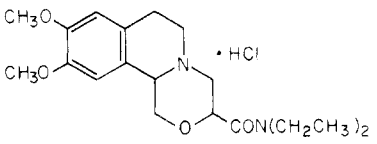


benzquinamide



tetrabenazine



16

Figure 1.

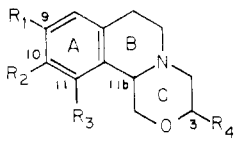


Figure 2.

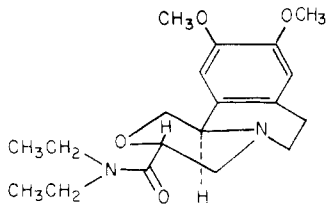
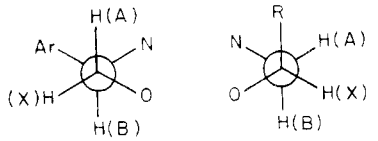


Figure 3.



A, C_1 and C_{11b} B, C_3 and C_4

Figure 4.

Table I lists the structures, melting points, recrystallization solvents, molecular formulas, and biological data for all the compounds in this series.

Pharmacology. Table I provides the results of screening procedures for the CNS evaluation of compounds of this series and selected standards by the intraperitoneal route. Although several compounds were classified as tranquilizers in the reflex test, only **17**, its hydrochloride salt **16**, and its (+) isomer **20** received a "2" rating in the Sidman avoidance test. Table III provides details of the rating system for selected compounds and standards in the reflex test. Detailed results of the evaluation of **16** and its optical isomers **19** and **20** in the Sidman avoidance test are provided in Table IV. In this table it is seen that the (+) isomer **20** is responsible for most of the activity of the racemate **16**. Thus, in the gerbil, by the intraperitoneal route, **20** displayed significant departure from control at 10 mg/kg, **16** required 16 mg/kg, and for the (−) isomer, **19**, 40 mg/kg were needed. However, in view of the low toxicity of the racemate (LD_{50} in mice, 1100 mg/kg intraperitoneally and 1400–1800 mg/kg orally), the optical isomer did not appear to offer a therapeutic advantage.

Further evaluation of **16** established its oral effectiveness in the Sidman avoidance test although the minimum effective dose (25 mg/kg) was high by this route. **16** also displayed marked taming effects without ataxia in the monkey and the wild fox at 16 mg/kg intraperitoneally. Comparative doses in the wild fox were 4 mg/kg for chlorpromazine and 32 mg/kg for diazepoxide. In the cat **16** was a muscle relaxant at the high dose of 20 mg/kg intravenously.

Although **16** is not a very potent neuroleptic by today's standards, it is of interest that of the compounds examined it is the one that most closely resembles benzquinamide and tetrabenazine in chemical structure (Figure 1).

Experimental Section

Compounds were checked by IR on a Perkin-Elmer Infracord and by NMR on a Varian A-60D spectrometer using Me_4Si as reference. Where the analyses are represented by symbols only, the values were found within ±0.4% of the theoretical values.

Glycidamide[8] (2). To a mixture of acrylamide (63.72 g, 0.9 mol), benzonitrile (111.16 g, 1.08 mol), methanol (270 mL), and 0.1 M disodium hydrogen phosphate (18 mL) were simultaneously added, with cooling at 10 °C and stirring, 30% hydrogen peroxide (108 mL, 1.08 mol) and 0.5 N sodium hydroxide (90 mL) over a period of 5 h. Stirring was continued for an additional 1 h and the mixture was allowed to stand at 0 °C overnight. The mixture was subjected to vacuum distillation below 35 °C until 190 mL of distillate had been collected, then cooled to 5 °C, and filtered to remove benzamide. The filtrate was concentrated under vacuum and filtered to remove a second crop of crystals. The filtrate was further evaporated under vacuum and the residual viscous yellow oil was taken up in tetrahydrofuran (200 mL), dried over $MgSO_4$, and filtered. The filtrate was found to contain 0.62 mol of glycidamide by titration as follows. A 5-mL sample of the glycidamide solution was added into a mixture of 0.1 N hydrochloric acid (125 mL) in saturated aqueous magnesium chloride. The mixture was allowed to stand at room temperature for 0.5 h and the excess of hydrochloric acid was titrated with 0.1 N sodium hydroxide.

3-(3,4-Dimethoxyphenethylamino)-2-hydroxypropionamide (3). To a stirred solution of glycidamide (0.62 mol) in tetrahydrofuran (500 mL) was added dropwise, under nitrogen, 112.87 g (0.62 mol) of homoveratrylamine over a period of 3 h. The temperature of the reaction mixture was maintained at 35–40 °C throughout the addition and for 2 h thereafter. The mixture was allowed to stand at room temperature overnight, the solid mass was treated with tetrahydrofuran (80 mL) and acetone (100 mL), and the solid was filtered, washed with a tetrahydrofuran–acetone mixture (1:7), and dried at 35 °C to constant weight (96 g, 58.6% yield). This material was used in the next step without further purification. An analytical sample was obtained by recrystallization from methanol: mp 124–126 °C. Anal. ($C_{13}H_{20}N_2O_4$) C, H, N.

4-(3,4-Dimethoxyphenethyl)-5-oxo-2-morpholinecarboxamide (5). A suspension of the amino alcohol, **3** (68.6 g, 0.25 mol), and anhydrous sodium acetate (25.6 g, 0.31 mol) in dimethylformamide (550 mL) was cooled to 0–5 °C and chloroacetyl chloride was added dropwise with stirring over a period of 1 h. The temperature of the reaction was maintained between 5 and 10 °C. Stirring was continued for an additional 1 h and the mixture was allowed to stand overnight below 10 °C. The mixture was poured into ice–water and extracted three times with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated under vacuum to yield the chloroacetamide **4** as a yellowish viscous oil. This substance was dissolved immediately in 2-propanol (540 mL), the solution was cooled to 5 °C, and 50% aqueous sodium hydroxide (243 g, 0.3 mol) was added dropwise over a period of 1.5 h. The internal temperature was maintained at 5–10 °C throughout the addition and 1 h thereafter. The mixture was then neutralized to pH 7–7.5 with 6 N aqueous hydrochloric acid (100 mL). The solvents were evaporated as much as possible under aspirator pressure; the

Table I. Substituted 1,3,4,6,7,11b-Hexahydro[1,4]oxazino[3,4-*a*]isoquinolines (See Figure 1)

no.	aromatic substituent	3-substituent	isomer[a]	recrystn[b] solvent	mp, °C	formula[c]	pharmacology[d] reflex test	pharmacology[d] Sidman avoidance	remarks
7	9,10-$(MeO)_2$	CN	c	B	183.5–185.5	$C_{15}H_{18}N_2O_3$	T		
8	9,10-$(MeO)_2$	CN	t	B/J	173–174	$C_{15}H_{18}N_2O_3$			
9	9,10-$(MeO)_2$	COOH	c	not isolated					
10	9,10-$(MeO)_2$	COOH	t	H	209–214				HCl salt mixed with KCl
11	9,10-$(MeO)_2$	COOMe	c	A	108–109	$C_{16}H_{21}NO_5$			
12	9,10-$(MeO)_2$	COOMe	t	A	123–124.5	$C_{16}H_{21}NO_5$			
13	9,10-$(MeO)_2$	COOEt	t	A	111.5–113.5	$C_{17}H_{23}NO_5$	O		
14	9,10-$(MeO)_2$	$CONH_2$	c	H	215–216 dec	$C_{15}H_{20}N_2O_4$	X	1	
15	9,10-$(MeO)_2$	$CONH_2$	t	H	237–240	$C_{15}H_{20}N_2O_4$	O	0	
16	9,10-$(MeO)_2$	$CONEt_2$	t	A	231–233 dec	$C_{19}H_{28}N_2O_4 \cdot HCl$	T	2	salt of 17
17	9,10-$(MeO)_2$	$CONEt_2$	t	B	122–124	$C_{19}H_{28}N_2O_4$	T	2	
18	9,10-$(MeO)_2$	$CONEt_2$	c	A	150–153	$C_{19}H_{28}N_2O_4$	X		
19	9,10-$(MeO)_2$	$CONEt_2$	t	A	133–135	$C_{19}H_{28}N_2O_4$	T	1	*l* isomer of 17
20	9,10-$(MeO)_2$	$CONEt_2$	t	A	133–134	$C_{19}H_{28}N_2O_4$	T	2	*d* isomer of 17
21	9,10-$(MeO)_2$	CONHEt	t	C	153–154	$C_{17}H_{24}N_2O_4$	X	1	
22	9,10-$(MeO)_2$	CONHEt	c	A	133–134	$C_{17}H_{24}N_2O_4$	X		
23	9,10-$(MeO)_2$	$CONMe_2$	t	A/G	212–213	$C_{17}H_{24}N_2O_4$	T		
24	9,10-$(MeO)_2$	CON(*n*-Pr)$_2$	t	A	224–226	$C_{21}H_{32}N_2O_4 \cdot HCl$			salt
25	9,10-$(MeO)_2$	CO-c-NC_4H_8	t	A	233–235	$C_{19}H_{26}N_2O_4$	T	1	
26	9,10-$(MeO)_2$	CO-c-NC_5H_{10}	t	B	200–201	$C_{20}H_{28}N_2O_4$	M	0	
27	9,10-$(MeO)_2$	CO-c-$N(CH_2CH_2)_2O$	t	A/B	211–213	$C_{19}H_{26}N_2O_5$	T	0	
28	9,10-$(MeO)_2$	CO-c-$N(CH_2CH_2)_2NH$	t	E/I	213–214	$C_{19}H_{27}N_3O_4$	X		
29	9,10-$(MeO)_2$	CO-c-$N(CH_2CH_2)_2N$-CH_3	t	B	155–157	$C_{20}H_{29}N_3O_4$	X	0	
30	9,10-$(MeO)_2$	CO-c-$N(CH_2CH_2)_2N$-$(CH_2)_2OH$	t	F	76.5–78.5	$C_{21}H_{31}N_3O_5 \cdot C_4H_8O_2$	O	0	
31	9,10-OCH_2O-	$CONEt_2$	t	A/I	117–118.5	$C_{18}H_{24}N_2O_4$	X	0	
32	9,10-OCH_2O-	$CONH_2$	t	H	226–228 dec	$C_{14}H_{16}N_2O_4$	O	1	
33	9,10,11-$(OMe)_3$	$CONEt_2$	t	J	94.5–95.5	$C_{20}H_{30}N_2O_5$	X	0	
34	9,10,11-$(OMe)_3$	$CONH_2$	t	H	203.5–205	$C_{16}H_{22}N_2O_5$	T	0	
35	9-OMe	$CONEt_2$	t	I	98.5–100	$C_{18}H_{22}N_2O_3$		0	

[a] t = trans, c = cis. [b] A = 2-propanol, B = ethyl acetate, C = methanol, D = benzene, E = methylene chloride, F = dioxane, G = acetone, H = ethanol, I = ether, J = hexane. [c] Satisfactory C, H, and N analyses were obtained in each instance in which the formula is provided. [d] Reflex test: T = tranquilizer, M = muscle relaxant, X = nonspecific, O = inactive. Sidman avoidance: selective neuroleptic activity on a scale of 0–2. See the Experimental Section for test descriptions.

Table II. Analysis of 100-MHz NMR Data

compd[b]	Figure 2	chemical shift X	A	B	coupling constant[a] AB	AX	BX
7 (cis)	A	425	380[c]	380[c]		11.5	3.1
	B	474	283	301	18	1.7	3.2
8 (trans)	A	433	334	354	10	11	3.6
	B	452	309	286.5[d]	11	3	10

[a] In hertz, $CDCl_3$ relative to internal Me_4Si. [b] The NMR spectra of **11**, **13**, **15**, **17**, and **18** and the results of spin-decoupling experiments were in agreement with the above assignments. [c] Signals were not located exactly because of superimposition of the methoxy resonances. [d] Determined from the 60-MHz NMR spectrum of the 3-deuterio derivative of **8**.

Table III. Reflex Test[a]

agent	ED_{50}, mg/kg ip[b] right-ing	trac-tion	prehensile	corneal	classifn[c]
chlorpro-mazine	115	6	74	160	T
phenobar-bital	140	64	82	100	X
meproba-mate	320	160	225	400	M
7		180	>640		T
13		no effect through 640 mg/kg			O
16		100	400		T
17		110	500		T
19		125	400		T
20		150	460		T
25		180	>640		T
26	280	180	280	450	M
27		200	>640		T

[a] For a detailed description see the Experimental Section. [b] Values are ED_{50} doses in mg/kg intraperitoneally administered to mice. The LD_{50} values were determined by eye fit of the data on log-probability paper. No statistical analysis was performed. [c] An agent is classified as a tranquilizer (T) if ED_{50}(preh)/ED_{50}(tract.) > 3; as a muscle relaxant (M) if it is not a tranquilizer and ED_{50}(corn)/ED_{50}(right.) > 1; and as a sedative-hypnotic (X) if it is not a tranquilizer and ED_{50}(corn.)/ED_{50}(right.) < 1. O = inactive.

Table IV. Sidman Avoidance Test[a]

no.	dose,[b] mg/kg	n[c]	shocks delivered[d] ± SE	escape latency,[d] s ± SE	rating score
16	control	16	18.9 ± 4.1	0.6 ± 0.1	
	2	4	25.3 ± 10.3	0.6 ± 0.1	
	4	4	21.3 ± 7.3	0.8 ± 0.1	2
	8	4	43.5 ± 22.5	0.5 ± 0.1	
	16	4	73.3 ± 10.5	0.8 ± 0.1	
19	control	12	15.7 ± 2.8	0.6 ± 0.1	
	20	4	15.5 ± 2.0	0.5 ± 0.1	
	40	4	45.8 ± 3.7	1.2 ± 0.3	1
	80	4	118.0 ± 5.8	2.2 ± 0.6	
20	control	16	8.3 ± 0.8	0.6 ± 0.1	
	2.5	4	11.5 ± 1.1	0.5 ± 0.1	
	5	4	26.0 ± 15.1	0.6 ± 0.1	2
	10	4	89.3 ± 9.5	1.2 ± 0.3	
	20	4	9.18 ± 28.2	2.4 ± 0.6	
chlorpro-mazine	control	9	3.4 ± 0.9	1.0 ± 0.4	
	0.5	3	6.3 ± 2.4	1.0 ± 0.1	
	1.0	3	9.0 ± 2.6	1.1 ± 0.1	2
	2.0	3	28.0 ± 8.7	0.8 ± 0.2	

[a] For a detailed description see the Experimental Section. [b] Intraperitoneally administered to the gerbil. [c] Number of animals. [d] Underlined numbers are significantly different from control, with $p < 0.05$ by Student's t test.

resulting residue was slurried in water (800 mL), filtered, washed with water, and dried at 50 °C in vacuo to yield the morpholinone **5** (52 g, 67% yield). Crystallization from acetone gave an analytical sample, mp 169–171 °C. Anal. ($C_{15}H_{20}N_2O_5$) C, H, N.

***cis*- and *trans*-9,10-Dimethoxy-1,3,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carbonitrile (7, 8).** A mixture of **5** (30 g, 0.097 mol) and phosphorus oxychloride (45 mL) was heated with stirring at 60 °C for 3 h. The excess of phosphorus oxychloride was then removed at reduced pressure (5 mmHg at a bath temperature of 50 °C). The residue **6** was dissolved in acetonitrile (45 mL), the solution was cooled to 20 °C, and sodium borohydride (3.75 g, 0.097 mol) was added in portions under nitrogen over a period of 1 h. The reaction mixture was stirred at 20–25 °C for 1 h and then slowly poured into a cold 0.2 N aqueous hydrochloric acid solution. To the resulting aqueous suspension was added, with slow stirring and cooling, aqueous sodium hydroxide (50% w/v, 53.5 g) over a period of 1 h while maintaining an internal temperature of 20–25 °C. The resulting suspension was stirred overnight and filtered. The solid was washed with distilled water several times, then triturated with methanol (75 mL), filtered, and dried at 80 °C in vacuo to yield a light yellow powder (20.5 g, 77% yield, mp 152–168 °C). Recrystallization from chloroform–methanol gave a mixture of cis and trans isomers as a white powder, mp 155–175 °C. A similar experiment using $NaBD_4$ gave the corresponding mixture of 11b-deuterionitriles.

Alternatively, the residue from the reaction of 9 g of **5** with phosphorus oxychloride was dissolved in cold water and treated with charcoal, and the solution was filtered and basified with NH_4OH. The crude base was extracted into ethyl acetate and hydrogenated with 2 g of 10% Pd/C catalyst. The catalyst was removed, the solvent was evaporated, and the residue was recrystallized from benzene–petroleum ether to give 2.2 g (27%) of the trans nitrile, mp 172–174 °C. Further recrystallization from benzene raised the melting point to 178–179 °C.

***trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxylic Acid Hydrochloride (10).** The mixture of nitriles **7** and **8** (42.3 g, 0.154 mol), ethanol (465 mL), water (127 mL), and potassium hydroxide (15.2 g) was refluxed under nitrogen for 18 h. The mixture was cooled to 20 °C and concentrated hydrochloric acid (40.8 mL) was slowly added while maintaining an internal temperature of 20–25 °C. The suspension was stirred for 2 h at room temperature; the crystals were collected, washed with ethanol (10 mL), and dried at 60 °C to yield a white powder (53.3 g) containing 77.1% of the desired carboxylic acid, as determined by titration with 0.01 N sodium hydroxide (81% yield).

***trans*-1,3,4,6,7,11b-Hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamides. Method A.** The use of oxalyl chloride is illustrated in the preparation of the *N*,*N*-diethylcarboxamido derivative **17**.

To a suspension of the carboxylic acid hydrochloride **10** (36 g, 77.1% pure, 0.084 mol), in benzene (70 mL), was added, with stirring and under nitrogen, oxalyl chloride (43.1 mL, 0.5 mol) over a period of 0.5 h. The suspension was heated slowly to reflux with stirring and the refluxing continued for 1 h. The solvents were removed under aspirator pressure; benzene (570 mL) was added and the solution was again evaporated under vacuum. Methylene chloride (95 mL) was then added; the suspension was stirred at 25 °C while diethylamine (21.5 g, 0.294 mol) was added with ice-bath cooling over a period of 1 h. The suspension was then stirred at room temperature overnight. Water (70 mL) was added, and the layers were separated. The organic phase was washed with water, dried, decolorized with charcoal, and evaporated. The residual solid was recrystallized from ethyl acetate–hexane to yield 25.8 g (88%) of the desired amide. The hydrochloride salt, **16**, was prepared by the addition of concentrated hydrochloric acid in 2-propanol.

Method B. The use of thionyl chloride is exemplified in the preparation of 9,10-dimethoxy-*N*-ethyl-1,3,4,6,7,11b-hexahydro[1.4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (**21**).

To a suspension of the carboxylic acid hydrochloride **10** (1.0 g) in 1,2-dichloroethane (20 mL) was added thionyl chloride (2.0 mL). The mixture was refluxed for 1.5 h, and the solvent and the excess of thionyl chloride were removed under vacuum. The brown solid residue was suspended in methylene chloride (10 mL)

and ethylamine (4.2 g) in methylene chloride (25 mL) was added dropwise with stirring and cooling in an ice–water bath. The mixture was stirred for 30 min; the solution was washed with 2 N aqueous sodium hydroxide solution and saturated aqueous sodium chloride solution, dried ($MgSO_4$), and evaporated to yield a brown crystalline residue. The residue was chromatographed on silica gel using methanol–ethyl acetate (1:1) as eluent. The product was recrystallized from methanol–ether twice to give an analytical sample (0.3 g, 33% yield).

Ethyl *trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxylate (13). A suspension of the carboxylic acid hydrochloride **10** (8 g) in dilute ethanolic hydrochloric acid (50 mL) was refluxed for 1 h. The reaction mixture was allowed to cool to room temperature and the crystalline material was filtered. The crystals (6 g) were dissolved in water (60 mL) and the solution was stirred with saturated aqueous sodium bicarbonate (250 mL) at room temperature for 1 h. The precipitate was filtered, dried (in vacuo, 50 °C), and recrystallized from 2-propanol to give colorless crystals (4.4 g). Similarly, methanolic hydrogen chloride gave the methyl ester.

***trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (15).** A suspension of ethyl 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxylate (5 g) in concentrated aqueous ammonium hydroxide (150 mL) was stirred at room temperature for 18 h. The insoluble material was filtered, dried, and recrystallized three times from ethanol to give colorless fine crystals (2.8 g).

***trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carbonitrile (8).** A suspension of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide in 2.5 mL of anhydrous toluene and 1.0 mL of phosphorus oxychloride was stirred for 5 h at 105 °C under nitrogen. The slurry was concentrated under vacuum and the brown solid residue was triturated with 1 N NaOH and ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residual solid was crystallized from ethyl acetate–hexane to yield 116 mg (42.3%) of the desired nitrile, mp 173–174 °C.

***cis*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino-[3,4-*a*]isoquinoline-3-carbonitrile (7).** The mixed cis and trans nitriles resulting from the cyclization of **5** (see above) were recrystallized from ethyl acetate three times to give the cis nitrile as colorless prisms; the melting point had a gradual phase change at 150 °C to give long needles which melted at 183.5–185.5 °C.

Methyl *cis*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxylate (11). Hydrogen chloride gas was passed into a suspension of the cis nitrile **7** (305.8 mg) in methanol (5 mL) and water (0.12 mL) for 30 min. The clear solution so obtained was allowed to stand at room temperature for a further 90 min. The solvents were evaporated under vacuum; the residue was treated with saturated aqueous sodium bicarbonate (10 mL) and extracted twice with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on neutral alumina (activity I, 1.30 g). The desired methyl ester (279.5 mg) was eluted with chloroform and was recrystallized from 2-propanol to give the analytically pure material.

***cis*-9,10-Dimethoxy-*N*-ethyl-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (22).** A suspension of the cis methyl ester **11** (2.32 g) in 70% aqueous ethylamine was stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the residue crystallized from ether. Recrystallization from 2-propanol gave pure amide (2.07 g).

***cis*-*N*,*N*-Diethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (18).** A suspension of the cis methyl ester **11** (2.14 g) in water (75 mL) and 1 N aqueous sodium hydroxide (8.4 mL) was stirred at room temperature for 1 h. The resulting solution was treated with 1 N aqueous hydrochloric acid (8.5 mL), the mixture was evaporated under vacuum, and the residue was dried in a vacuum desiccator (over P_2O_5) for 24 h. The dry material was suspended in methylene chloride (50 mL), the suspension was treated with triethylamine (1.07 mL), the mixture was cooled in an ice bath for 15 min, and isobutyl chloroformate (1.058 g) in methylene chloride (10 mL) was added with stirring. After 0.5 h of cooling and stirring, the mixture was treated with diethylamine (0.9 mL); the stirring was continued at 0 °C for 0.5 h and then at room temperature for 20 h. The solvent was removed under vacuum, the solid residue was treated with 1 N aqueous hydrochloric acid (50 mL), and the solution was washed twice with ether. The ether extracts were discarded. An excess of solid sodium bicarbonate was added to the aqueous solution, and the mixture was extracted twice with methylene chloride. The combined extracts were dried ($MgSO_4$) and evaporated and the residue was crystallized from ether. Recrystallization from 2-propanol afforded colorless prisms (1.55 g).

***cis*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino-[3,4-*a*]isoquinoline-3-carboxamide (14).** To a solution of methyl *cis*-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxylate (3 g) in ethanol (15 mL) was added ammonium hydroxide (30 mL) with stirring. The solution was allowed to stand at room temperature for 3 days and then evaporated. The residue was triturated with benzene and filtered to give 1.5 g (60%) of the cis amide. It was recrystallized from absolute ethanol to give colorless crystals.

2-Hydroxy-3-(3,4-methylenedioxyphenethylamino)-propionamide. 3,4-Methylenedioxyphenethylamine hydrochloride[9] (49.2 g) was dissolved in water (1.25 L) and the solution treated with 10% aqueous sodium carbonate to pH 9–10. The mixture was extracted with methylene chloride; the extracts were dried ($MgSO_4$) and evaporated in vacuo (90 °C) to give the free amine. The amine was dissolved in 1,2-dimethoxyethane (25 mL) and the solution treated with a 2.56 M solution of glycidamide in 1,2-dimethoxyethane (96 mL) with stirring and cooling at 0 °C for 20 h. Acetone was added to give a slurry of crystalline material which was filtered and washed with acetone to give the amino alcohol (32.3 g, 43.8%). Recrystallization from 2-propanol afforded the analytical sample, mp 141–143 °C. Anal. ($C_{12}H_{16}N_2O_4$) C, H, N.

4-(3,4-Methylenedioxyphenethyl)-5-oxomorpholine-3-carboxamide. To a solution of 2-hydroxy-3-(3,4-methylenedioxyphenethylamine)propionamide (26.2 g) in dimethylformamide (500 mL), anhydrous sodium acetate (11 g) was added and the mixture stirred and cooled in an ice–water bath. A solution of chloroacetyl chloride (8 mL) in dimethylformamide (80 mL) was added over 2 h, maintaining the reaction at a temperature of 10 °C. The reaction mixture was stirred with cooling for a further 1 h and then allowed to stand overnight at room temperature. It was poured into cold water (600 mL) and extracted with methylene chloride (3 × 100 mL). The extracts were dried ($MgSO_4$) and evaporated in vacuo (80 °C) to give an oil. The oil was dissolved in 2-propanol (200 mL), the solution cooled in an ice–water bath, and 50% aqueous sodium hydroxide (12 mL) added dropwise with stirring. After stirring for an additional 1 h, the white precipitate was collected, then suspended in water (200 mL) for 18 h, again collected, and dried in vacuo (50 °C) to give the morpholinone (14.7 g, 48.4%). Recrystallization from ethanol gave an analytical sample, mp 236–237 °C. Anal. ($C_{14}H_{16}N_2O_5$) C, H, N.

1,3,4,6,7,11b-Hexahydro-9,10-methylenedioxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carbonitrile. A mixture of 4-(3,4-methylenedioxyphenethyl)-5-oxomorpholine-3-carboxamide (4 g), phosphorus oxychloride, (6.3 mL), and 1,2-dichloroethane (40 mL) was refluxed for 2 h and evaporated under vacuum. The gummy residue was dissolved in methanol (45 mL) and 50% aqueous sodium hydroxide (2 mL) was added. Sodium borohydride (1.67 g) was then added portionwise, with stirring and cooling in an ice–water bath. After stirring overnight, the finely divided pink solid was collected. This material was suspended in water (50 mL) and the mixture extracted with methylene chloride (3 × 150 mL). The extracts were dried and evaporated to give the crude crystalline nitrile (1.686 g). An additional amount of nitrile (0.8 g) was recovered from the original aqueous filtrate by evaporating it to dryness in vacuo (90 °C), treating the residue with saturated sodium hydrogen carbonate (30 mL), extracting the mixture with methylene chloride (4 × 20 mL), drying the combined extracts ($MgSO_4$), and evaporating and crystallizing the residue from ethanol. Recrystallization from ethanol gave an analytical sample, mp 168–183 °C. The NMR spectrum showed that the sample

was a mixture of cis and trans nitriles. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

***trans*-*N*,*N*-Diethyl-1,3,4,6,7,11b-hexahydro-9,10-methylenedioxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (31).** The above mixture of cis and trans nitriles was refluxed with 0.5 N ethanolic potassium hydroxide (40 mL) and water (8 mL) for 4 h. The solvents were removed in vacuo (80 °C) to give a gummy residue which was dissolved in 2.5 N aqueous hydrochloric acid (15 mL) and allowed to crystallize on standing overnight. The solid was collected and dried in vacuo (50 °C) to give the crude amino acid hydrochloride (3.22 g). The crude amino acid hydrochloride was refluxed with thionyl chloride (5.25 mL) and 1,2-dichloroethane (65 mL) for 2 h. The solvent was evaporated in vacuo (80 °C) to give a pale brown solid which was suspended in methylene chloride (60 mL) and treated with an excess of diethylamine (3.2 mL). The solvent was evaporated, the residue was suspended in 0.4 N aqueous sodium hydroxide (50 mL), and the mixture was extracted with methylene chloride (4 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give a dark red gum (4.76 g). This gum was chromatographed on neutral alumina (activity I, 200 g) using methylene chloride as eluent to give 3.60 g of product which crystallized from ether. Recrystallization from ether–2-propanol gave analytically pure material.

***trans*-1,3,4,6,7,11b-Hexahydro-9,10-methylenedioxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (32).** A mixture of the above nitriles (1.72 g), 0.51 N potassium *tert*-butoxide in *tert*-butyl alcohol (14.0 mL), and *tert*-butyl alcohol (170 mL) was refluxed for 2.5 h and evaporated. The residue was dissolved in 1 N aqueous hydrochloric acid and the solution was neutralized with saturated aqueous sodium bicarbonate. The precipitate was filtered, washed with water, and recrystallized from ethanol to give the amide **32** (1.52 g). An analytical sample was prepared by recrystallization from ethanol.

2-Hydroxy-3-(3,4,5-trimethoxyphenethylamino)propionamide. A mixture of 3,4,5-trimethoxyphenethylamine hydrochloride[10] (45.84 g) and water (500 mL) was treated with 10% aqueous sodium carbonate and extracted with methylene chloride, and the extracts were dried ($MgSO_4$) and evaporated to give the free amine as a heavy oil. This was dissolved in 1,2-dimethoxyethane (20 mL) and the solution treated with a 2.56 N solution of glycidamide in 1,2-dimethoxyethane (72 mL) with stirring and cooling in a cold-water bath. Stirring and cooling was continued for 24 h, during which time a heavy crystalline precipitate was formed. Sufficient acetone was added to give a slurry which was filtered. Recrystallization from 2-propanol gave the amino alcohol (27.0 g, 48.9%). Further recrystallization from 2-propanol gave the analytical sample, mp 136–137 °C. Anal. ($C_{14}H_{22}N_2O_5$) C, H, N.

5-Oxo-4-(3,4,5-trimethoxyphenethyl)morpholine-2-carboxamide. Anhydrous sodium acetate (7.27 g) was added to a solution of the above amino alcohol (25.2 g) in dimethylformamide (350 mL) and cooled to 5 °C. A solution of chloroacetyl chloride (6.7 mL) in dimethylformamide (67 mL) was added dropwise while maintaining the temperature at 5–8 °C. Stirring was continued for 1 h at 0 °C and 1 h at room temperature. The reaction mixture was poured into ice–water (650 mL), the pH was adjusted to 7 with 1 N aqueous sodium hydroxide, and the product was extracted with methylene chloride (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give an oil. This oil was dissolved in 2-propanol (250 mL), the solution was cooled in an ice–water bath, and 10.8 N aqueous sodium hydroxide (2.5 mL) was added dropwise with stirring (pH 8–9). After stirring for 1 h, the white precipitate was collected and then stirred with water (200 mL) for 5 h. The product was again collected and dried in vacuo (60 °C) (20.61 g). Recrystallization from 2-propanol gave an analytical sample, mp 204.5–204.6 °C. Anal. ($C_{16}H_{22}N_2O_6$) C, H, N.

1,3,4,6,7,11b-Hexahydro-9,10,11-trimethoxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carbonitrile. A mixture of the preceding morpholinone (5.01 g), phosphorus oxychloride (7.5 mL), and 1,2-dichloroethane (75 mL) was refluxed for 90 min. The solvents were evaporated under vacuum and the residual red gum was dried in a vacuum desiccator overnight. The material was dissolved in methanol (75 mL), the solution was cooled in an ice–water bath, and water (5 mL) was added, followed by sodium borohydride (3.95 g) which was added portionwise with stirring. The reaction mixture was stirred for 30 min, after which time the white precipitate was collected and washed with water. The filtrate was extracted with methylene chloride (4 × 10 mL); the combined extracts were dried ($MgSO_4$) and evaporated. The residue was combined with the original white precipitate and the mixture was recrystallized from ethanol to give the desired nitrile (3.75 g). Further recrystallization from ethanol gave an analytical sample, mp 151–152 °C. Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

***trans*-1,3,4,6,7,11b-Hexahydro-9,10,11-trimethoxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (34).** A mixture of the above nitrile (3.7 g), 0.51 N potassium *tert*-butoxide in *tert*-butyl alcohol (25 mL), and *tert*-butyl alcohol (370 mL) was refluxed for 2 h and evaporated. The residue was treated with 1 N aqueous hydrochloric acid, then neutralized with saturated aqueous sodium hydrogen carbonate, and extracted with methylene chloride (4 × 20 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to yield a crude crystalline mass (4.05 g). Recrystallization from ethanol gave the amide **34** (3.3 g).

***trans*-*N*,*N*-Diethyl-1,3,4,6,7,11b-hexahydro-9,10,11-trimethoxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (33).** A solution of 1,3,4,6,7,11b-hexahydro-9,10,11-trimethoxy[1,4]oxazino[3,4-*a*]isoquinoline-3-carbonitrile (2.03 g) in 0.5 N ethanolic potassium hydroxide (26.3 mL) and water (5.3 mL) was refluxed for 4 h and evaporated. The residue was treated with 2.5 N aqueous hydrochloric acid (13 mL) and evaporated to dryness to give a yellow crystalline product which was dried under vacuum overnight. This material was suspended in 1,2-dichloroethane (20 mL), thionyl chloride (8 mL) was added, and the mixture was refluxed for 1 h. The solvent was evaporated; the dry residue was suspended in methylene chloride (25 mL) and treated with diethylamine (8 mL) with cooling and stirring in an ice–water bath. After it had stood overnight at room temperature, the mixture was treated with 2.5 N aqueous sodium hydroxide (20 mL), the organic layers were separated, and the aqueous layer was washed with methylene chloride (4 × 10 mL). The combined methylene chloride solutions were dried ($MgSO_4$) and evaporated to give a brown gum (3.12 g). This material was chromatographed on neutral alumina (activity I, 200 g), using methylene chloride–methanol (99:1) as eluent, and afforded a brown gum (2.9 g) which crystallized upon standing at room temperature. Recrystallization from hexane gave analytically pure material.

2-Hydroxy-3-(3-methoxyphenethyl)propionamide. A mixture of 3-methoxyphenethylamine (834.3 mg) and a 2.14 N solution of glycidamide in 1,2-dimethoxyethane (3 mL) was allowed to stand for 3 days with cooling in a water bath at room temperature. The colorless crystalline material was collected and washed with 1,2-dimethoxyethane. The crude amino alcohol (1.109 g) was recrystallized from absolute ethanol to give an analytical sample, mp 109–110 °C. Anal. ($C_{12}H_{18}N_2O_3$) C, H, N.

4-(3-Methoxyphenethylamino)-5-oxomorpholine-2-carboxamide. A solution of chloroacetyl chloride (8.04 mL) in dimethylformamide (240 mL) was added dropwise to a stirred mixture of the above amino alcohol (23.15 g) and anhydrous sodium acetate (11.94 g) in dimethylformamide (242 mL), maintaining the temperature at 5 °C. After completion of the addition, the reaction mixture was stirred for 1 h at 5 °C and then 1 h at room temperature. The reaction mixture was then poured into ice–water (500 mL), the pH adjusted to 7 by the addition of 50% aqueous sodium hydroxide, and the mixture extracted with chloroform (6 × 75 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give an oily residue. This was dissolved in 2-propanol (300 mL) and the pH adjusted to 8.5 using 50% aqueous sodium hydroxide. After 30 min the reaction mixture was evaporated in vacuo (90 °C), and the residue was triturated with chloroform and filtered. The filtrates were evaporated in vacuo (90 °C) to yield the crude crystalline morpholinone (27.25 g). Recrystallization from 2-propanol afforded an analytical sample, mp 146.5–147 °C. Anal. ($C_{14}H_{18}N_2O_4$) C, H, N.

***cis*- and *trans*-1,3,4,6,7,11b-Hexahydro-9-methoxy[1,4]oxazino[3,4-*a*]isoquinolinecarbonitrile.** Phosphorus oxychloride (26 mL) was added to a solution of the above morpholinone (15.25 g) in 1,2-dichloroethane (175 mL), and the mixture was refluxed for 90 min. The solvent and an excess of

phosphorus oxychloride were removed in vacuo (90 °C) to give a dark red gum which was dried in a vacuum desiccator (P_2O_5) overnight. The residue was dissolved in methanol (225 mL) and water (22.5 mL) with cooling, and the pH of the solution was adjusted to 8 by the addition of 50% aqueous sodium hydroxide. Sodium borohydride (1.05 g) was added portionwise to the stirred solution with cooling in an ice–water bath. After 1 h, the crystalline material was collected and washed with water. It was dried in a vacuum desiccator (P_2O_5) and recrystallized from ethanol to give a pure mixture of cis and trans nitriles.

***trans*-*N*,*N*-Diethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide (35).** A suspension of the above nitrile mixture (3.6 g) in 0.5 N ethanolic potassium hydroxide (59 mL) was refluxed for 4 h. Water (11.88 mL) was then added and the mixture was refluxed for an additional 1 h. After cooling, 2.5 N aqueous hydrochloric acid (13.25 mL) was added and the mixture was evaporated in vacuo (90 °C). The yellow solid residue was treated with benzene (10 mL) and the mixture again evaporated in vacuo (90 °C). The residue was dried in a vacuum desiccator (P_2O_5) for 24 h. This material was suspended in methylene chloride (90 mL), triethylamine (2.26 mL) was added, the mixture was stirred with cooling in an ice–water bath, and a solution of isobutyl chloroformate (2.12 mL) in methylene chloride (21.6 mL) was added dropwise. After 30 min of stirring in the cooling bath, diethylamine (1.89 mL) was added. The mixture was stirred in the cooling bath for 30 min and then at room temperature for 24 h. The solvent was evaporated in vacuo (90 °C), the residue was dissolved in 2 N aqueous hydrochloric acid (60 mL), and the aqueous solution was washed with ether (2 × 25 mL). The aqueous layer was treated with an excess of solid sodium hydrogen carbonate and the mixture extracted with methylene chloride (5 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give a brown oil (2.8 g). This material was purified by chromatography on neutral alumina (activity I, 200 g), using methylene chloride–methanol (99:1) as eluent to give the pure amide (1.95 g). Recrystallization from ether gave colorless prisms.

Resolution of 17. A solution of **17** (11.55 g) and (−)-malic acid (4.443 g) in 2-propanol (50 mL) was prepared by heating the components together. This solution was allowed to stand at room temperature. After 18 h, the crystals were collected, washed with a little cold 2-propanol, and dried in vacuo (40 °C). The material so obtained was recrystallized from 2-propanol to give (−)-**17** (−)-malate (6.28 g) as colorless prisms: mp 91–96 °C; $[\alpha]^{25}_{589}$ −59.8° (*c* 2.03, MeOH). The (−)-malate was dissolved in methylene chloride (75 mL) and shaken with 10% aqueous sodium carbonate (50 mL). The aqueous layer was washed once more with methylene chloride (2 × 25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give colorless crystals (4.039 g): $[\alpha]^{25}_{589}$ −90.3° (*c* 1.68, MeOH).

A solution of the partially resolved free base recovered above, having $[\alpha]^{25}_{589}$ +39.3° (9.57 g), and (+)-malic acid (3.69 g) in 2-propanol (50 mL), prepared by warming the constituents, was allowed to stand at room temperature for 4 days. The crystals were filtered off and washed with a little cold 2-propanol. Recrystallization from 2-propanol afforded 6.93 g of white prisms: mp 91–96 °C; $[\alpha]^{25}_{589}$ +58.6° (*c* 1.98, MeOH).

The (+)-malate (6.65 g) in methylene chloride (50 mL) was shaken with 10% aqueous sodium hydroxide (25 mL). The aqueous layer was washed with methylene chloride (2 × 25 mL) and the combined extracts were dried ($MgSO_4$) and evaporated to give a pale yellow gum which afforded colorless crystals (4.50 g) upon trituration with ether: $[\alpha]^{25}_{589}$ +90.8° (*c* 1.98, MeOH).

Pharmacological Test Procedures.[11] Reflex Test[12] (Tables I and III). Tranquilizer and muscle relaxant actions were correlated with the patterning of doses required for blocking the righting reflex, the traction reflex, the prehensile reflex, and the corneal reflex of mice.

Righting Reflex. The mouse is placed on its back. The reflex is considered blocked if the mouse fails to right itself to a normal position within 30 s.

Traction Reflex. When a mouse's forepaws are placed on a taut horizontal wire, the normal response is for the mouse to draw the hind paws up to the wire. The reflex is considered blocked if the mouse fails to grasp the wire with the hind paws in less than 5 s.

Prehensile Reflex. When the traction reflex is blocked, mice may hang with the forepaws grasping the wire. The prehensile reflex is considered blocked if the mouse fails to hang for at least 5 s.

Corneal Reflex. The corneal reflex is considered blocked if the mouse fails to blink when a stiff hair is applied to the cornea of the eye.

Rating Criteria. The ED_{50} is the estimated dose of a drug which will block a reflex in half of the mice tested. Five mice were used for each test. The criteria noted in Table III are based on the effects of standard drugs.

Sidman Avoidance[13] (Tables I and IV). Gerbils were trained to avoid electrical shocks by depressing a lever mounted on one wall of the metal box which constituted the experimental chamber. In 50-min experimental sessions, shocks were delivered through the floor and walls of the box at the end of every 20-s period in which no lever-pressing response occurred. When shocks did occur, they continued until terminated by a lever-pressing (escape) response, and the time from the onset of the shock to its termination (i.e., the "escape latency") was recorded. A drug-induced increase in the number of shocks delivered in a session, with no concomitant increase in escape latency, is interpreted as a specific neuroleptic effect. A drug-induced increase in escape latency is regarded as a nonspecific interference with the psychomotor functioning of the gerbil in making the lever-press response. Drugs were administered intraperitoneally and rated for effectiveness on a scale of 0–2. Four animals were used for each dose level for each test compound (see Table IV).

Acknowledgment. Appreciation is expressed to Jeffrey Saelens for assistance with the pharmacological data and to Werner Heiber for repeating a number of the chemical experiments to provide additional physical constants.

References and Notes

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