cis-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline: A New Atypical Antidepressant

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Molecular modelling studies suggested the synthesis of *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline (**7a**) as a rigid analogue of the atypical antidepressant mianserin. Acylation of 2,2-diphenylethylamine with chloroacetyl chloride gives the chloroacetamide (**2**). Cyclization of **2** with P_2O_5 in xylene provides 1-(chloromethyl)-3,4-dihydro-4-phenylisoquinoline (**3**). Amination of **3**, followed by reduction, gives the isomeric (aminomethyl)tetrahydroisoquinolines (**4a** and **5**). Treatment of **4a** with diethyl oxalate, followed by reduction of the diamide with borane, provides **7a**. A variety of N-substituted, aromatic substituted, and optically resolved derivatives were prepared and evaluated for anticholinergic, antihistaminic, and antidepressant activity. In particular, the target cis isomer **7a** as predicted from the modelling studies appears to possess excellent atypical antidepressant activity. This activity resides in the (+)-*S,S* optical isomer **10**, which has the same absolute configuration as (+)-mianserin.

The term "atypical antidepressant" has been used to describe some recently discovered novel antidepressant agents, such as mianserin and iprindole, that have little or no activity as catecholamine uptake inhibitors in the manner of the classical tricyclic antidepressants (TCA's) or the newer 5HT-uptake inhibitors, yet demonstrate potent activity in numerous clinical trials. The discovery of the atypical antidepressants has led to renewed efforts on the part of neuropharmacologists to develop screens such as β-receptor subsensitivity,[1] [^{3}H]mepyramine binding,[2] inhibition of histamine-stimulated adenylate cyclase,[3,4] and quantitative electroencephalography (QEEG),[5,6] which are capable of detecting such agents. It is fair to say that no single assay system or receptor binding system has yet gained wide acceptance as a definitive measure of antidepressant activity, for all types of antidepressant agents.

Faced with a divergence of biochemical correlates for atypical antidepressants, we attempted to apply the technique of three-dimensional molecular modelling utilizing Drieding models and, ultimately, a Trigraph computer graphics system[7] to search for molecular commonality between the TCA's and mianserin in particular. A three-point molecular overlay model was developed, which was used as the fitting basis to compare novel hypothetical structures supplied by the chemist. From this study, it was determined that, among others, the novel pyrazino-[2,1-*a*]isoquinoline ring system, in particular, *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino-[2,1-*a*]isoquinoline (**7a**), provided a rigid molecule with excellent fit (see Figure 1) to the molecular model represented by the centers of the two phenyl rings and the remote tertiary nitrogen atoms of imipramine and mianserin. In addition, the pK_a of the critical N(2) nitrogen atom and the lipophilicity (log *P*) was predicted apriori to be nearly identical with mianserin.

On this basis, we were encouraged to investigate the 7-phenylpyrazino[2,1-*a*]isoquinoline ring system, in particular compound **7a**. (For ring numbering and stereochemistry, see Figure 2.) Here we report the stereocontrolled synthesis, optical resolution, and pharmacological activities of **7a** and a variety of related derivatives.

Chemistry. The requirement for phenyl substitution on the 4-position of the isoquinoline ring ruled out synthetic approaches based on the Reissert reaction similar to those used to construct unsubstituted pyrazino[2,1-*a*]-isoquinolines.[8,9] We therefore opted for a new stereocontrolled approach to 1-(aminomethyl)-4-phenyl-1,2,3,4-tetrahydroisoquinolines based on the Bischler–Napieralski isoquinoline construct, which would provide an activated leaving group at the 1-methylene position and take advantage of the symmetry element in the amide precursor during cyclization. Amination, followed by stereocontrolled reduction of the 3,4-dihydroisoquinoline intermediate, would provide the desired isomeric aminoisoquinoline precursors from which the pyrazino[2,1-*a*]isoquinoline C ring could be formed by traditional closure methods.

The synthesis is outlined in Scheme I. 2,2-Diphenylethylamine was acylated with chloroacetyl chloride in $CHCl_3$/TEA (triethylamine) to give the chloroacetamide (**2**) in 90% yield. Bischler–Napieralski cyclization of **2** with P_2O_5 in hot xylene gave 1-(chloromethyl)-3,4-dihydro-4-phenylisoquinoline (**3**) as a very air-sensitive oil that could be isolated in 70% yield as the stable hydrochloride salt. Treatment of **3** with an excess of methylamine in CH_3OH gave the amino imine, which again was extremely sensitive and could not be isolated but rather was reduced directly to a mixture of the *cis*- and *trans*-1-[(methylamino)-methyl]-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**4a** and **5**). Reduction with $NaBH_4$ gave a 6:4 ratio of cis/trans isomers; however, catalytic hydrogenation gave very high stereoselectivity for the desired cis isomer with a ratio of ~10:1. The isomers were readily separated on large scale by fractional crystallization of the dihydrochloride salts. By variation of the amine and this methodology, derivatives **4b** and **4c** were also prepared. Treatment of **4c** with HCOOH and borane reduction of the formate gave the fully methylated analogue **6**.

The secondary 1,2-diamines were easily cyclized to the corresponding piperazines by established methodology.[10] Treatment of either **4a**, **4b**, or **5** in situ with TEA to free the salts and then diethyl oxalate in refluxing $CHCl_3$ gave

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[‡] Department of Pharmacology.

(1) Banerjee, S. P.; Kung, L. S.; Riggi, S. J.; Chandra, S. K. *Nature (London)* **1977**, *268*, 455.
(2) Tran, V. T.; Chang, R. S. L.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 6920.
(3) Kanof, P. D.; Greengard, P. *Nature (London)* **1978**, *272*, 329.
(4) Gilman, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 305.
(5) Itil, T. M.; Polvan, N.; Hsu, W. *Curr. Ther. Res.* **1972**, *14*, 395.
(6) Frankenheim, *J. Drug. Dev. Res.* **1982**, *2*, 197.
(7) This system was developed by Tripos Associates, St. Louis, MO 63117.
(8) Leonard, J. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3405.
(9) Thesing, J.; Seitz, G.; Pohlke, R.; Sommer, S.; Muller-Calgan, H.; Gotz, M. U.S. Patent 3 393 195, 1968.
(10) Riebsomer, J. L. *J. Org. Chem.* **1950**, *15*, 68.

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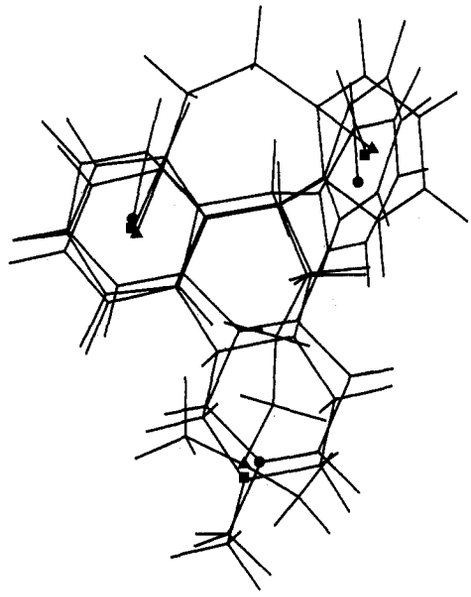


Figure 1. Computer-generated three-point molecular overlays of (+)-(*S*)-mianserin (●), imipramine (▲), and **10** (■). The structures were generated from X-ray coordinates,[15,16] the conformational energies were minimized with MM2 or SEARCH,[7] and the molecular fits were obtained by least-squares regression analysis (FIT)[7] by using the centers of the phenyl rings (indicated by the dummy bonds and symbols) and the remote tertiary nitrogen atoms (indicated by the symbols) as the common three-point pharmacophore. The dummy bonds, which extend from the edge to the center of the phenyl rings, are constructed from corresponding atoms, such that they provide a visual aid for the relative coplanarity of the rings.

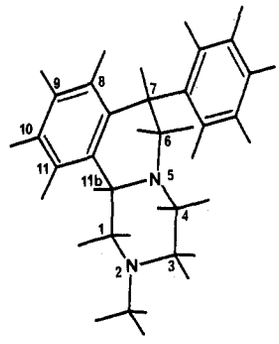
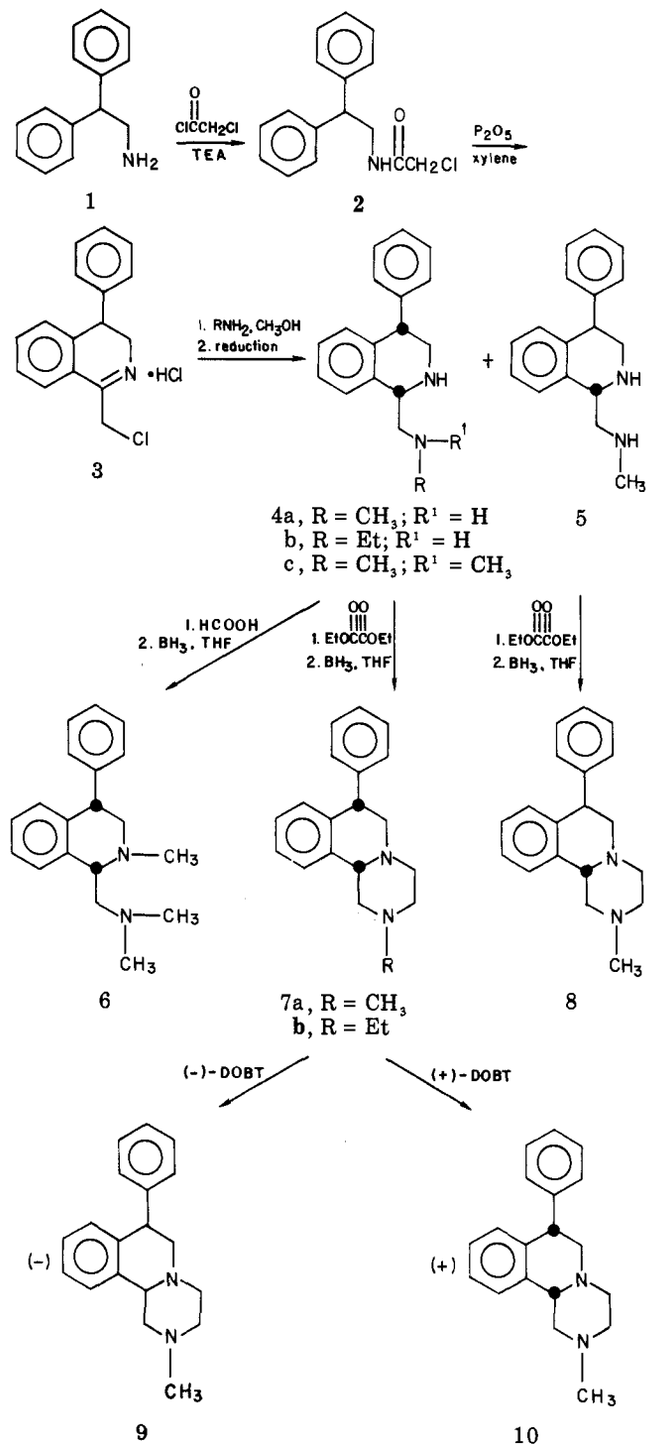


Figure 2. Stereochemistry, ground-state conformation, and ring atom numbering system for **7a** (enantiomer **10**).

the cyclic diamides in 95% yield, which were conveniently reduced with BH_3 in tetrahydrofuran (THF) to give the target pyrazino[2,1-*a*]isoquinolines **7a**, **7b**, and **8** (Scheme I).

The racemic cis isomer **7a** was resolved into its two optical antipodes by diastereomeric salt formation with (+)- or (−)-dibenzoyltartaric acid (DOBT). These resolving agents were extremely efficient, giving fully resolved salts after a single recrystallization. In addition, the composition of the DOBT salts were 2:1, 1 mol of DOBT providing 2 mol of resolved amine. Thus, treatment of **7a** with (−)-DOBT in refluxing 95% ethanol gave 2:1 (−)-amine·(−)-DOBT after one recrystallization.[11] The resolved (−)-amine (**9**) was isolated as the hydrochloride salt after

Scheme I



neutralization of the DOBT salt with dilute NH_4OH. Similar treatment with (+)-DOBT provided the (+)-amine (**10**).

In order to prepare a variety of N(2)-substituted derivatives most expeditiously, we investigated the dealkylation of **7a**. The N-demethylated compound (**11**) was prepared by reaction of **7a** with methyl chloroformate/hydrazine[12] (Scheme II). The alkylated derivatives (**12a–e**) were then prepared from **11** by acylation to the amides, followed by diborane reduction.

We also investigated direct aromatic nitration of **7a** as a simple means for the synthesis of aromatic substituted

(11) The description of this salt as fully resolved is based on the fact that no further increases in optical rotation at wavelengths from 360 to 589 nm are observed for either the (−)-DOBT salt or the hydrochloride **9** after four additional recrystallizations and that analysis of diastereomer composition by NMR showed no detectable (+)-amine (−)-DOBT.

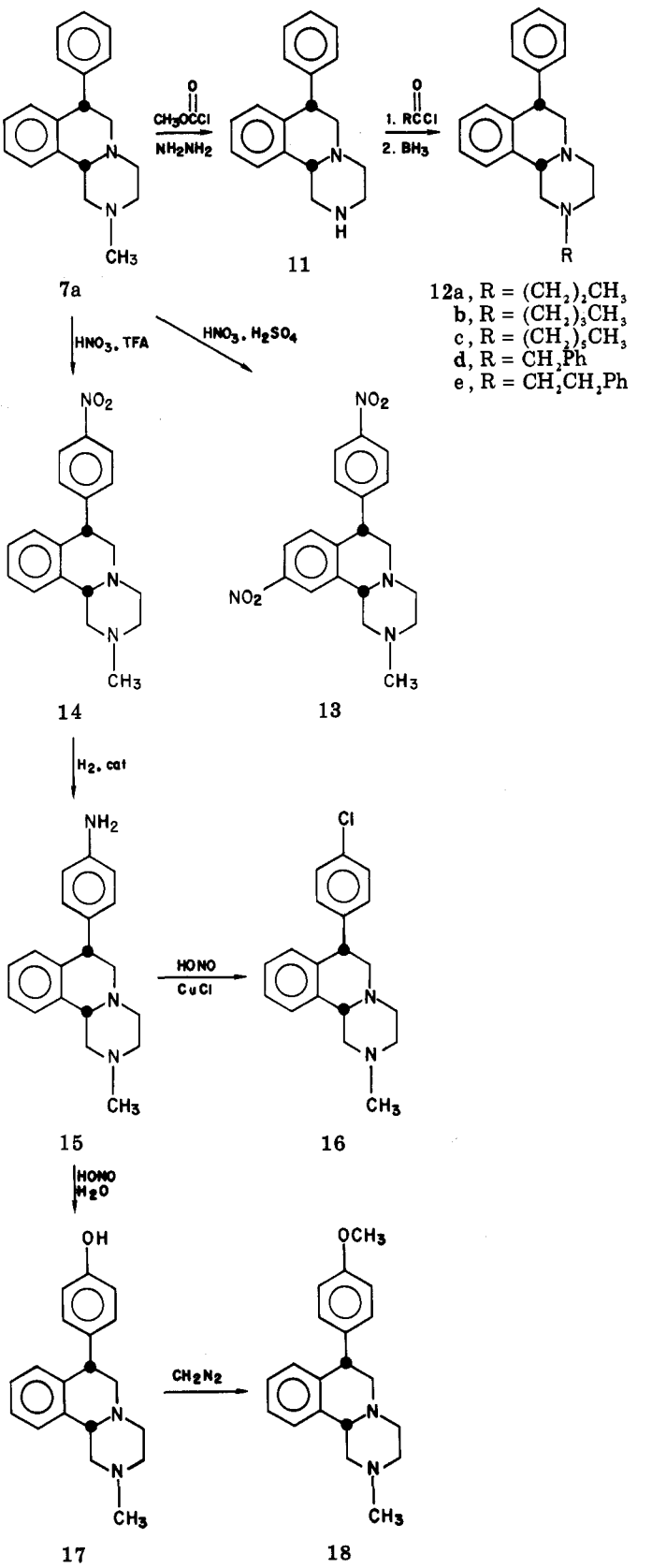
(12) Brine, G. A.; Boldt, K. G.; Hart, C. K.; Carroll, F. I. *Org. Prep. Proc. Int.* **1976**, *8*, 103.

analogues. Nitration of **7a** at 0 °C in 98% H_2SO_4 gave exclusively the dinitrated product **13**. Selective nitration of **7a** to the mononitro derivative **14** was accomplished by switching from sulfuric acid to anhydrous TFA.[13] With this *p*-nitro compound in hand, we were able to prepare several aromatic substituted compounds. Reduction of **14** in acidic methanol over Pd/C gave quantitatively the triamine **15**. This compound could be selectively diazotized with HONO, and the diazonium salt could be decomposed with CuCl to give the *p*-chlorophenyl analogue **16**, or it could be decomposed with water to give the phenol **17**. Methylation of the phenol with diazomethane provided the methyl ether **18**.

Determination of Stereochemistry and Absolute Configuration. Compounds **4a** and **5** were recognized as isomeric forms on the basis of identical analysis and nearly identical IR, NMR, and UV spectral properties. Configurational assignment was made by chemical conversion of each individual isomer to the corresponding pyrazino-[2,1-*a*]isoquinoline, i.e., **4a** to **7a** and **5** to **8**, which maintained their isomeric relationship. These two rigid isomers were then subjected to detailed analysis by high-field (270 MHz) NMR and FTIR and compared to configurationally established model compounds provided by the elegant studies of Marynoff et al.[14] The presence of typical "Bohlmann bands" in the IR's of both **7a** and **8** established the trans relationship and conformational inflexibility of the N5 to C11b ring junction. In this attitude, the 7-phenyl ring of the cis isomer (**7a**) occupies a pseudoaxial position, and the 7-H proton nearly bisects the angle of the adjacent 6-axial and 6-equatorial protons. At 270 MHz, the 7-H proton of **7a** appears at δ 4.04 as a narrow triplet with coupling constants $J_{6a,7}$ = 3.4 Hz and $J_{6e,7}$ = 3.4 Hz, in accordance with expectation for the cis isomer. In the trans isomer, the phenyl ring occupies the pseudoequatorial position, and the axially oriented 7-H proton forms a large transoid angle (~160°) to the adjacent 6-axial proton and a small angle (~40°) to the 6-equatorial proton. At 270 MHz, the 7-H proton of **8** appears downfield at δ 4.42 as a doublet of doublets with coupling constants $J_{6a,7}$ = 11.4 Hz and $J_{6e,7}$ = 5.9 Hz, in accordance with expectation for the trans isomer. These findings are virtually identical with those obtained by Marynoff[14] for a large number of structurally related *cis*- and *trans*-phenylbenzoquinolizidines. On this basis, the structures of **7a** and **8** were assigned cis and trans stereochemistry, respectively, and since the ring-closure procedure was carried out at remote centers and does not affect the isomer relationships, the isoquinoline precursors **4a** and **5** were then assigned corresponding cis and trans geometries, respectively (Scheme I).

The marked preference (~10:1) for formation of the cis isomer **4a**, during catalytic hydrogenation of the imine double bond of the 3,4-dihydroisoquinoline intermediate, follows from the argument of steric approach control. Cis addition of hydrogen to the 1,2-imine double bond occurs preferentially from the face of the molecule opposite to the hindering effect of the 4-phenyl substituent.

Scheme II



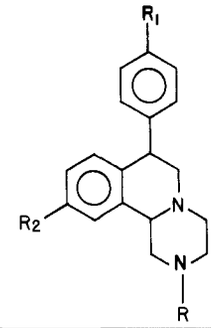
The absolute configuration of the (+) and (−) optical isomers of **7a** was determined by single-crystal X-ray studies.[15] The fully resolved (+) optical isomer (**10**) was converted to a 1:1 salt with D-tartaric acid, which was isolated as a highly crystalline monomethanolate. X-ray

(13) This compound **14** was readily identified as the *p*-NO_2 isomer by 200-MHz NMR analysis of the free base, which clearly displays an AA'BB' pattern for the aromatic protons of the 7-phenyl ring. Indeed, this pattern is observed for the free bases of all derivatives **14**–**18**. HPLC analysis of the crude product from this reaction indicates the presence of 10–15% of the *m*-NO_2 isomer (identified by NMR of the *m*-NH_2 conversion product), with no detectable mononitration of the other disubstituted aromatic ring.

(14) Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79.

(15) Hite, G.; Rapposch, M.; Griffith, R. C.; Gentile, R. J.; Albrecht, W. L. *Acta Crystallogr.*, submitted for publication.

Table I. Biological Data for the 1,3,4,5,6,11b-Hexahydro-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinolines



compd	isomer	R	R_1	R_2	IC_{50},[a] μM [^{3}H]QNB[b]	IC_{50},[a] μM [^{3}H]MEP[c]
7a	cis	CH_3	H	H	0.43	0.02–0.06
7b	cis	CH_2CH_3	H	H	1.3	0.28
8	trans	CH_3	H	H	7.2	>10
9	(−)-cis	CH_3	H	H	46	0.04
10	(+)-cis	CH_3	H	H	0.13	2.8
11	cis	H	H	H	0.86	>10
12a	cis	$(CH_2)_2CH_3$	H	H	6.6	>10
12b	cis	$(CH_2)_3CH_3$	H	H	18	>10
12c	cis	$(CH_2)_5CH_3$	H	H	20	>10
12d	cis	CH_2Ph	H	H	>100	>10
12e	cis	CH_2CH_2Ph	H	H	>100	>10
13	cis	CH_3	NO_2	NO_2	45	>10
14	cis	CH_3	NO_2	H	3.5	0.52
15	cis	CH_3	NH_2	H	4.0	0.86
16	cis	CH_3	Cl	H	0.9	0.38
17	cis	CH_3	OH	H	2.1	0.19
18	cis	CH_3	OCH_3	H	5.6	0.68
imipramine					0.3	0.03
mianserin					1.9	0.014

[a] IC_{50} is the micromolar concentration of test substance required to inhibit by 50% the specific binding of [^{3}H]QNB (0.8 nM) or [^{3}H]MEP (3 nM) to membranes of rat brain without cerebellum. The IC_{50} values were generated with 11 concentrations in triplicate with SEM's of less than 20% for the QNB assay and 30% for the MEP assay. [b] [^{3}H]Quinuclidinyl benzilate (QNB) binding assay (see ref 18). [c] [^{3}H]Mepyramine (MEP) binding assay (see ref 2).

analysis of this salt, which contained an asymetric marker (the D-tartaric acid), allowed us to confirm positively the cis geometry of **10** as assigned by the NMR studies and to establish the absolute configuration at atoms C7 and C11b as *S,S*. A computer-generated ORTEP drawing of **10**·*d*-tartrate·CH_3OH is given in Figure 3. Thus, the absolute configuration of the (+) optical isomer **10** is identical with that determined by X-ray analysis for (+)-mianserin (i.e., *S*),[16] which was used in the modelling studies.[17] By default then, the absolute configuration of the (−) optical isomer **9** is *R,R*.

Results and Discussion

The tricyclic antidepressants uniformly block the reuptake of norepinephrine and/or serotonin at presynaptic nerve terminals, and a variety of screens have been developed over the years that are capable of measuring this phenomena either directly or indirectly. However, atypical antidepressants, such as mianserin and iprindole, are not active in these types of assays. Recently, new methods have been developed that are capable of detecting the TCA's and atypical antidepressants, and two of the reported in vitro procedures have been adopted in our laboratories as useful markers for antidepressant activity. We evaluated compounds **4–18** for their ability to interact with muscarinic acetylcholine receptors by measuring in vitro the inhibition of [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) binding to rat brain homogenates, according to the procedures of Yamamura and Snyder.[18] We also evaluated their ability to interact with brain histamine receptors by measuring in vitro the inhibition of [^{3}H]mepyramine ([^{3}H]MEP) specific binding to rat brain homogenates, according to the procedure of Tran, Chang, and Snyder.[2] Activity for the test compounds was compared to that for the standards imipramine and mianserin. The results are given in Tables I and II. Compounds **7a**, **9**, and **10** were also evaluated in two in vivo assays: the chronic β-receptor subsensitivity assay by the procedure by Banerjee, Riggi, and Chandra[1] and quantitative electroencephalography (QEEG) in conscious beagles as developed by Frankenheim.[6]

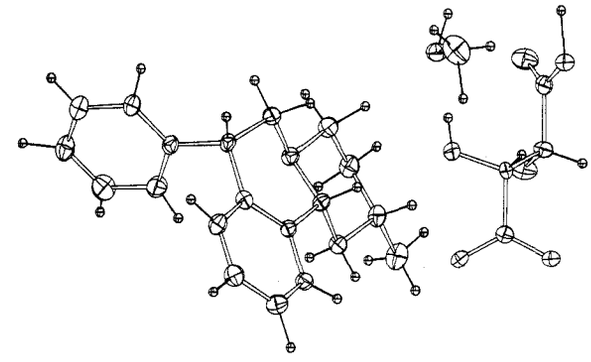
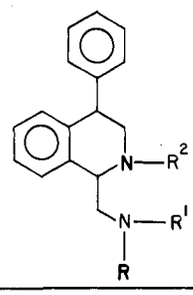


Figure 3. ORTEP plot including 50% probability for 10·(+)-bitartrate methanol.

(16) Van Rij, C.; Feil, D. *Tetetrahedron* **1973**, *29*, 1891.
(17) The antidepressant activity of mianserin has been reported to be localized in the (+)-*S* optical isomer: Schoemaker, H.; Berendsen, J. H. G.; Stevens, H. J. T.; Nickolson, J. J. *Psychopharmacology* **1981**, *74*, 137.
(18) Snyder, S. H.; Yamamura, H. I. *Arch. Gen. Psychiatry* **1977**, *34*, 236.

Table II. Biological Data for the 1-(Aminomethyl)-4-phenyl-1,2,3,4-tetrahydroisoquinolines



compd	isomer	R	R^1	R^2	IC_{50},[a] μM [^{3}H]QNB[b]	[^{3}H]-MEP[c]
4a	cis	CH_3	H	H	2.6	3.5
4b	cis	Et	H	H	7.0	5.0
4c	cis	CH_3	CH_3	H	4.0	2.0
5	trans	CH_3	H	H	6.3	0.17
6	cis	CH_3	CH_3	CH_3	1.2	>10

[a] IC_{50} is the micromolar concentration of test substance required to inhibit by 50% the specific binding of [^{3}H]QNB (0.8 nM) or [^{3}H]MEP (3 nM) to membranes of rat brain without cerebellum. The IC_{50} values were generated with 11 concentrations in triplicate with SEM's of less than 20% for the QNB assay and 30% for the MEP. [b] [^{3}H]Quinuclidinyl benzilate (QNB) binding assay (see ref 18). [c] [^{3}H]Mepyramine (MEP) binding assay (see ref 2).

The target *cis*- and *trans*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline isomers **7a** and **8** gave markedly different results when evaluated in the in vitro assays for antihistaminic and anticholinergic activity. As predicted from the modelling studies, the cis isomer **7a**, which provides a good three-dimensional fit to the inverted conformer of mianserin,[19] demonstrated good antihistaminic activity in the [^{3}H]mepyramine assay, with an IC_{50} in the 0.02–0.06 μM range (mianserin ≈ 0.012 μM; imipramine ≈ 0.03 μM), and activity in the QNB assay at 0.43 μM. The trans isomer **8**, which was prepared to test the validity of the structural model and does *not* fit the mianserin template, was virtually inactive in inhibiting [^{3}H]MEP binding and 20-fold less potent in the QNB assay. The *N*-ethyl analogue of **7a** (i.e., **7b**) gave a similar activity profile with reduced potency, whereas the N-demethylated derivative (**11**) exhibited a total loss of antihistaminic activity. In in vivo evaluations, compound **7a** exhibited potent activity in the β-receptor subsensitivity assay, and an "antidepressant profile" was obtained at 1 mg/kg in the QEEG procedure.[20]

In order to determine the relative importance of the complete rigid pyrazino[2,1-*a*]isoquinoline ring system, we evaluated several C-ring-opened derivatives (**4** and **5**), including the exact *cis*-trimethyldiamine replica **6**. With the exception of some weak [^{3}H]MEP activity for compound **5**, these open-ring analogues, especially **6**, were much less active in these assays (Table II). This result may be attributed to the increased degrees of conformational freedom inherent in **6** relative to its conformationally restricted analogue **7a**.

The effects of N(2)-substitution were investigated by evaluating the activity of compounds **7a**, **7b**, and **12a–e**. Increases in substitution from methyl through hexyl to benzyl and phenethyl resulted in nearly stepwise loss of QNB activity and a total loss of MEP activity above the C2 (ethyl) substitution level (Table I). With respect to aromatic substituted derivatives of **7a**, the dinitro analogue **13** was inactive, while the various para-7-phenyl substituted derivatives **14–18** seemed to maintain the activity of the parent **7a**, albeit at slightly lower activity levels.

Perhaps the most intriguing results were obtained from evaluation of the (+) and (−) optical isomers of **7a**. We fully expected that the activity of **7a** would be localized in one of its enantiomers. These thoughts were temporarily befuddled by the experimental results in the in vitro assays, which showed that the cholinergic activity of **7a**[21] resides in the (+) optical isomer **10**, while the antihistaminic activity resides in the (−) isomer **9**. This condition was resolved by the in vivo assays in which only **10** was potently active in both the β-receptor subsensitivity and QEEG experiments. We tentatively conclude that this type of central antihistaminic effect is a typical but perhaps not necessary condition for atypical antidepressant activity.

In conclusion, the target molecule of this study, *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino-[2,1-*a*]isoquinoline (**7a**), as predicted from the modelling studies, appears to possess excellent atypical antidepressant activity. This activity resides predominantly in the (+)-*S*,*S* optical isomer (**10**), which has the same absolute configuration as (+)-mianserin. Other studies have demonstrated that **7a** and **10** do not inhibit the reuptake of norepinephrine or dopamine into nerve terminals and that unlike mianserin, **7a** is not a potent postsynaptic 5-HT antagonist. Compounds **7a** and **10** have received complete pharmacological profiling and have been recommended for safety evaluations.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 225 grating spectrometer or a Nicolet MX-1 FTIR spectrometer. NMR spectra were recorded on a Varian EM-360, an IBM WP-200SY, or a Bruker HX-270 superconducting Fourier-transform spectrometer, with Me_4Si as an internal standard. Mixtures of $CDCl_3$ and Me_2SO-d_6 (2:1 v/v) were sometimes used as NMR solvents (0.5 mL), and under conditions when trifluoroacetic acid (TFA) was used, and additional 0.1 mL was added to shift exchangeable protons. Ultraviolet spectra were obtained on a Varian-Cary 219 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter. Elemental analyses were performed by Galbraith Laboratories. All solvents were ACS Reagent grade and were used without additional purification. 2,2-Diphenylethylamine (**1**) was purchased from Aldrich Chemical Corp.

***N*-(Chloroacetyl)-2,2-diphenylethylamine (2).** To a stirred solution of 2,2-diphenylethylamine (100.0 g, 0.5 mol) and triethylamine (123.0 g, 1.2 mol) in chloroform (2 L) maintained under nitrogen at ambient temperature was added dropwise chloroacetyl chloride (124.2 g, 1.1 mol), and the mixture was stirred for 2 h. Thin-layer chromatography (TLC) analysis showed the reaction to be complete. The mixture was transferred to a separatory funnel and washed with 10% HCl (3 × 1 L) and water (1 L), and the organic phase was dried over $MgSO_4$. The solvent was evaporated to a dark oil, which was treated with cyclohexane (1 L), and upon standing a solid crystallized, which was collected by filtration, washed with cyclohexane, and air-dried to give 122.0 g of **2** as a tan solid: mp 73–74 °C; IR (KBr) 3280, 3080, 1160, 1560, 1125, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.7–6.9 (10 H, m), 4.4–3.7 (5 H,m with s at 3.94). Anal. ($C_{16}H_{16}ClNO$) C, H, N, Cl.

1-(Chloromethyl)-3,4-dihydro-4-phenylisoquinoline Hydrochloride (3). A stirred suspension of phosphorus pentoxide (373.0 g, 2.6 mol) in xylene (8 L) maintained under nitrogen was

(19) The conformation of (+)-*S*-mianserin in which the diphenylazepine ring is inverted from that observed in the X-ray studies[16] provides the best fits to imipramine and **7a**.

(20) These pharmacological studies will be reported in detail elsewhere.

(21) In isolated tissue preparations and in vivo studies, compounds **7a** and **10** have been characterized as weak "partial agonist" cholinergic agents.[20]

heated to a gentle reflux (~140 °C) and then treated portionwise with **2** (90.0 g, 0.328 mol), and the mixture was maintained at reflux for 2 h and then allowed to cool to ambient temperature overnight. The xylene was decanted off, the reaction flask was cooled in an ice bath, and the solid residue was carefully treated with water (10 L). This mixture was stirred for 0.5 h and then basified to pH 11 with 50% NaOH and extracted with chloroform (3 × 3 L), and the extracts were dried over $MgSO_4$. The solvents were evaporated to a dark oil, which was immediately dissolved in a mixture of acetone (500 mL) and ether (200 mL) and acidified with HCl gas. Upon standing, a solid crystallized, which was collected by filtration and air-dried to give 88.1 g of **3**·HCl: mp 206–207 °C dec; IR (KBr) 3020, 1660, 1598, 1563, 1490, 760 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 8.2–6.9 (9 H, m), 5.15 (2 H, s), 4.8–4.1 (3 H, m). Anal. ($C_{16}H_{14}ClN$·HCl) C, H, N, Cl.

***cis*- and *trans*-1,2,3,4-Tetrahydro-1-[(methylamino)methyl]-4-phenylisoquinoline Dihydrochloride (4a and 5).** To a stirred solution of methanol (1 L) and methylamine (300 mL) maintained under nitrogen and cooled in an ice bath was added portionwise **3**·HCl (83.0 g, 0.28 mol), and the mixture was heated to reflux (~50–55 °C) for 2 h. After cooling, the solution was poured into a pressure bottle and hydrogenated on a Parr apparatus over 5% Pd/C catalyst (5.0 g) at 40 psi for 16 h. The catalyst was removed by filtration, and the solvent was evaporated to a gummy residue. This was dissolved in a mixture of methanol (200 mL) and 2-propanol (200 mL) and acidified with HCl gas. After the mixture was cooled and left standing, a white solid crystallized, which was collected by filtration and dried to give 64.0 g of the cis isomer **4a**·2HCl, mp 276–277 °C dec. A second crop of solid was obtained from the crystallization (6.1 g), which consisted (TLC) mostly of the trans isomer. Two recrystallizations of this crop provide the pure trans isomer **5**·2HCl, mp 269–270 °C dec.

Compound **4a**: IR (KBr) 3475, 3259–2200, 1610, 1500, 1455, 760, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 10.6–9.6 (3 H, br s), 7.70–6.50 (9 H, m), 5.40–5.05 (1 H, m), 4.80–3.10 (5 H, m), 2.70 (br s, 3 H). Anal. ($C_{17}H_{20}N_2$·2HCl·0.5H_2O) C, H, N, Cl.

Compound **5**: IR (KBr) 3300–3200, 3040, 1640, 1590, 1540, 1380, 840, 750, 740 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.5–6.8 (9 H, m), 5.5 (1 H, br s), 4.8–4.4 (1 H, m), 4.2–3.3 (4 H, m), 2.95 (3 H, br s). Anal. ($C_{17}H_{20}N_2$·2HCl) C, H, N, Cl.

1,2,3,4-Tetrahydro-1-[(ethylamino)methyl]-4-phenylisoquinoline Dihydrochloride (4b). To a stirred solution of ethylamine (100 mL) in methanol (250 mL) maintained under nitrogen and cooled in an ice bath was added portionwise **3**·HCl (10.0 g, 0.033 mol), and the mixture was heated to 50–52 °C for 2 h. After cooling, the solution was poured into a pressure bottle and hydrogenated on a Parr apparatus over 10% Pd/C catalyst (2.0 g) at 40 psi for 1 h. The catalyst was removed by filtration, and the solvent was evaporated to a gummy residue. This residue was dissolved in methanol (50 mL) and 2-propanol (50 mL) and acidified with HCl gas. A white solid crystallized, which was recrystallized from methanol/2-propanol/water and vacuum dried to give 7.6 g of the cis isomer **4b**·2HCl: mp 241–242 °C dec; IR (KBr) 3030, 1590, 1495, 1455, 775 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 11.0–9.5 (3 H, br s), 7.9–6.6 (9 H, m), 5.4 (1 H, br s, $J \approx 10$ Hz), 4.9–2.9 (6 H, m), 1.4 (3 H, t, $J = 7$ Hz). Anal. ($C_{18}H_{22}N_2$·2HCl·H_2O) C, H, N, Cl.

1,2,3,4-Tetrahydro-1-[(dimethylamino)methyl]-4-phenylisoquinoline Dihydrochloride (4c). To a stirred solution of dimethylamine (250 mL) in methanol (1 L) maintained under nitrogen and cooled in an ice bath was added portionwise **3**·HCl (25.0 g, 0.084 mol), and the mixture was stirred for 4 h while being allowed to warm to ambient temperature. The solution was poured into a pressure bottle and hydrogenated on a Parr apparatus over 5% Pd/C catalyst (5.0 g) at 40 psi for 16 h. The catalyst was removed by filtration, and the solvent was evaporated to a gummy residue. The residue was dissolved in methanol (300 mL) and 2-propranol (100 mL) and acidified with HCl gas. After the mixture was cooled and left standing, a solid crystallized, which was collected by filtration. Recrystallization from methanol/2-propanol/water gave 12.2 g of the cis isomer·2HCl: **4c** mp 278–279 °C dec; IR (KBr) 3050, 1585, 1495, 1390, 755, 700 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 9.3 (4 H, br s), 7.7–6.7 (9 H, m), 5.5 (1 H, br d; $J \approx 10$ H), 4.7–2.7 (11 H, m with $2CH_3$'s). Anal. ($C_{18}H_{22}N_2$·2HCl·0.75H_2O) C, H, N, Cl.

1,2,3,4-Tetrahydro-2-methyl-1-[(dimethylamino)methyl]-4-phenylisoquinoline Dihydrochloride (6). To a stirred solution of 4c base (9.5 g, 0.035 mol) in toluene (100 mL) under nitrogen was added formic acid (8.05 g, 0.175 mol), and the mixture was heated to reflux in a Dean–Stark apparatus. After 3 mL of water was collected, the mixture was cooled, treated with 250 mL of 5% NaOH, and extracted with ether (1 × 150 mL) and then chloroform (3 × 100 mL), and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents gave 12.6 g of 1,2,3,4-tetrahydro-2-formyl-1-[(dimethylamino)methyl]-4-phenylisoquinoline as a yellow oil. This material was used directly for additional chemical processing without further purification. To a stirred solution of 1 M borane in tetrahydrofuran (100 mL, 0.1 mol) maintained under nitrogen was added 1,2,3,4-tetrahydro-2-formyl-1-[(dimethylamino)methyl]-4-phenylisoquinoline (12.6 g, 0.04 mol), and the mixture was heated to reflux for 4 h. The mixture was cooled in an ice bath and carefully treated with 200 mL of 10% HCl and refluxed for 1 h. After the mixture was cooled, the solvents were evaporated to dryness, and the residue was dissolved in water and extracted with chloroform (3 × 100 mL). The aqueous phase was basified to pH 11 with 50% NaOH and extracted with ether (3 × 150 mL), and the ether extracts were dried over $MgSO_4$. Evaporation of the solvent at an aspirator gave 9.3 g of a pale yellow oily residue. This was dissolved in methanol (20 mL) and 2-propanol (30 mL) and acidified with HCl gas. After the solution was cooled and left standing, a white solid crystallized, which was collected by filtration to give 5.0 g. Recrystallization from methanol/2-propanol and vacuum drying at 100 °C for 40 h gave 4.2 g of **6**·HCl: mp 186–187 °C dec; IR (KBr) 3060, 3030, 2970, 1640, 1600, 1510, 1450, 745, 710 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.6–6.7 (9 H, m), 6.7–5.3 (2 H, br s), 5.4–3.3 (6 H, m), 3.3–2.7 (6 H, 2 br s). Anal. ($C_{19}H_{24}N_2$·1.5 HCl·H_2O) C, H, N.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione.** To a stirred solution of **4a**·2HCl (30.6 g, 0.094 mol) in chloroform (500 mL) maintained under nitrogen at ambient temperature were added triethylamine (42.6 g, 0.42 mol) and then in one portion diethyl oxalate (30.1 g, 0.206 mol), and the mixture was heated to reflux for 4 h. The mixture was cooled and washed with 10% HCl (3 × 150 mL) and water (150 mL) and then dried over $MgSO_4$. The solvent was evaporated to give 22.3 g of *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione as a pale yellow solid. A sample, recrystallized from 2-propranol, had mp 193–194 °C.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (7a).** To a stirred solution of 1.0 M borane in tetrahydrofuran (450 mL) maintained under nitrogen at ambient temperature was added a solution of *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione (22.3 g, 0.0728 mol) in tetrahydrofuran (100 mL), and the mixture was heated to reflux for 3 h. The mixture was cooled in an ice bath, carefully treated with 10% HCl (250 mL), and refluxed for 1 h, and the solvent was removed on an aspirator, leaving a solid residue. This was treated with water (250 mL), basified to pH 11 with 50% NaOH, and extracted with chloroform (3 × 250 mL). The chloroform extracts were dried over $MgSO_4$ and evaporated to a pale yellow oil. This was dissolved in methanol (200 mL) and 2-propanol (100 mL) and acidified with HCl gas. While the solution was left standing, a white solid crystallized, which was collected by filtration, washed with 2-propanol/ether, and vacuum dried to give 18.1 g of **7a**·2HCl: mp 272–273 °C dec; IR (KBr) 3020, 2955, 1600, 1495, 1455, 1375, 760, cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.5–6.8 (9 H, m), 5.4 (1 H, br m), 4.9–3.5 (9 H, m), 3.10 (3 H, br s). Anal. ($C_{19}H_{22}N_2$·2HCl) C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione.** To a stirred solution of **4b**·2HCl (19.5 g, 0.057 mol) in chloroform (250 mL) maintained under nitrogen at ambient temperature were added triethylamine (26.0 g, 0.25 mol) and then in one portion diethyl oxalate (36.4 g, 0.23 mol), and the mixture was heated to reflux for 6 h. The mixture was cooled and washed with 10% HCl (3 × 150 mL) and water (200 mL) and dried over $MgSO_4$. The solvent was evaporated to a yellow oil, which was dissolved in 200 mL of ethanol and decolorized with Norite. After the solution was cooled and

left standing, a white solid crystallized, which was collected by filtration and dried to give 11.2 g of *cis*-1,3,4,6,7,11b-hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione.

***cis*-1,3,4,5,6,11b-Hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (7b).** To a stirred solution of 1.0 M borane in tetrahydrofuran (200 mL) maintained under nitrogen at ambient temperature was added *cis*-1,3,4,6,7,11b-hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione (9.9 g, 0.03 mol), and the mixture was heated to reflux for 2 h. The mixture was cooled in an ice bath, carefully treated with 10% HCl (125 mL), and refluxed for 1 h, and the solvent was removed on an aspirator. The residue was treated with water (300 mL), basified to pH 11 with 50% NaOH, and extracted with chloroform. The extracts were dried over $MgSO_4$ and evaporated to a pale yellow oil. This oil was dissolved in methanol (100 mL) and 2-propanol (100 mL) and acidified with HCl gas. After the solution was cooled and left standing, a white solid crystallized, which was collected by filtration. Recrystallization and vacuum drying gave 4.0 g of **7b**·2HCl: mp 276–277 °C dec; IR (KBr) 3050, 2960, 1640, 1540, 1480, 780, 720 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.1–6.5 (9 H, m), 5.4–4.3 (2 H, m), 4.3–3.0 (10 H, m), 1.35 (3 H, t, J = 7 Hz). Anal. ($C_{20}H_{24}N_2$·2HCl·0.5H_2O) C, H, N.

***trans*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione.** Using the procedure as described for the preparation of the *cis*-dione hereinabove, we reacted 4.8 g of **5**·2HCl with 4.5 g of diethyl oxalate in the presence of triethylamine to provide 4.2 g of *trans*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione.

***trans*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (8).** Using the procedure as described for the preparation of **7a** hereinabove, we reduced 4.2 g of *trans*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione with 150 mL of 1.0 M borane in tetrahydrofuran to produce, after salt formation, recrystallization, and drying, 1.0 g of **8**·2HCl: mp 279–280 °C dec; IR (KBr) 3075, 3050, 1605, 1460, 1340, 750, 700 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.5–6.8 (9 H, m), 5.4 (1 H, br d, $J \approx 12$ Hz), 5.1–4.4 (2 H, m), 4.3–3.5 (7 H, m), 3.2 (3 H, s). Anal. ($C_{19}H_{22}N_2$·HCl·0.25H_2O) C, H, N, Cl.

(−)-*cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline (−)-Dibenzoyl-L-tartrate (2:1) [9·(−)-DOBT]. A stirred solution of **7a** (21.8 g, 0.0784 mol) in 95% ethanol (300 mL) was heated to reflux and then treated with a solution of (−)-dibenzoyl-L-tartaric acid monohydrate (14.32 g, 0.04 mol) in hot 95% ethanol (100 mL). A white solid crystallized immediately. The suspension was stirred and refluxed for 15 min and then allowed to cool to ambient temperature, and the solid was collected by filtration and dried to give 17.51 g of salt $[\alpha]^{20}_D$ −135.5° (*c* 0.2, CH_3OH). This solid was resuspended in 95% ethanol, stirred, heated to reflux for 1 h, and then allowed to cool, and the white solid was collected by filtration and vacuum dried to give 16.95 g of fully resolved **9**·(−)-DOBT (2:1) mp 203–204 °C dec, $[\alpha]^{20}_D$ −136° (*c* 0.2, CH_3OH).

(−)-*cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (9). **9**·(−)-DOBT (2:1) (16.9 g, 0.01886 mol) was dissolved in chloroform (300 mL), treated with water (600 mL), and then basified to pH 11 with 28% aqueous ammonia. The layers were shaken vigorously and separated, and the aqueous phase was extracted with chloroform (2 × 250 mL). The combined chloroform extracts were washed with water (2 × 100 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 10.1 g (96% yield) of the white solid base. This was dissolved in methanol (200 mL) and filtered while hot, and the filtrate was acidified with HCl gas. The white solid salt crystallized rapidly. The mixture was stirred and heated to reflux for 10 min and then allowed to cool. The solid was collected by filtration, washed with methanol, and vacuum dried at 85 °C for 24 h to give 12.7 g of **9**·2HCl: mp 274–276 °C dec; $[\alpha]^{20}_D$ −80.5° (*c* 1, 95% ethanol); IR (KBr) 3065, 3030, 2960, 1605, 1500, 765, 705 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.5–6.8 (9 H, m), 5.4 (1 H, br m), 5.0–3.4 (9 H, m), 3.08 (3 H, s). Anal. ($C_{19}H_{22}N_2$·2HCl·0.25 H_2O) C, H, N, Cl.

(+)-*cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline (+)-Dibenzoyl-D-tartrate (2:1) (10·(+)-DOBT). The first filtrate from the preparation of the (−)-dibenzoyl-L-tartrate salt above was evaporated to dryness to a foamy residue, which was dissolved in chloroform (400 mL) and treated with water (500 mL), and the mixture was basified to pH 11 with 28% aqueous ammonia. The layers were shaken vigorously and separated, and the aqueous phase was extracted with chloroform (2 × 200 mL). The combined chloroform extracts were washed with water, dried over $MgSO_4$, and evaporated to a white solid: yield 10.9 g. The solid was dissolved in 95% ethanol (300 mL), and the stirred solution was heated to reflux and then treated with a solution of (+)-dibenzoyl-D-tartaric acid (7.16 g, 0.02 mol) in hot 95% ethanol (100 mL). A white solid crystallized immediately. The suspension was stirred, heated to reflux for 5 min, and then allowed to cool. The white solid was collected by filtration and vaccum dried to give 17.0 g of **10**·(+)-DOBT (2:1): mp 205–206 °C dec; $[\alpha]^{20}_D$ +136.5° (*c* 0.2, CH_3OH).

(+)-*cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (10). **10**·(+)-DOBT (2:1) (16.9 g, 0.01886 mol) was dissolved in chloroform (300 mL), treated with water (600 mL), and then basified to pH 11 with 28% aqueous ammonia. The layers were shaken vigorously and separated, and the aqueous phase was extracted with chloroform (2 × 250 mL). The combined chloroform extracts were washed with water (2 × 100 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 10.2 g of the white solid base. This was dissolved in methanol (200 mL) and filtered while hot, and the filtrate was acidified with HCl gas. The white solid salt crystallized rapidly. The mixture was stirred and heated to reflux for 10 min and then allowed to cool. The solid was collected by filtration, washed with methanol, and vacuum dried at 85 °C for 24 h to give 10.8 g of **10**·2HCl: mp 274–276 °C dec; $[\alpha]^{20}_D$ +81.2° (*c* 1, 95% ethanol); IR (KBr) 3065, 3030, 2960, 1600, 1585, 1455, 768, 705 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.5–6.8 (9 H, m), 5.4 (1 H, br m), 5.0–3.4 (9 H, m), 3.1 (3 H, s). Anal. ($C_{19}H_{22}N_2$·2HCl·0.25H_2O) C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (11).** To a stirred solution of **7a** (11.0 g, 0.039 mol) in chloroform (1.5 L) was added sodium bicarbonate (83.1 g, 0.99 mol) and methylchloroformate (45.3 g, 0.48 mol), and the mixture was heated to reflux for 48 h. The salts were removed by filtration, and the organic phase was washed with 5% HCl (3 × 300 mL) and water (300 mL) and dried over $MgSO_4$. The solvent was evaporated, and the oily residue was treated with 95% hydrazine (250 mL) and refluxed for 24 h. Water (500 mL) was added, and the mixture was evaporated to an oily residue. This was treated with water (500 mL) and a small amount of 50% NaOH to ensure pH 11, and the mixture was extracted with chloroform (3 × 250 mL). The extracts were dried over $MgSO_4$ and evaporated to a yellow oil. This was dissolved in methanol (50 mL) and 2-propanol (50 mL) and acidified with HCl gas. After the solution was cooled and left standing, a white solid crystallized, which was collected by filtration. Recrystallization from methanol/2-propanol/water and vacuum drying gave 6.4 g of **11**·2HCl: mp 275–277 °C dec; IR (KBr) 3050, 3025, 2950, 1605, 1500, 1380, 760, 700 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 10.3 (2 H, br s), 7.8–6.6 (9 H, m), 5.3–2.9 (10 H, m). Anal. ($C_{18}H_{20}N_2$·2HCl·0.25H_2O) C, H, N.

***cis*-1,3,4,6,7,11b-Hexahydro-7-phenyl-2-propionyl-2*H*-pyrazino[2,1-*a*]isoquinoline.** To a stirred solution of **11**·2HCl (7.0 g, 0.20 mol) and triethylamine (8.4 g, 0.08 mol) in chloroform (100 mL) maintained at 0 °C under nitrogen was added dropwise propionyl chloride (2.9 g, 0.031 mol). The mixture was allowed to warm to ambient temperature, stirred for 16 h, and then treated with 10% HCl (50 mL). The layers were separated, and the organic phase was washed with 10% HCl (2 × 50 mL) and water (50 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a solid residue, which was slurried with ether and filtered to give 2.1 g of *cis*-1,3,4,6,7,11b-hexahydro-7-phenyl-2-propionyl-2*H*-pyrazino[2,1-*a*]isoquinoline, mp 250–251 °C. An additional 3.2 g of good purity product was recovered from the ether to give a total of 5.3 g (82%).

***cis*-1,3,4,6,7,11b-Hexahydro-7-phenyl-2-propyl-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (12a).** To a stirred solution of 1.0 M borane in tetrahydrofuran (44 mL) maintained under nitrogen at 0 °C was added *cis*-1,3,4,6,7,11b-hexahydro-7-phenyl-2-propionyl-2*H*-pyrazino[2,1-*a*]isoquinoline

(5.3 g, 0.016 mol), and the mixture was heated to reflux for 3 h, cooled in an ice bath, and carefully treated with 10% HCl (100 mL). This mixture was heated to reflux for 1 h and then cooled, and the tetrahydrofuran was removed on an aspirator. The remaining aqueous solution was basified to pH 11 with 50% NaOH and extracted with chloroform. The extracts were dried over $MgSO_4$ and evaporated to a solid residue (6.0 g). This was dissolved in methanol (50 mL) and 2-propanol (50 mL) and acidified with HCl gas. After the solution was cooled and left standing, a white solid crystallized, which was collected by filtration and vacuum dried at 80 °C for 24 h to give 4.6 g of **12a**·2HCl: mp 273–274 °C dec; IR (KBr) 3060, 3030, 2965, 1600, 1500, 1453, 1390, 765, 700 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.6–6.7 (9 H, m), 5.45 (1 H, br s), 4.8–3.0 (11 H, m), 2.3–1.5 (2 H, m), 1.0 (3 H, t, $J \approx 7$ Hz). Anal. ($C_{21}H_{26}N_2$·2HCl) C, H, N, Cl.

By the same type acylation/reduction procedures, **12b–e** were prepared and had the following melting points: 261–262, 221–222, 203–204, and 265–266 °C dec.

***cis*-1,3,4,6,7,11-Hexahydro-2-methyl-10-nitro-7-(4-nitrophenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (13).** To a stirred solution of **7a**·2HCl (5.2 g, 0.015 mol) in 98% sulfuric acid (30 mL) maintained under nitrogen and cooled to ca. −5 °C in an ice–salt bath was added dropwise a solution of 90% nitric acid (5 mL) in 98% H_2SO_4 (20 mL) over a period of 30 min. The mixture was stirred for 30 min and then poured onto ice (250 cm^3), and the resulting solution was extracted with chloroform (3 × 150 mL). The extracts were dried over $MgSO_4$ and evaporated to an off-white solid residue, 4.4 g. This residue was dissolved in a mixture of water (200 mL) and chloroform (200 mL), basified to pH 11 with 50% NaOH, and extracted with chloroform. The dried extracts were evaporated to a solid residue, which was dissolved in methanol (50 mL) and acidified with HCl gas to give, after filtration, 3.66 g of salt. Recrystallization from methanol/water/ether and vacuum drying at 100 °C for 40 h gave 1.36 g of **13**·2HCl mp 244–245 °C dec; IR (KBr) 3058, 2960, 1610, 1592, 1526, 1460, 1348, 852, 825, cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.4–7.0 (7 H, m), 5.6–3.8 (3 H, m), 3.8–2.8 (10 H, m). Anal. ($C_{19}H_{20}N_4O_4$·2HCl·0.25H_2O) C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-nitrophenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (14).** To a stirred solution of **7a**·2HCl (10.0 g, 0.0285 mol) in trifluoroacetic acid (100 mL) maintained at 0 °C under nitrogen was added dropwise over a period of 30 min 90% nitric acid (25 mL). The mixture was stirred for 2 h and then poured onto ice (1000 cm^3). Chloroform (200 mL) was added, and the mixture was basified to pH 11 with 50% NaOH. The layers were separated, and the aqueous phase was extracted with chloroform (2 × 200 mL). The combined chloroform extracts were washed with water (500 mL), dried over $MgSO_4$, and evaporated to a yellow oil (9.8 g). This was dissolved in methanol (200 mL) and filtered, and the filtrate was acidified with HCl gas. A white solid crystallized upon standing, which was collected by filtration. This solid was recrystallized twice from methanol (200 mL) and water (10 mL) and vacuum dried at 95 °C for 24 h to give 4.04 g of 14·2HCl: mp 251–252 °C dec; IR (KBr) 3045, 2955, 1608, 1521, 1460, 1349, 783, 761 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6 + TFA) δ 8.2 (2 H, d, J = 8.5 Hz, A of AA′BB′), 8.0–6.7 (6 H, m containing B of AA′BB′), 3.1 (3 H, s). Anal. ($C_{19}H_{21}N_3O_2$·2HCl·0.5H_2O).

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-aminophenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Hydrochloride (15).** A solution of 14 (5.2 g, 0.014 mol) in methanol (500 mL), water (100 mL), and concentrated HCl (5 mL) was hydrogenated on a Parr apparatus over 2.0 g of palladium on carbon catalyst at 40 psi for 1 h. The catalyst was removed by filtration, and the solvents were evaporated to a solid residue. This was dissolved in water (500 mL), basified to pH 11 with 50% NaOH, and extracted with ether (3 × 200 mL). The extracts were dried over $MgSO_4$ and evaporated to an oil: yield 4.04 g. This crude product was purified by chromatography on silica gel with a Prep 500 HPLC, eluting with 2% ammoniated methanol/chloroform. Pure fractions were combined and evaporated to give an oil (1.12 g). This was dissolved in methanol (30 mL) and acidified with HCl gas. While the solution was left standing, a white solid crystallized, which was collected by filtration and vacuum dried at 95 °C for 24 h to give 1.08 g of 15·2.5HCl·0.5H_2O: mp 274–276 °C dec; IR (KBr) 3120–2000, 1618, 1510, 1460, 828, 770 cm^{-1}; NMR (Me_2SO-d_6 + TFA) δ 8.3–6.4 (8 H, m), 5.2–2.6 (13 H, m). Anal. ($C_{19}H_{23}N_3$·2.5HCl·0.5H_2O), C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-chlorophenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (16).** To a stirred solution of 15 (6.0 g, 0.0205 mol) in concentrated HCl (40 mL) maintained under nitrogen at 0 °C was added dropwise a solution of sodium nitrate (1.55 g, 0.0225 mol) in water (10 mL) over a period of 30 min. The mixture was stirred for an additional 15 min and then added dropwise to a solution of cuprous chloride (4.0 g, 0.04 mol) in concentrated HCl (20 mL) maintained at 0 °C. After the addition was complete, the ice bath was removed, and the mixture was allowed to warm to ambient temperature and stirred for 3 h, during which time nitrogen evolution was observed. The mixture was heated briefly to 60 °C for 3 min, then cooled and poured onto 1000 cm^3 of ice/water, treated with chloroform (300 mL), and then basified to pH 11 with 50% NaOH. The mixture was stirred for 15 min, and then a jelly-like precipitate was removed by filtration through glass-wool. The filtrate was transferred to a separatgory funnel, the layers were separated, the aqueous phase was extracted with chloroform (2 × 100 mL), and the combined chloroform extracts were dried and evaporated to a yellow oil (5.84 g). This material was purified by chromatography on a Prep 500 HPLC on silica gel, eluting with 1.5% ammoniated methanol/chloroform. The pure fractions were combined and evaporated to an oil (2.82 g). This was dissolved in methanol (30 mL) and acidified with HCl gas. Upon standing, a solid crystallized and was collected by filtration and vacuum dried at 90 °C for 24 h to give 2.31 g of 16·2HCl: mp 274–276 °C dec; IR (KBr) 3020, 2968, 1590, 1488, 1459, 1410, 855, 756 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.7–6.7 (8 H, m), 5.8–3.5 (10 H, m), 3.15 (3 H, s). Anal. ($C_{19}H_{21}ClN_2$·2HCl) C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-hydroxyphenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (17).** To a stirred solution of 15 (6.14 g, 0.0209 mol) in a mixture of water (100 mL) and 98% sulfuric acid (100 mL) maintained under nitrogen at 0 °C was added dropwise a solution of sodium nitrate (1.446 g, 0.0217 mol) in water (20 mL). The mixture was stirred at 0 °C for 30 min and at 20 °C for 30 min and then heated to 80–90 °C for 1 h, after which time all nitrogen evolution had ceased. The mixture was cooled and poured onto 100 cm^3 of ice, then basified carefully to pH 7 with NaOH, and extracted with chloroform (3 × 300 mL). The extracts were dried over $MgSO_4$ containing decolorizing carbon and filtered, and the filtrate was evaporated to give a pale yellow residue (5.20 g). This was purified by chromatography on a Prep 500 HPLC on silica gel, eluting with 1.5% ammoniated methanol/chloroform. The pure fractions were combined and evaporated to give 2.14 g of a white solid. This was dissolved in methanol (150 mL) and acidified with HCl gas. A white solid crystallized, which was collected by filtration and vacuum dried to give 2.2 g of 17·2HCl: mp 284–288 °C dec; IR (KBr) 3018, 2955, 1615, 1514, 1460, 1425, 1230, 838, 760 cm^{-1}; NMR ($CDCl_3$ + TFA) δ 7.6–6.7 (8 H, m), 5.4 (1 H, br s), 4.9–3.5 (9 H, m), 3.12 (3 H, s). Anal. ($C_{19}H_{22}N_2O$·2HCl) C, H, N, Cl.

***cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-methoxyphenyl)-2*H*-pyrazino[2,1-*a*]isoquinoline Dihydrochloride (18).** A solution of 17 (2.0 g, 0.0068 mol) in methanol (200 mL) maintained at 5 °C was treated with a solution of diazomethane in ether (100 mL), which was prepared by treating *N*-nitrosomethylurea (10.0 g) with 40% potassium hydroxide (30 mL) at 0 °C and extracting the resulting diazomethane into ether. The mixture was allowed to warm to ambient temperature and hand swirled occasionally for 6 h. Acetic acid (5 drops) was added to decompose any remaining diazomethane, and the solvent was evaporated to an oily residue. This was treated with ether (200 mL) and 5% NaOH (200 mL) and agitated until all the residue was dissolved, and the layers were separated. The aqueous phase was extracted with ether (2 × 100 mL), and the combined ether extracts were washed with 5% NaOH (3 × 100 mL) and dried over $MgSO_4$. Evaporation of the solvent gave an oily residue (1.9 g), which was dissolved in methanol (30 mL) and filtered, and the filtrate was acidified with HCl gas. While the solution was left standing, an off-white solid crystallized, which was collected by filtration, washed with methanol/ether, and vacuum dried at 95 °C for 24 h to give 2.03 g of 18·2HCl: mp 272–274 °C dec; IR (KBr) 3050, 2972, 2830, 1610, 1513, 1255, 1030, 838, 758 cm^{-1};

NMR ($CDCl_3$ + TFA) δ 7.5–6.6 (8 H, m), 5.4 (1 H, s), 5.1–3.4 (12 H, m, s), 3.1 (3 H, s). Anal. ($C_{20}H_{24}N_2O$·2HCl) C, H, N, Cl.

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Registry No. 1, 3963-62-0; 2, 90065-24-0; (±)-3, 90065-25-1; (±)-3·HCl, 90065-26-2; (±)-4a, 90065-27-3; (±)-4a·2HCl, 90065-28-4; (±)-4b, 90065-29-5; (±)-4b·2HCl, 90083-49-1; (±)-4c, 90065-30-8; (±)-4c·2HCl, 90083-50-4; (±)-5, 90065-31-9; (±)-5·2HCl, 90065-32-0; (±)-6, 90065-33-1; (±)-6·2HCl, 90065-34-2; (±)-7a, 90065-35-3; (±)-7a·2HCl, 90065-36-4; (±)-7b, 90065-37-5; (±)-7b·2HCl, 90065-38-6; (±)-8·2HCl, 90065-39-7; (−)-9, 90130-07-7; (−)-9·0.5(−)-DOBT, 90191-34-7; (−)-9·2HCl, 90191-35-8; (+)-10, 90130-08-8; (+)-10·D-tartarate, 90191-38-1; (+)-10·0.5(+)-DOBT, 90191-36-9; (+)-10·2HCl, 90191-37-0; (±)-11, 90065-40-0; (±)-11·2HCl, 90065-41-1; (±)-12a, 90065-42-2; (±)-12a·2HCl, 90065-43-3; (±)-12b, 90065-44-4; (±)-12c, 90065-45-5; (±)-12d, 90065-46-6; (±)-2e, 90065-47-7; (±)-13, 90065-48-8; (±)-13·2HCl, 90065-49-9; (±)-14, 90065-50-2; (±)-14·2HCl, 90065-51-3; (±)-15, 90065-52-4; (±)-15·2.5HCl, 90065-53-5; (±)-16, 90065-54-6; (±)-16·2HCl, 90065-55-7; (±)-17, 90065-56-8; (±)-17·2HCl, 90065-57-9; (±)-18, 90065-58-0; (±)-18·2HCl, 90065-59-1; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; Me_2NH, 124-40-3; EtOC(O)C(O)OEt, 95-92-1; (±)-1,2,3,4-tetrahydro-2-formyl-1-[(dimethylamino)methyl]-4-phenylisoquinoline, 90065-60-4; (±)-*cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione, 90065-61-5; (±)-*cis*-1,3,4,6,7,11b-hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione, 90083-51-5; (±)-*trans*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]-isoquinoline-3,4-dione, 90065-62-6; (±)-*cis*-1,3,4,6,7,11b-hexahydro-7-phenyl-2-propionyl-2*H*-pyrazino[2,1-*a*]isoquinoline, 90065-63-7.

C_1-Methylated 5-Hydroxy-2-(dipropylamino)tetralins: Central Dopamine-Receptor Stimulating Activity

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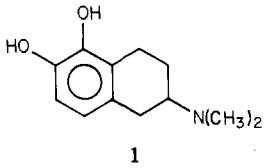
C_1-Methylated derivatives of the potent dopaminergic agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (**6**) have been synthesized and tested for central dopamine (DA) receptor stimulating activity, by using biochemical and behavioral tests in rats. Both *cis*- and *trans*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**4** and **3**) may be classified as central DA-receptor agonists, albeit of lower potency than **6**. The results obtained indicate that both **4** and **3** display DA-autoreceptor stimulation capacity. However, only one of the isomers, *trans*-**3**, is able to elicit clear-cut postsynaptic DA receptor agonist actions at larger doses. 5-Hydroxy-1,1-dimethyl-2-(*n*-propylamino)tetralin (**5**) was found to be inactive.

In 1972 Cannon et al.[1] reported that 5,6-dihydroxy-2-(dimethylamino)tetralin (**1**, "M7") possesses a potency



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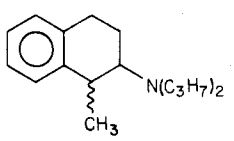

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comparable to that of apomorphine in eliciting emesis in the dog and compulsive gnawing in the mouse, thereby demonstrating high dopaminergic potency.

Cannon's study initiated the synthesis and testing of a large number of related compounds, and several subsequent papers have discussed structure–activity relationships of 2-aminotetralins;[2] particularly well documented are changes in biological effects resulting from variations of the N-substituents[3] and of the position(s) of the phenolic hydroxyl groups(s).[4] However, to our knowledge only one 2-aminotetralin that is alkyl substituted in the nonaromatic ring has been tested for dopaminergic activity. This compound, 1-methyl-2-(di-*n*-propylamino)tetralin (**2**), showed moderate potency in eliciting stereotyped behavior in the rat.[3a] A considerably higher dopaminergic potency might be expected from phenolic analogues of **2**.[5] We have therefore synthesized and tested the *cis*-1-methyl, *trans*-1-methyl, and 1,1-dimethyl derivatives (**4**, **3**, and **5**, respectively, Table I) of the potent DA-receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (**6**),[3b] which is included here as a reference.

Chemistry. The stereoselective syntheses of *cis*- and *trans*-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (**14** and **12**) are outlined in Scheme I.

trans-2-Amino-5-methoxy-1-methyltetralin (**9**) was conveniently prepared from the oxime of 5-methoxy-1-

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(4) See, for example, ref 3a and Arvidsson, L. E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Sanchez, D.; Lindberg, P.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921.
(5) Compare ref 3a and Rusterholz, D. B.; Long, H. P.; Flynn, H. P.; Cannon, J. G.; Lee, T.; Pease, H. P.; Clemens, H. A.; Wong, D. T.; Bymaster, F. P. *Eur. J. Pharmacol.* **1979**, *55*, 73.

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