profile. (2) β-Lipoprotein cholesterol was measured after heparin–$CaCl_2$ precipitation according to Burnstein.[27] (3) Total phospholipids were measured chemically by using the molybdate/vanadate reaction (Boehringer kit) or the enzymatic method phospholipid B test (Wako kit). (4) Total triglycerides were measured by the enzymatic method (Boehringer kit or Ames kit). Applying these methods, the typical range of control values obtained with a set of over 30 experiments are as follows (mean ± SD): triglycerides 44 ± 12 mg/100 mL, HDL phospholipids 124 ± 31 mg/100 mL, HDL cholesterol 53 ± 12 mg/100 mL, β-cholesterol 9 ± 11 mg/100 mL, α-/β-cholesterol ratio 5.9 ± 2.3.

Acknowledgment. We thank Yves Guyon for technical assistance and Patricia Aebi for secretarial assistance.

Pyrroloisoquinoline Antidepressants. 2. In-Depth Exploration of Structure–Activity Relationships†

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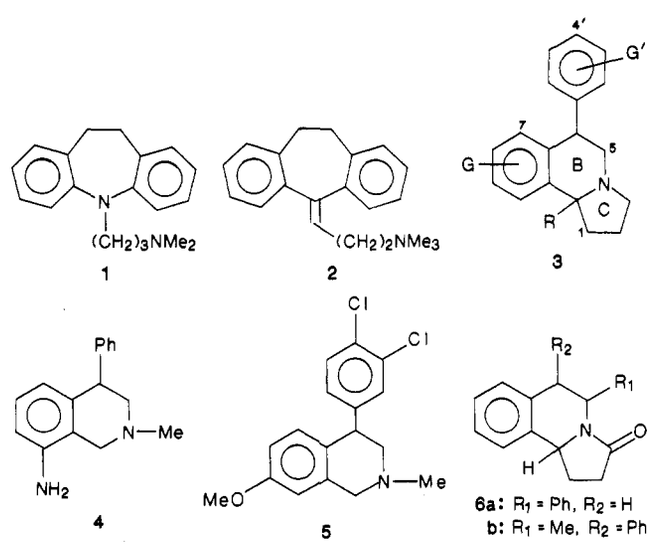
A series of pyrrolo[2,1-*a*]isoquinolines, and related compounds, were examined for antidepressant-like activity, by virtue of their antagonism of tetrabenazine-induced ptosis and sedation, and inhibition of biogenic amine uptake. Thus, we have identified some of the most potent antagonists of TBZ-induced ptosis and some of the most potent inhibitors of the uptake of dopamine, norepinephrine, and serotonin (in rat brain synaptosomes) ever reported. Compounds of particular note, in this regard, are **52b**, **29b**, **22b**, and **48b**, respectively. Biological activity was chiefly manifested by the trans isomeric class. Also, through resolution of four compounds, **7b**, **24b**, **37b**, and **48b**, biological activity was found to be associated with the (+) enantiomer subgroup (salts measured at 589 nm in MeOH), corresponding to the 6*S*,10b*R* absolute configuration for **7b**, **37b**, and **48b**, and the 6*R*,10b*R* configuration for **24b**. An X-ray determination on (+)-**24b**·HBr established its absolute configuration; configurations for the other compounds were verified by enantiospecific synthesis starting with (+)-(*R*)-2-phenylpyrrolidine. Regarding the pendant phenyl ring, diverse substitution patterns were investigated. Those substitutions that were particularly unfavorable were 3′,4′,5′-trimethoxy (**20b**), 2′,3′,4′,5′,6′-pentafluoro (**34b**), 2′-trifluoromethyl (**38b**), 3′,5′-bis(trifluoromethyl) (**42b**), 4′-*n*-butyl (**44b**), 2′-cyano (**47b**), 4′-methylsulfonyl (**50b**), and 2′-carboxy (**58b**). Exceedingly potent compounds, in one way or another, were **10b–12b**, **22b**, **23b**, **25b**, **28b**, **29b**, **33b**, **45b**, **48b**, **51b–53b**. The pattern of aromatic substitution had a strong impact on selectivity in the uptake tests (NE vs. DA vs. 5-HT). Activity was significantly diminished by methyl substitution of **7b** at the 5 (**65**, **66**), 6 (**61b**), or 10b (**60b**) position, by changing the phenyl group of **7b** to cyclohexyl (**67b**), benzyl (**68b**), or H (**72**), by moving the phenyl group of **7b** to the 5 (**69**) or 10b (**70**) position, by expansion of ring B to an azepine (**78b**), and by modification of ring C to an azetidine (**77b**), piperidine (**75b**), or azepine (**74b**). The interaction of selected analogues with various CNS receptors is reported. Little affinity was shown for the muscarinic cholinergic receptor, suggesting a lack of anticholinergic side effects. Interestingly, **24b** and **33b** displayed a high affinity for the serotonin-2 receptor, analogous to mianserin and clomipramine. After the body of data was reviewed, derivatives **24b** and **48b** were chosen for advanced development.

Because of the shortcomings of classical antidepressant drugs,[1] such as *imipramine* (**1**) and *amitriptyline* (**2**), the search for novel agents continues apace. In the past decade, much emphasis has been placed on the discovery of molecular series lacking the tricyclic, "butterfly-like" structure that characterizes the classical antidepressants. These newer "nontricyclic" compounds have been referred to as "nonclassical" antidepressants.

For several years, we have been conducting research in this direction.[2,3] Our CNS testing program has uncovered a new series of compounds, possessing a hexahydropyrrolo[2,1-*a*]isoquinoline structure (viz. **3**), which exhibit significant activity in pharmacological and biochemical assays indicative of their potential in the treatment of depression. Recently, we published a preliminary account to disclose, in particular, representative compounds that are the most potent uptake inhibitors presently known for norepinephrine (NE), dopamine (DA), and serotonin (5-HT).[3] These compounds are also potent antagonists of tetrabenazine-induced ptosis. Another salient aspect of this series is the high enantioselectivity demonstrated in the pharmacological and biochemical tests. Herein we describe the details of our work, with an emphasis on structure–activity relationships (SAR).



1 2 3 4 5

† Presented at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 8–13, 1984 (MEDI 23, 24), and in the Symposium on Non-Classical Antidepressants at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 26–31, 1984 (MEDI 94).

(1) For reviews on antidepressant agents, including their side effects and deficiencies, see: (a) Kaiser, C.; Setler, P. E. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1981; Part III, Chapter 58. (b) Csaky, T. Z. *Cutting's Handbook of Pharmacology*, 6th ed.; Appleton-Century-Crofts: New York, 1979; pp 630–637.

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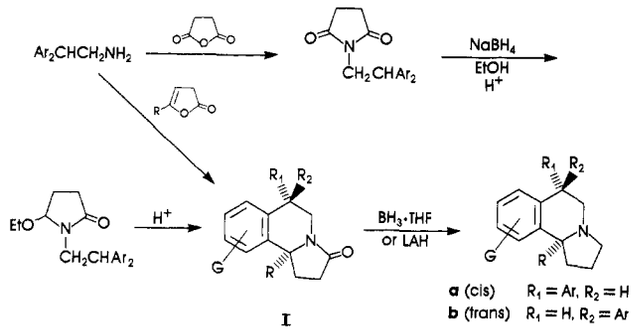
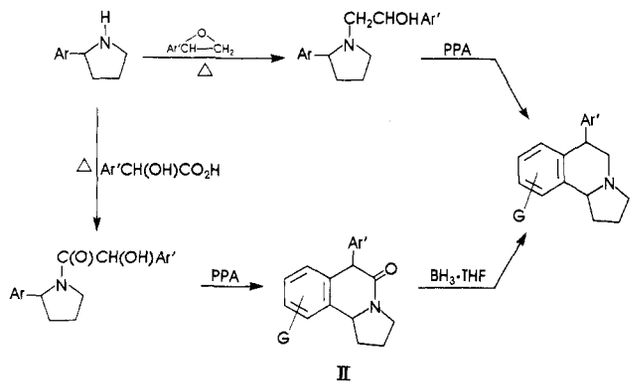
Scheme I



I

Scheme II



II

Our pyrroloisoquinoline series bears a structural resemblance to the tetrahydroisoquinoline antidepressants nomifensine (**4**)[4] and diclofensine (**5**).[5] However, our SAR study will make it abundantly clear that a tetrahydroisoquinoline array of this sort does not necessarily provide the basis for antidepressant-like activity. There are important subtleties of stereochemistry, ring size, and substitution, which not only modulate activity but also determine whether it may exist at all.

Results and Discussion

Chemistry. Two major synthetic routes, illustrated in Scheme I (*the N-acyliminium cyclization route*) and Scheme II (the mandelic acid and styrene oxide routes), were employed for many of our target compounds (Tables I–III). The schemes depict the principal reaction type; some substitution patterns (Table II) and ring sizes or varieties (Table III) are not represented.

Since the *N*-acyliminium route is the subject of separate articles,[6,7] we will refrain from discussing this chemistry at length. The general stereochemical features are summarized here. For compounds with the 6-R-pyrroloisoquinoline or 7-R-benzo[*a*]quinolizine substructure, unsubstituted α to the nitrogen, when R_1/R_2 = an aryl group and a hydrogen, the acyliminium route is highly stereoselective for the cis (e.g., 6α,10bα; Ia) relative stereochemistry. The trans (e.g., 6α,10bβ; Ib) diastereomers were subsequently obtained by base-catalyzed epimerization of the cis-rich lactam, or its amine counterpart (after reduction).[6] When R_1/R_2 = a phenyl and a methyl, or a benzyl and a hydrogen, a nearly 1:1 mixture of diastereomeric lactams was realized.[6] However, when R_1/R_2 = a cyclohexyl and a hydrogen, the stereoselectivity was dramatically reversed; thus, an 88:12 trans-rich mixture of lactams was produced.[7] With only phenyl substitution adjacent to nitrogen (viz. **6a**), the cis (e.g., 5α,10bα) isomer was formed exclusively (and this was converted to **69a** with borane–THF).[6] Vicinal disubstitution complicated matters. For **6b**, three of the four possible diastereomers were obtained from the acyliminium ion cyclization in a 4:2:1 ratio (5α,6β,10bα-**6b**, 5α,6α,10bα-**6b**, and 5α,6β,10bβ-**6b**, respectively; corresponding to amines **65b**, **65a**, and **66b**).[8]

In the styrene oxide route, depicted in Scheme II, a suitable 2-arylpyrrolidine and styrene oxide are reacted in refluxing ethanol, or at 150 °C in dimethylformamide (DMF) or sulfolane, to give intermediate amino alcohols. These are cyclized with polyphosphoric acid (PPA) at 100 °C to afford a mixture of amine products, in which the cis isomer generally predominates by a 3:1 ratio. In the mandelic acid procedure, depicted in Scheme II, a suitable 2-arylpyrrolidine and mandelic acid are condensed in refluxing xylenes, with concomitant removal of water, to give intermediate hydroxy amides. These are cyclized with PPA at 100 °C to a mixture of lactams, II, enriched in the cis isomer. In either process in Scheme II, the 2-arylpyrrolidine can be replaced by a nitrogen heterocycle with a larger ring, or 2-benzylpyrrolidine (e.g., in the preparation of **74a/b** or **78a/b**, respectively).

The lactams from Scheme I (viz. I) or Scheme II (viz. II), wherein R_1/R_2 = aryl and hydrogen, were either epimerized with potassium carbonate in aqueous dimethyl sulfoxide (Me_2SO) to improve the ratio of the cis and trans diastereomers, then reduced with borane–THF to the target amines, or reduced directly to amines, then epimerized with NaOH in aqueous Me_2SO. Base-induced equilibration was also applied to comparably substituted lactams not represented in the schemes. Lactams from Scheme I devoid of an aryl substituent could not be epimerized because of competitive decomposition during the prolonged reaction.[7] Before base-induced epimerization was used on a synthetic scale, a test reaction was performed to check for sufficient enhancement of the desired trans isomer.

The diastereomers were generally separated by preparative HPLC at the amine stage, then purified by recrystallization as acid-addition salts (or infrequently as free bases). Occasionally, the lactam diastereomers were separated by preparative HPLC.

Phenols and catechols **9a**, **9b**, **11a**, **11b**, **13a**, **13b**, **15b**, **19a**, and **19b** were prepared from the corresponding methyl ethers by reaction with 48% HBr in acetic acid at reflux, or with boron tribromide in methylene chloride at −65 °C (see Table I).

Nitro compounds **51a** and **51b** were prepared by the styrene oxide route or by regioselective mononitration of

(2) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F. *J. Med. Chem.* **1984**, *27*, 1067.
(3) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Setler, P. E.; Gardocki, J. F.; Shank, R. P.; Schneider, C. R. *J. Med. Chem.* **1984**, *27*, 943.
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(5) Cherpillod, C.; Omer, L. M. O. *J. Int. Med. Res.* **1981**, *9*, 324. Omer, L. M. O. *Intl. J. Clin. Pharmacol. Ther. Toxicol.* **1982**, *20*, 320. Hillier, K. *Drugs Future* **1979**, *4*, 510.
(6) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.
(7) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *J. Org. Chem.* **1986**, *51*, 1341.

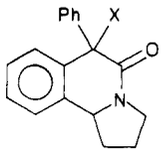
(8) These results will be published separately along with ^1H NMR and X-ray diffraction studies that corroborate the stereochemical assignments. X-ray determinations were conducted on **66b**·HBr and the lactam predecessor to **65b**.

7a or **7b** with nitric acid in trifluoroacetic acid. Catalytic reduction (H_2/PtO_2) of the nitro group in **51a** or **51b** furnished anilines **52a** or **52b** in excellent yield. These anilines were acetylated conventionally to give **53a** and **53b**, or reacted with appropriate aryl isocyanates to give ureas **54a**, **54b**, **55a**, and **56a**.

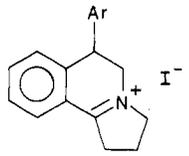
Oxidation of the lactam precursors (II in Scheme II) of **48a/48b** with *m*-chloroperbenzoic acid afforded the sulfonyl lactams, each of which was selectively reduced with borane–THF to amino sulfones **50a** and **50b** (see Experimental Section, preparation of **50b**).

Nucleophilic displacement on the bromo congener of **32a/b** (formed via the styrene oxide route) with copper(I) cyanide in the presence of tetrakis(triphenylphosphine)-palladium (2 mol %) gave cyano compounds **46a/b**.[8] Likewise, **47a/b** were prepared from **35a/b**. Hydrolysis of nitrile **46b** with KOH in refluxing *tert*-butyl alcohol produced amide **57b**. By the same token, a mixture of **47a** and **47b** was converted to the amide stage, with potassium carbonate in aqueous Me_2SO at 100 °C; further hydrolysis with 6 N HCl furnished acids **58a** and **58b**. Reaction of the iodo congener of **32b** (formed via the styrene oxide route) with (trimethylsilyl)acetylene, in the presence of copper(I) iodide, tetrakis(triphenylphosphine)palladium, and triethylamine,[9] gave the silyl-protected acetylene, which generated ethynyl derivative **45b** on reaction with potassium carbonate and methanol.

To prepare **62a/b**, the isomeric mixture of lactams **83** was reacted with sodium hexamethyldisilazide and molecular oxygen, followed by a sodium sulfite workup (use of lithium diisopropylamide gave incomplete reaction).



83: X = H
84: X = OH
85: X = F



86: Ar = 4-ClC_6H_4
87: Ar = Ph

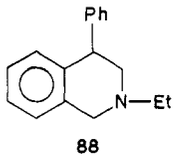
The resultant hydroxy lactams, **84a** and **84b**, were reduced as a mixture with borane–THF, employing a methanol workup (acid workup gave substantial dehydration/decomposition), to furnish **62a/b**. We also reacted the enolate from treatment of lactams **83** with sodium hexamethyldisilazide with methyl iodide, but little formation of the 6-methyl lactams was observed. Reaction of **83a/b** with a variety of bases, followed by perchloryl fluoride gave fluoro lactams **85**, but reaction was incomplete. We preferred to react **84a/b** with (diethylamino)sulfur trifluoride (DAST),[10] which gave **85** in good yield. These fluoro lactams were separated and reduced with borane–THF to fluorides **63a** and **63b** (methanol workup). Reaction of **62a/b** with DAST provided little **63a/b**.

Compound **70** was prepared by condensing 3-benzoylpropionic acid with 2-phenethylamine, treatment with PPA to effect cyclization to a lactam, and reduction with $LiAlH_4$.[11] Erythrinanes **73a** and **73b** were prepared from 2,2-diphenylethylamine and cyclohexanone-2-acetic ester and **71** was prepared from 2-phenylethylamine and α-angelicalactone.[6] Ethano-bridged compounds **59a** and **59b**, 5-phenyl derivative **69a**, indolo compounds **82a** and **82b**, thienyl compounds **79a/b** and **80a/b**, and pyrrolo compounds **81a/b** were prepared via *N*-acyliminium ion chemistry from the appropriate succinimides.[6]

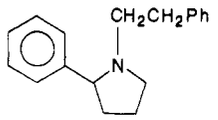
Parent pyrroloisoquinoline **72** was synthesized from 1-(2-phenylethyl)-2-pyrrolinone by PPA cyclization to an enamine, followed by $NaBH_4$–HOAc reduction.[12]

Oxidation of a mixture of **22a** and **22b** with mercuric acetate, followed by addition of H_2S (to remove mercury ion) and hydroiodic acid, gave iminium salt **86**.[13] Treatment with methylmagnesium bromide produced a mixture of amines **64a** and **64b** in ca. a 1:1 ratio. Similarly, iminium salt **87**, generated from **7a/b**, was reacted with MeMgBr to give a 1:1 mixture of **60a** and **60b** (these were also prepared via the acyliminium route). Diastereomer **69b** was obtained by Hg(II) oxidation of **69a**, followed by basification of the intermediate iminium salt(s) and hydrogenation over platinum (an ca. 1:4 mixture of **69a/b** was generated by this process).

Seco analogue **88** was prepared from 4-phenyl-1,2,3,4-tetrahydroisoquinoline and acetyl chloride, followed by $LiAlH_4$ reduction. Seco analogue **89** was synthesized from 2-phenylpyrrolidine and phenylacetyl chloride, followed by $LiAlH_4$ reduction.



88



89

Enlargement of the B ring was accomplished by reaction of 2-benzylpyrrolidine with styrene oxide, followed by cyclization with PPA to **78a** and **78b**.

Resolution of Enantiomers and Absolute Configuration. Some of the more interesting pyrroloisoquinoline derivatives were resolved classically by recrystallization of diastereomeric salts. Compound **7b** was resolved by using (+)- and (−)-di-*p*-toluoyltartaric acid, as already reported.[14a] Compounds **37b**, **48b**, and **24b** were resolved by using (+)- and (−)-tartaric acid for the first two and (+)- and (−)-camphorsulfonic acid for the latter. The enantiomeric purities were determined by 360-MHz ^1H NMR of salts with Mosher's acid for **7b**, **37b**, and **48b**, and by HPLC on an OT(+) column for **24b**, to be 98–100%.[14]

We have already reported[14a] that the absolute configuration of (+)-**7b**·HCl (optical rotation at 589 nm in methanol) is 6*S*,10b*R*, as established by chemical correlation with (+)-(*R*)-2-phenylpyrrolidine. Although this result could be used to assign other enantiomers in this series, there is no guarantee of correspondence. So, we similarly determined the absolute stereochemistry of (+)-**48b**·$HClO_4$ (mandelic acid route) and (+)-**37b**·HCl (styrene oxide route) as 6*S*,10b*R* by chemical correlation with (+)-(*R*)-2-phenylpyrrolidine (75% ee). Additionally, we ascertained the absolute configuration of (+)-**24b**·HBr by X-ray crystallography, via the anomalous dispersion technique.

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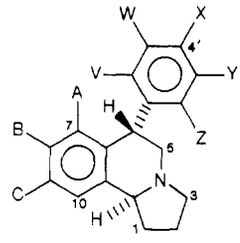
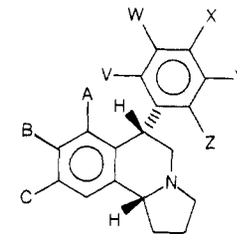
(13) Ban, Y.; Yonemitsu, O.; Terashima, M. *Chem. Pharm. Bull.* **1960**, *8*, 183. Leonard, N. J.; Morrow, D. F. *J. Am. Chem. Soc.* **1958**, *80*, 371 and references cited therein.
(14) (a) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (b) Also, for the general use of of Mosher's acid salts in measuring enantiomeric purity by ^1H NMR, see: Villani, F. J., Jr.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.

Table I. Chemical Data for 1,2,3,5,6,10b-Hexahydro-6-arylpyrrolo[2,1-*a*]isoquinolines Unsubstituted on Positions 1, 2, 3, 5, 6, or 10b[a]



a = cis (6α, 10bα)



b = trans (6α, 10bβ)

compd	V	W	X	Y	Z	A	B	C	mol formula[b]	mp, °C (solv)[c]	dp, %[d]	syn method[e]
7a[f]	H	H	H	H	H	H	H	H	$C_{18}H_{19}N\cdot HCl$[g]	236.5–241.5 (M/EA)	≥99	A
7b[f]	H	H	H	H	H	H	H	H	$C_{18}H_{19}N\cdot C_4H_4O_4$[g]	170–172 (E)	>99	A–I
(–)-7b[h]	H	H	H	H	H	H	H	H	$C_{18}H_{19}N\cdot HCl$[g]	237–240 (P)	>99[i]	G
(+)-7b[h]	H	H	H	H	H	H	H	H	$C_{18}H_{19}N\cdot HCl$[g]	232–239 (P)	>99[i]	G
8a[f]	H	H	H	H	H	H	OMe	OMe	$C_{20}H_{23}NO_2\cdot HBr$	212–213.5 (I)	>99	A
8b[f]	H	H	H	H	H	H	OMe	OMe	$C_{20}H_{23}NO_2\cdot C_4H_4O_4$[j]	129–132 (M/I)	>95	A–I
9a	H	H	H	H	H	H	OH	OH	$C_{18}H_{19}NO_2\cdot HBr$	252–254 (I/W)	>99	E
9b[k]	H	H	H	H	H	H	OH	OH	$C_{18}H_{19}NO_2\cdot HBr$	255–257 (M)	>95	E
10a	H	H	OMe	H	H	H	H	H	$C_{19}H_{21}NO\cdot HBr$[l]	202.5–204 (M/I)	95	D
10b[k]	H	H	OMe	H	H	H	H	H	$C_{19}H_{21}NO\cdot HBr$	241–244 (M/I)	95	D
11a	H	H	OH	H	H	H	H	H	$C_{18}H_{19}NO\cdot HBr$	257–260.5 (M/I)	97	E
11b[k]	H	H	OH	H	H	H	H	H	$C_{18}H_{19}NO\cdot HBr$	257–260 (M/I)	97	E
12a	H	OMe	H	H	H	H	H	H	$C_{19}H_{21}NO\cdot HBr$	161–167 (D/An)	95	D
12b	H	OMe	H	H	H	H	H	H	$C_{19}H_{21}NO\cdot 1.5C_4H_4O_4$[l]	185–191 (I)	97	D
13a	H	OH	H	H	H	H	H	H	$C_{18}H_{19}NO\cdot HBr$	252–253 d (E/EE)	95	F
13b	H	OH	H	H	H	H	H	H	$C_{18}H_{19}NO\cdot HBr$	244–246 (I)	97	F
14a	OMe	H	H	H	H	H	H	H	$C_{19}H_{21}NO\cdot C_4H_4O_4$[l]	176–178 (I)	97	D
14b	OMe	H	H	H	H	H	H	H	$C_{19}H_{21}NO\cdot C_4H_4O_7$[m]	182–184 (I)	≥99	D
15b	OH	H	H	H	H	H	H	H	$C_{18}H_{19}NO\cdot HBr$[l]	267–269 (M/I)	>99	E
16a	H	H	H	H	H	OMe	H	H	$C_{19}H_{21}NO$	122–123 (EA/H)	96[n]	C
16b	H	H	H	H	H	OMe	H	H	$C_{19}H_{21}NO$	151–152 (EA)	≥98	C
17a	H	H	H	H	H	H	H	OMe	$C_{19}H_{21}NO\cdot HBr$[o]	209–212 (98% E)	~95	C
17b	H	H	H	H	H	H	H	OMe	$C_{19}H_{21}NO\cdot C_4H_4O_4$[p]	198–201 (98% E)	~98	C
18a	H	OMe	OMe	H	H	H	H	H	$C_{20}H_{23}NO_2\cdot 1.5C_4H_4O_4$[q]	161–163 (M/EA)	99	D
18b[k]	H	OMe	OMe	H	H	H	H	H	$C_{20}H_{23}NO_2\cdot HBr$[r]	235–237 (An)	~96	D
19a	H	OH	OH	H	H	H	H	H	$C_{18}H_{19}NO_2\cdot HBr$	246–248 d (M/B)	99	E
19b[k]	H	OH	OH	H	H	H	H	H	$C_{18}H_{19}NO_2\cdot HBr$[s]	244–248 d (M/B)	~90	E
20a	H	OMe	OMe	OMe	H	H	H	H	$C_{21}H_{25}NO_3\cdot HBr$	197–214 (An)	97	D
20b	H	OMe	OMe	OMe	H	H	H	H	$C_{21}H_{25}NO_3\cdot HBr$	235–245 (An)	91	D
21a/b	H	OMe	OMe	H	H	H	OMe	OMe	$C_{22}H_{27}NO_4\cdot C_4H_4O_4$[t]	181–187 (E/EA)	*v*	A
22a	H	H	Cl	H	H	H	H	H	$C_{18}H_{18}ClN\cdot C_4H_4O_4$[w]	179–181 (M/I)	>99	D
22b[k]	H	H	Cl	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	290–293.5 (M)	96.5	D
23a	H	Cl	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	247–249 (M/I)	99	C
23b	H	Cl	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	238–241 (An/EE)	98	C
24a	Cl	H	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	217–220 (M/I/EE)	98.4	C
24b	Cl	H	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	213–220 (M/I)	98.3	C
(–)-24b	Cl	H	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	256–259 (I)	>99[x]	G
(+)-24b	Cl	H	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot HBr$	257–260 (I)	>99[x]	G
25b	H	H	H	H	H	H	H	Cl	$C_{18}H_{18}ClN\cdot HBr$	254–255 (I)	>99	D
26a	H	H	H	H	H	Cl	H	H	$C_{18}H_{18}ClN\cdot HBr$	246–248 (I)	98	D
26b	H	H	H	H	H	Cl	H	H	$C_{18}H_{18}ClN\cdot HClO_4$[y]	188–189 (I)	98	D
27b[z]	H	H	H	H	H	H	H	H	$C_{18}H_{18}ClN\cdot C_4H_4O_4$[aa]	147–148 (I)	>99	D
28a[f]	H	H	Cl	H	H	H	H	Cl	$C_{18}H_{17}Cl_2N\cdot C_7H_8O_3S$	182–184 (M/EE)	≥98	A
28b[f]	H	H	Cl	H	H	H	H	Cl	$C_{18}H_{17}Cl_2N\cdot HClO_4$	244–246 d (M)	≥98	A–I
29a	H	Cl	Cl	H	H	H	H	H	$C_{18}H_{17}Cl_2N\cdot C_4H_4O_4$	199–205 d (95% E)	98.5	C
29b[k]	H	Cl	Cl	H	H	H	H	H	$C_{18}H_{17}Cl_2N\cdot 1.33C_4H_4O_4$	196–201 d (M/An)	98.5	C
30a	Cl	H	Cl	H	H	H	H	H	$C_{18}H_{17}Cl_2N\cdot C_4H_4O_4$	184–186 (M/I)	98	C
30b	Cl	H	Cl	H	H	H	H	H	$C_{18}H_{17}Cl_2N\cdot HCl$	225–230 (An)	>99	C
31a	Cl	H	H	H	F	H	H	H	$C_{18}H_{17}ClFN\cdot HBr$	272–276 (M/I)	>95	C
31b	Cl	H	H	H	F	H	H	H	$C_{18}H_{17}ClFN\cdot HCl$[l]	232–237 (I)	>99	C
32a	H	H	F	H	H	H	H	H	$C_{18}H_{18}FN$	119–120 (I)	>99	C
32b	H	H	F	H	H	H	H	H	$C_{18}H_{18}FN\cdot HBr$[bb]	265–267 (I)	95	C
33a	H	H	F	H	H	H	H	F	$C_{18}H_{17}F_2N\cdot HBr$	189–191 (I/EE)	99	A
33b	H	H	F	H	H	H	H	F	$C_{18}H_{17}F_2N\cdot HBr$	271–274 (M/I/T)	98	A–I
34a	F	F	F	F	F	H	H	H	$C_{18}H_{14}F_5N\cdot HBr$[o]	266–269 (M/I)	≥98	C
34b	F	F	F	F	F	H	H	H	$C_{18}H_{14}F_5N\cdot HBr$[o]	267–268 (M/I)	≥98	C
35b	Br	H	H	H	H	H	H	H	$C_{18}H_{18}BrN\cdot HBr$	257–260 (M/E)	96	C
36a	H	H	CF_3	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot C_4H_4O_4$[l]	179–181.5 (I)	>99	C
36b	H	H	CF_3	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HCl$[cc]	186–188 (A)	>99	C
37a[k]	H	CF_3	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HCl$	204.5–206.5 (D/EA)	>99	C
37b[k]	H	CF_3	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HCl$[dd]	180–183 (D/EA)	99	C
(–)-37b	H	CF_3	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HCl$	207–209 (I)	>99[x]	G
(+)-37b	H	CF_3	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HCl$[w]	205–208 (EA)	>99[x]	G
38a	CF_3	H	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HClO_4$	185–187 (I)	>99	C

Table I (Continued)

compd	V	W	X	Y	Z	A	B	C	mol formula[b]	mp, °C (solv)[c]	dp, %[d]	syn method[e]
38b	CF_3	H	H	H	H	H	H	H	$C_{19}H_{18}F_3N\cdot HBr$[bb]	218–220 (I)	96	C
39a	H	H	H	H	H	H	H	CF_3	$C_{19}H_{18}F_3N\cdot HClO_4$[l]	211–214 (I)	98	D
39b	H	H	H	H	H	H	H	CF_3	$C_{19}H_{18}F_3N\cdot HCl$[ee]	210–211 (I)	95	D
40a/b	H	CF_3	H	H	H	H	H	Cl	$C_{19}H_{17}ClF_3N\cdot HCl$	230–233 (EA/I/H)	*ff*	C
41a[gg]	H	CF_3	H	H	H	Cl	H	H	$C_{19}H_{17}ClF_3N\cdot HBr$	303–305 (I)	>99	C
41b[gg]	H	CF_3	H	H	H	Cl	H	H	$C_{19}H_{17}ClF_3N$	108–111 (95% E)	98	C
42a	H	CF_3	H	CF_3	H	H	H	H	$C_{20}H_{19}F_6N\cdot HBr$	298–306 (M/I)	99	C
42b	H	CF_3	H	CF_3	H	H	H	H	$C_{20}H_{17}F_6N\cdot HCl$	266–270 (An/EE)	97	C
43a	CH_3	H	H	H	H	H	H	H	$C_{19}H_{21}N\cdot HBr$	224–227 (I)	98	C
43b	CH_3	H	H	H	H	H	H	H	$C_{19}H_{21}N\cdot HCl$	227–230 (An)	>99	C
44a	H	H	Bu	H	H	H	H	H	$C_{22}H_{27}N\cdot HBr$[w]	140–142 (B/EE)	97	C
44b	H	H	Bu	H	H	H	H	H	$C_{22}H_{27}N\cdot C_4H_4O_4$	153–155 d (An)	95	C
45b	H	H	E	H	H	H	H	H	$C_{20}H_{19}N_2\cdot HCl$[hh]	262–265 (M)	96	H
46b	H	H	CN	H	H	H	H	H	$C_{19}H_{18}N_2\cdot HCl$	271–276 (M)	98.6	H
47b	CN	H	H	H	H	H	H	H	$C_{19}H_{18}N_2\cdot HCl$	216–220 (An)	99	H
48a	H	H	SMe	H	H	H	H	H	$C_{19}H_{21}NS\cdot HBr$[ii]	203–204 (I)	>99	D
48b[k]	H	H	SMe	H	H	H	H	H	$C_{19}H_{21}NS\cdot HClO_4$	200–202 (An/EE)	99	D
(−)-**48b**	H	H	SMe	H	H	H	H	H	$C_{19}H_{21}NS\cdot HClO_4$	184–188 (E)	>99[x]	G
(+)-**48b**	H	H	SMe	H	H	H	H	H	$C_{19}H_{21}NS\cdot HClO_4$	189–190 (E)	>99[x]	G
49b	SMe	H	H	H	H	H	H	H	$C_{19}H_{21}NS\cdot C_4H_4O_4$[bb]	197–199 (M/I)	98	D
50a	H	H	SO_2Me	H	H	H	H	H	$C_{19}H_{21}NO_2S\cdot HBr$[ii]	278–280 (I)	≥95[jj]	H
50b	H	H	SO_2Me	H	H	H	H	H	$C_{19}H_{21}NO_2S\cdot HBr$[ii]	283–290 (I)	≥95[jj]	H
51a	H	H	NO_2	H	H	H	H	H	$C_{18}H_{18}N_2O_2$	148–149 (95% E)	≥99[jj]	C
51b[k]	H	H	NO_2	H	H	H	H	H	$C_{18}H_{18}N_2O_2\cdot HBr$	227–229 d (96% E)	≥99[jj]	C
52a[k]	H	H	NH_2	H	H	H	H	H	$C_{18}H_{20}N_2\cdot HBr$	252–258 d (M/I)	>99	H
52b[k]	H	H	NH_2	H	H	H	H	H	$C_{18}H_{20}N_2\cdot HBr$[kk]	242–249 (M)	95	H
53a	H	H	AcNH	H	H	H	H	H	$C_{20}H_{22}N_2O$	171–175 d (EA)	>99[jj]	H
53b	H	H	AcNH	H	H	H	H	H	$C_{20}H_{22}N_2O\cdot HBr$[ll]	296–300 (M/I)	~95	H
54a	H	H	Q	H	H	H	H	H	$C_{25}H_{25}N_3O$	188–190 d (E)	≥99[jj]	H
54b	H	H	Q	H	H	H	H	H	$C_{25}H_{25}N_3O$	140–143 (E)	>98[jj]	H
55a	H	H	R	H	H	H	H	H	$C_{26}H_{27}N_3O_2$[mm]	181–182 (E)	>98[jj]	H
56a	H	H	S	H	H	H	H	H	$C_{26}H_{24}F_3N_3O$[nn]	155–158 (EA)	>98[jj]	H
57b	H	H	$CONH_2$	H	H	H	H	H	$C_{19}H_{20}N_2O\cdot 0.5C_4H_4O_4$[oo]	191–196 (M/I)	≥98[jj]	H
58a	COOH	H	H	H	H	H	H	H	$C_{19}H_{19}NO_2\cdot HCl$[pp]	165–168 (An)	>99[qq]	H
58b	COOH	H	H	H	H	H	H	H	$C_{19}H_{19}NO_2\cdot HCl$	250–260 d (W)	99[qq]	H
59a[f,rr]	H	H	H	H			H	H	$C_{20}H_{21}N\cdot C_4H_4O_4$	213–214.5 (W)	99	A
59b[f,rr]	H	H	H	H			H	H	$C_{20}H_{21}N\cdot HBr$[pp]	215–218 (M/I)	≥99	A–I

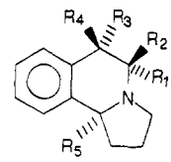
[a] Substituent abbreviations: Bu = *n*-butyl, E = ethynyl, Ac = acetyl, Q = PhNHC(O)NH, R = 4-$OMeC_6H_4NHC(O)NH$, and S = 3-$CF_3C_6H_4NHC(O)NH$. The compound numbers represent the free base forms. [b] The new compounds were characterized by IR, ^1H NMR, and elemental microanalysis. All compounds analyzed within ±0.4% for C, H, and N unless otherwise noted; some compounds were also analyzed for Cl, Br, or water (±0.4%, unless otherwise indicated). For acid-addition salts: $C_4H_4O_4$ = fumaric acid and $C_7H_8O_3S$ = *p*-toluenesulfonic acid. Water composition was verified by Karl–Fischer analysis (unless otherwise noted) and solvent additives were verified by ^1H NMR analysis. All melting point data are corrected. The letter "d" means decomposition on melting. [c] The recrystallization solvent is given in parentheses: M = methanol, EA = ethyl acetate, I = 2-propanol, EE = ethyl ether, E = ethanol, D = dichloromethane, A = acetone, An = acetonitrile, W = water, H = hexane, P = precipitated from ether, B = *tert*-butyl alcohol, T = tetrahydrofuran. [d] Diastereomeric purity, represented as percent major diastereomer, was generally determined by GLC on an SE-30 or OV-17 column (assuming a detector response ratio of 1.0 between the isomers), and occasionally evaluated by TLC and ^1H NMR. [e] Principal synthetic method: A = *N*-acyliminium cyclization starting with a succinimide, B = *N*-acyliminium cyclization starting with a keto acid (or its equivalent), C = styrene oxide procedure with a 2-arylpyrrolidine, D = mandelic acid procedure with a 2-arylpyrrolidine, E = boron tribromide demethylation of corresponding ether, F = HBr demethylation of corresponding ether, G = resolution of the racemate, H = see text, I = equilibration with base. [f] Synthesis and characterization have already been reported in detail; see ref 6. [g] C, H analysis only. [h] Synthesis and characterization have already been reported in detail; see ref 14. [i] Enantiomeric purity is ≥99% (see ref 14). [j] Contains 0.5 mol of water and 0.15 mol of 2-propanol. [k] Reported in our preliminary communication; see ref 3. [l] Contains 0.05 mL of 2-propanol. [m] Contains ca. 0.01 mol of 2-propanol. [n] Contains 4% of **17b**; no **16a** or **17a**. [o] C, H, and Br analysis. [p] 0.2 mol of water was applied to the formula; no water analysis was performed. [q] Contains 0.06 mol of ethyl acetate. [r] Contains 0.1 mol of acetonitrile. Carbon analysis was off by 0.46% (Calcd: C, 61.51. Found: C, 61.05). [s] Contains 0.07 mol of *tert*-butyl alcohol. [t] Carbon analysis was off by 0.47% (Calcd: C, 64.32. Found: C, 64.81). [v] Isomer ratio: **21a/21b** = 62:38. [w] Contains 0.25 mol of water. [x] Enantiomeric purity is ≥99%; see Experimental Section for details. [y] Contains 0.08 mol of 2-propanol. [z] Substituted at the 10-position by Cl. [aa] Contains 0.2 mol of 2-propanol and 0.2 mol of water. [bb] Contains 0.2 mol of water. [cc] Contains 0.5 of water. [dd] Contains 0.75 mol of water. [ee] Contains 0.4 mol of 2-propanol. [ff] Isomer ratio: **40a/40b** = 58:42. [gg] The α and β isomers are readily distinguished by ^1H NMR. The resonance for H_6 in the free bases is especially diagnostic: for **41a**, δ 4.48 (dd, *J* = 6, 6 Hz); for **41b**, δ 4.32 (dd, *J* = 0.5, 3.5 Hz). A similar difference was observed for **16a** and **16b**. [hh] Contains 0.08 mol of methanol and 0.05 mol of water. Cl analysis also. Carbon analysis is off by 1.6% (Calcd: C, 77.00. Found: C, 75.40). [ii] Contains 0.1 mol of 2-propanol. [jj] Estimated by TLC and ^1H NMR analysis. [kk] Contains 0.25 mol of methanol. [ll] Contains 0.25 mol of 2-propanol. [mm] Contains 0.12 mol of ethanol. [nn] Contains 0.15 mol of ethyl acetate. [oo] Contains 0.12 mol of water. [pp] Contains 0.67 mol of water and 0.1 mol of acetonitrile. [qq] GLC analysis of the methyl ester, formed by using diazomethane. [rr] This compound was previously reported, but as a different salt form (Bruderlein, F. T.; Humber, L. G., U.S. Patent 3 657 250, 1972).

The molecular structure, showing the 6*R*,10b*R* configuration,[15] is presented in Figure 1; details on the X-ray analysis are contained in the Experimental Section and the supplementary material.[16] The biological activity (see below) resides in the (+) acid-addition salts (measured in methanol at 589 nm). These active enantiomers, (+)-**7b**·HCl, (+)-**37b**·HCl, (+)-**48b**·$HClO_4$, and (+)-**24b**·HBr, possess the same absolute stereochemistry.

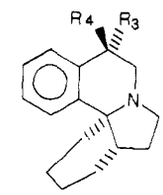
(15) (a) Note: Because of the *o*-chloro substituent, the priority assignment for the absolute configuration at C6 is reversed.[15b] The stereochemical structural relationship is the same throughout the series. (b) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(16) See the paragraph regarding supplementary material at the end of this paper.

Table II. Chemical Data for Miscellaneous 1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolines[a]



60-72



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compd	R_1	R_2	R_3	R_4	R_5	mol formula[b]	mp, °C (solv)[c]	dp, %[d]	syn method[e]
7b[f]	H	H	H	Ph	H	*f*	*f*	*f*	*f*
60a[g]	H	H	Ph	H	Me	$C_{19}H_{21}N\cdot HCl$[h]	204.5–205.5 (EA/M)	≥99	A
60b[f]	H	H	H	Ph	Me	$C_{19}H_{21}N\cdot C_6H_{13}NO_3S$[i]	136.5–138 (I/EE)	≥99	A–I/H
61a[g,j]	H	H	Ph	Me	H	$C_{19}H_{21}N\cdot HBr$	219–226 (M/I/EE)	≥99	A
61b[g,j]	H	H	Me	Ph	H	$C_{19}H_{21}N\cdot HBr$	261.5–265.5 (M/I)	≥99	A
62a[k]	H	H	Ph	OH	H	$C_{18}H_{19}NO\cdot HBr$	211.5–212 (M/I)	≥99	H
62b[k]	H	H	OH	Ph	H	$C_{18}H_{19}NO\cdot C_4H_4O_4$[l]	178.5–181 (E)	98	H
63a[m]	H	H	Ph	F	H	$C_{18}H_{18}FN\cdot HCl$[n]	180–181 (I/EE)	≥99	H
63b[m]	H	H	F	Ph	H	$C_{18}H_{18}FN\cdot HBr$[o]	192–193 (I)	>95	H
64a	H	H	ClPh	H	Me	$C_{19}H_{20}ClN\cdot HClO_4$[p]	224–246 d (M)	≥99	H
64b	H	H	H	ClPh	Me	$C_{19}H_{20}ClN\cdot C_4H_4O_4$[o]	145–150 (I)[q]	>95	H
65a	Me	H	Ph	H	H	$C_{19}H_{21}N\cdot C_7H_5NO_3S$	222–228 (95% M)	97[r]	A
65b[s]	Me	H	H	Ph	H	$C_{19}H_{21}N\cdot HCl$[t]	245–250 (EA/M)	~95	A
66b[u]	H	Me	Ph	H	H	$C_{19}H_{21}N\cdot HBr$[v]	272–278 d (I/EA)	≥98	A
67a[w]	H	H	c-Hx	H	H	$C_{18}H_{25}N\cdot 1.125C_4H_4O_4$	216–218 (M/I)	≥99	A
67b[w]	H	H	H	c-Hx	H	$C_{18}H_{25}N\cdot HBr$	169–172 (M/EA)	≥99	A
68a	H	H	Bn	H	H	$C_{19}H_{21}N\cdot C_4H_4O_4$	190–193.5 d (90% I)	~70	A
68b	H	H	H	Bn	H	$C_{19}H_{21}N\cdot HBr$[v]	199–202 (I)	99	A
69a	Ph	H	H	H	H	$C_{18}H_{19}N\cdot HBr$	230–232.5 (E)	≥99	A
69b	H	Ph	H	H	H	$C_{18}H_{19}N\cdot HBr$	264–268 (M/I)	>95	H
70	H	H	H	H	Ph	$C_{18}H_{19}N\cdot HI$[x]	116–118 (A)		A
71	H	H	H	H	Me	$C_{13}H_{17}N\cdot C_7H_5NO_3S$[y]	170–171.5 (M/EA)		A
72	H	H	H	H	H	$C_{12}H_{15}N\cdot C_7H_5NO_3S$[z]	155–157 (M/EA)		H
73a[g]	H	H	Ph	H	$(CH_2)_4$[aa]	$C_{22}H_{25}N\cdot HCl$[bb]	290–305 d (M/EA)	≥98	A
73b[g]	H	H	H	Ph	$(CH_2)_4$[aa]	$C_{22}H_{25}N\cdot C_6H_{13}NO_3S$	178.5–179.5 d (I)	98	A–I

[a] Substituent abbreviations: c-Hx = cyclohexyl, ClPh = 4-chlorophenyl, and Bn = benzyl. **a** = α Ph, ClPh, c-Hx or Bn; **b** = β Ph, ClPh, c-Hx, or Bn. The compound numbers represent the free base forms. [b] See *Table I, footnote b. For acid-addition salts:* $C_7H_5NO_3S$ = saccharin, $C_6H_{13}NO_3S$ = hexamic acid. [c] See Table I, footnote *c*. [d] See Table I, footnote *d*. [e] See Table I, footnote *e*. [f] Data are contained in Table I; **7b** is shown for structural reference. [g] Synthesis and characterization has already been reported in detail; see ref 6. [h] Contains 1.0 mol of water. C, H, H_2O *analysis.* [i] *Contains 0.5 mol of water.* [j] Isomer assignment was verified by X-ray analysis of HBr salts of **61a** and **61b** (see ref 6). [k] The isomer assignment was effected by X-ray analysis of **62a**·HBr (to be published elsewhere). [l] Contains 0.08 mol of ethanol. [m] Isomer assignment for **63a** and **63b** was based on proton–fluorine vicinal coupling constants (see Experimental Section). [n] Contains 0.06 mol of 2-propanol. [o] Contains 0.3 mol of 2-propanol. [p] Contains 0.1 mol of methanol. [q] Partially melted at 115 °C, then resolidified. [r] Contains ca. 3% of **65b**; no other diastereomers (**66a** or **66b**) were present. [s] Isomer assignment for **65b** was confirmed by X-ray analysis of its lactam (3-one) precursor (to be published elsewhere). [t] C, H, and Cl analysis; Cl was off by 0.47% (Calcd: Cl, 11.82. Found: Cl, 12.29). [u] Isomer assignment for **66b** was confirmed by X-ray analysis (to be published elsewhere). We thank Prof. Roy Olofson (The Pennsylvania State University) for the X-ray data. [v] C, H, Br analysis. [w] Isomer assignment was verified by X-ray analysis of the lactam (3-one) precursor to **67b**; see ref 7. [x] This compound was previously reported, but not as a hydriodide salt (see ref 11). [y] This compound was previously reported, but not as a saccharinate salt (Winn, M.; Zaugg, H. E. *J. Org. Chem.* **1968**, *33*, 3779). [z] This compound was previously reported, but not as a saccharinate salt (ref 70 and Sarto, S. et al. *Chem. Pharm. Bull.* **1965**, *13*, 786). [aa] Tetramethylene chain, as shown in the structural diagram. [bb] C, H, and Cl analysis.

Circular dichroism (CD) spectra for (+)-**7b**·HCl, (+)-**37b**·HCl, and (+)-**24b**·HBr were used to characterize their chirality.[17] The CD spectra in 95% ethanol agreed well with UV spectra. All of the compounds showed a low-intensity negative CD band, with much fine structure between 252 and 272 nm, a medium negative CD band with fine structure between 215 and 225 nm, and a high-intensity negative CD maximum between 198 and 203 nm. Except for amplitude variation, the three CD spectra were essentially superimposable in sign and position of bands. The CD curves for (−)-**7b**·HCl and (−)-**24b**·HBr were opposite in sign and compared within 5% to the corresponding enantiomers. The CD spectra were consistent with the assigned absolute configuration.[17b]

The biologically active absolute stereochemistry at the 6-position of the pyrroloisoquinolines corresponds to the active enantiomer of the structurally related antidepressants, diclofensine (**5**)[18] and nomifensine (**4**).[19] Furthermore, it is interesting to note that the active enantiomer of the 3′,4′-dihydroxy metabolite of nomifensine (**4**), responsible for dopaminergic activity, possesses the parallel *S* configuration.[9a] This facet will be expanded upon later in a discussion of structural features of antidepressant agents.

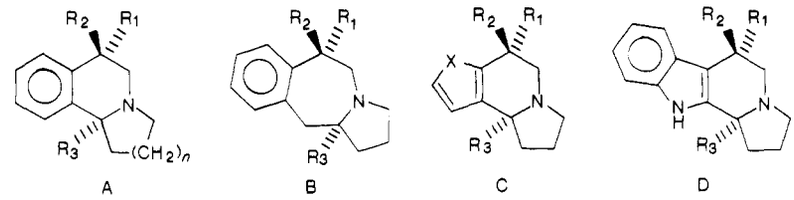
Structure–Activity Relationships. Compounds were screened for their ability to antagonize tetrabenazine-induced depression, as measured by two parameters, motor activity (MA) and ptosis. Also, the test compounds were studied for their ability to inhibit the uptake of tritiated NE, DA, and 5-HT into rat brain synaptosomes (Table IV).

(17) (a) We express our appreciation to Prof. J. Cymerman Craig (University of California, San Francisco) for the CD spectral data. (b) Details of the CD work, along with appropriate discussion, will be published elsewhere.

(18) For diclofensine, biological activity exclusively resides in the *S* enantiomer, (+)-**5**·HCl, see: Drugs *Future* **1985**, *10*, 592.

(19) (a) Kruse, H. *Drug Dev. Res.* **1987**, *10*, 1. (b) Kunstman, R.; Gerhards, H.; Kruse, H.; Leven, M.; Paulus, E. F.; Schacht, U.; Schmitt, K.; Witte, P. U. *J. Med. Chem.* **1987**, *30*, 798. (c) Schacht, U.; Leven, M. *Eur. J. Pharmacol.* **1984**, *98*, 275.

Table III. Chemical Data for Ring-Modified Derivatives[a]



compd	type	R_1	R_2	R_3	n	X	mol formula[b]	mp, °C (solv)[c]	dp, %[d]	syn method[e]
7b[f]	A	H	Ph	H	1		*f*	*f*	*f*	*f*
74a	A	Ph	H	H	3		$C_{20}H_{23}N$·HBr[g]	221–224 (M/I)	≥99	C
74b	A	H	Ph	H	3		$C_{20}H_{23}N$·HBr	252–258 (M/I)	98	C
75a[h]	A	Ph	H	H	2		$C_{19}H_{21}N$·$C_4H_4O_4$[i]	204–204.5 (M/EE)	98	*h*
75b[h]	A	H	Ph	H	2		$C_{19}H_{21}N$·$C_4H_4O_4$	195–203 (E)	98	*h*
76a[h]	A	Ph	H	Me	2		$C_{20}H_{23}N$	107–110 (M/W)	≥99	A
76b[h]	A	H	Ph	Me	2		$C_{20}H_{23}N$·$C_7H_5NO_3S$	194–197 (I)	≥99	A–I
77a	A	Ph	H	H	0		$C_{17}H_{17}N$·$C_4H_4O_4$[j]	163–164 (I)	≥99	H
77b	A	H	Ph	H	0		$C_{17}H_{17}N$·$C_4H_4O_4$[j]	145–146 (I)	≥99	H
78a	B	Ph	H	H			$C_{19}H_{21}N$·HBr	245–249 (E)	≥99	C
78b	B	H	Ph	H			$C_{19}H_{21}N$·HBr	285–290 (E)	>99	C
79a	C	Ph	H	H		S	$C_{16}H_{17}NS$·HBr	198–200 (M/I)	≥99	A
79b	C	H	Ph	H		S	$C_{16}H_{17}NS$·HBr	236–239 (M/I)	≥99	A–I
80a	C	2Th	H	H		S	$C_{14}H_{15}NS_2$·HBr[k]	154–155.5 (I)	>99	A
80b	C	2Th	H	H		S	$C_{14}H_{15}NS_2$·HBr	238–239 (M/I/EE)	>95	A–I
81a	C	Ph	H	H		NMe	$C_{17}H_{20}N_2$·HBr[j]	183–186 (I)	≥99	A
81b	C	H	Ph	H		NMe	$C_{17}H_{20}N_2$·HBr[l]	203–204 (I)	>95	A–I
82a	D	Ph	H	H			$C_{20}H_{20}N_2$·HBr	305–316 (M)[m]	≥99	A
82b	D	H	Ph	h			$C_{20}H_{20}N_2$·HBr	276–280 (M/I)	≥99	A–I

[a] Substituent abbreviation: 2Th = 2-thienyl. **a** = α Ph or 2H; **b** = β Ph or 2Th. Compound number represents free base form. [b] See Tables I and II, footnote *b*. [c] See Table I, footnote *c*. [d] See Table I, footnote *d*. [e] See Table I, footnote *e*. [f] Data are contained in Table I; **7b** is shown for reference purposes. [g] Contains 0.06 mol of 2-propanol. [h] Synthesis and characterization have already been reported in detail; see ref 6. [i] C, H analysis. [j] Contains ca. 0.08 mol of 2-propanol. [k] C, H, N, S, and Br analysis. [l] Contains 0.25 mol of water; water analysis was off by 1.5% (Calcd: H_2O, 1.33. Found: H_2O, 2.78). [m] Melting point is uncorrected.

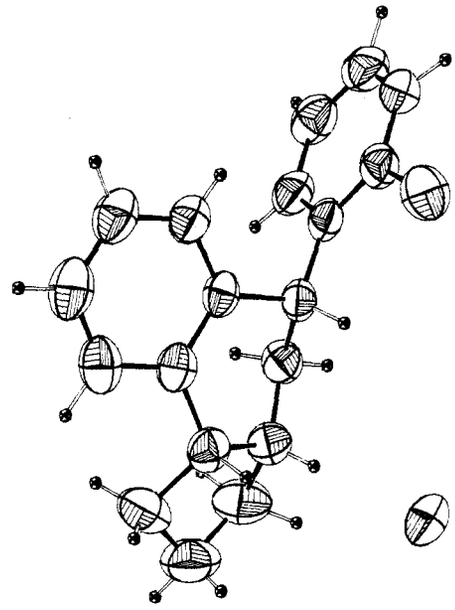


Figure 1. Molecular structure of (+)-**24b**·HBr as determined by X-ray crystallography (ORTEP diagram).

Since agents that inhibit the uptake of 5-HT may also adversely affect the MA parameter in the TBZ model,[20] such compounds are assessed more reliably in this model by the ptosis parameter. For SAR purposes, we will use only the ptosis parameter of the TBZ assay.

We reported earlier[3] on some of the more potent, representative compounds in the pyrroloisoquinoline series. For all of the compounds examined, the trans diastereomers ("**b**" set) were more active than the cis diastereomers ("**a**" set). Several of these compounds, in particular **7b–9b**, **11b**, **19b**, **22b**, **29b**, and **52b**, caused significant CNS behavioral stimulation in animal models. Thus, we directed our attention to finding compounds in the series devoid of overt stimulant activity, while retaining activity in the TBZ and monoamine uptake tests. At the same time, we sought compounds that are selective inhibitors of one monoamine over the others. From the neurobiochemical data, in particular, a SAR for this series has been elaborated.

When antidepressant-like activity is present, the trans diastereomeric ("**b**") series is generally the active one. However, it should be noted that certain cis isomers (viz. **10a**, **11a**, **13a**, **17a**, **19a**, **22a**, **24a**, **29a**, **33a**, **52a–55a**, **62a**, **69a**) demonstrate significant activity (TBZ ptosis <15 mg/kg). In many cases the activity of the cis isomer is considerably less than that of the trans counterpart. Since the cis isomer may be contaminated by a small amount (1–5%) of the potent trans isomer (note the diastereomeric purity in Tables I–III), the activity of the former may be attributed, in whole or in part, to something other than its intrinsic structure. For example, the TBZ ED_{50} values for **10a/b** and **29a/b** are 3.0/0.03 and 8.0/0.14 mg/kg, respectively, differences that are in reasonable accord with the diastereomeric purities of **10a** and **29a**. Nevertheless, we are convinced on the basis of high diastereomeric purity that some of the cis diastereomers, especially **19a**, **22a**, **52a–55a**, **62a**, and **69a**, do possess moderate activity of their own. Enantioselectivity, also demonstrated in this pyrroloisoquinoline series, will be discussed below.

Various aromatic substituents were introduced into the prototype, **7b** (McN-4612-Z), to evaluate SAR (Table I). Antidepressant-like activity is manifested by a wide assortment of derivatives (Table IV). It is helpful to designate first those substitutions that deliver particularly

(20) Maj, J.; Rogoz, Z.; Skuza, G. *J. Pharm. Pharmacol.* **1983**, *35*, 128 and references cited therein.

Table IV. General Biological Data[a]

compd	TBZ ED_{50}, mg/kg[b]		uptake inhibn, K_i, nM[c]			gen beh[d]
	MA	ptosis	DA	NE	5HT	
7a	I-30	>30	160	64.9	1%	C
7b	0.34	0.07	11.3	0.60	23.5	S
(−)-7b	>30	8.3	1340	557	4810	W
(+)-7b	0.59	0.05	4.4	0.37	12.4	S
8a	I-30	>30	106	16%	10%	C
8b	15.1	3.8	15.0	53.7	1540	S
9a	>60	>60	22%	35%	0%	W
9b	0.87	0.53	43.5	10.5	124	S
10a	~50	3.0	119	27.6	18.3	W
10b	0.27	0.03	5.2	0.79	1.7	W
11a	I-30	2.0	26%	78%	~100	W
11b	0.40	0.09	5.1	0.74	3.2	S
12a	>60	>60	35%	16.1	166	W
12b	~0.2	0.07	15.8	0.65	7.2	W
13a	>30	3.1	44.8	15.1	624	S
13b	>10	0.11	10.1	0.85	24.6	S
14a			−3%	65%	−2%	
14b	~0.6	~0.3	278	3.3	3.2	W
15b	>3	~2	360	8.8	451	W
16a	20.7	13.9	0%	5%	31%	W
16b	10.0	1.2	12.3	11.5	455	W
17a	~40	8.0	38.9	20.9	21%	D
17b			2.8	2.2	4.5	
18a	I-60	29.4	11%	9%	27%	W
18b	2.0	0.13	71.9	3.4	18.1	W
19a	>30	1.8	32.6	22.3	331	W
19b	0.19	0.11	10.1	0.81	33.1	S
20a	I-30	I-30	0%	9%	12%	W
20b	>60	2.5	~2000	164	100	W
21a/b	I-30	I-30	355	18%	10%	C
22a	8.1	5.4	40.0	14.7	55.6	W
22b	0.55	0.34	1.7	0.16	1.5	S
38a			67%	~100	11%	
23b	~0.1	<0.1	2.5	0.45	7.3	S
24a	>30	2.5	9%	41%	19%	W
24b	1.6	0.44	35.9	1.9	8.5	W
(−)-24b			775	261	537	
(+)-24b			17.5	1.1	5.5	
25b	~0.3	~0.5	2.5	0.62	4.8	
26a	>3	>3	6%	3%	0%	
26b			25.3	11.6	298	
27b			45%	4%	22%	
28a	>100	~37	65.1	33.8	234	W
28b	37.4	~4	3.2	3.2	2.9	W
29a	~41	8.0	30.8	16.0	45.7	W
29b	0.39	0.14	0.99	0.68	1.8	S
30a			34%[e]	31%	52%[e]	
30b	~2	~1	111	17.1	8.1	
31b	>3	>3	279	11.5	72.0	
32a	>60	>10	43%	61%	3%	W
32b	~0.2	~0.2	8.4	1.4	8.5	W
33a	>60	1.6	38%	~100	21%	W
33b	>30	0.05	7.7	0.55	4.4	W
34a			0%	12%	4%	
34b			14%	42%	2%	
35b	~0.6	~1	26.5	1.5	5.5	
36a			7%	−1%	15%	
36b	>3	~2	128	10.6	4.9	
37a	I-60	>60	8%	23%	9%	W
37b	0.78	0.58	54.3	0.95	23.0	W
(−)-37b			7690	2570	2920	
(+)-37b			25.7	1.5	9.1	W
38a			0%	12%	4%	
38b	>3	>3	14%	42%	2%	
39b			11.2	3.1	12.3	
40a/b			168	32.6	119	
41a			4%	~100	22%	
41b			8%	~100	5%	
42a			−3%	0%	−3%	
42b			5%	58%	25%	
43a			−1%	12%	−6%	
43b	~1	~1	117	5.6	23.1	
44a	>30	I-30	5%	13%	3%	W
44b	>60	9.1	230	29.9	110	W
45b	~0.5	~0.5	2.6	0.94	1.0	S

Table IV (Continued)

compd	TBZ ED_{50}, mg/kg[b]		uptake inhibn, K_i, nM[c]			gen beh[d]
	MA	ptosis	DA	NE	5HT	
46b	~2	~2	83.0	13.8	7.9	
47b	>3	>3	33%	71%	6%	
48a	>75	10.9	1740	127	16.6	W
48b	>30	0.30	41.2	3.0	0.62	W
(−)-**48b**			1450	280	58.4	
(+)-**48b**			23.5	1.8	0.39	
49b	~0.6	~0.6	187	4.5	12.7	
50a	>30	17.7	2890	304	44.0	W
50b	I-30	>30	2110	78.7	29.2	I
51a	>30	>30	21%	10%	25%	W
51b	0.17	0.08	94.2	3.4	5.3	W
52a	1.0	0.20	77%	89%	17%	W
52b	~0.02	~0.01	0.86	0.20	44	S
53a	4.4	1.8	57%	27%	829	W
53b	0.037	0.042	43.7	58.8	15.6	D[f]
54a	>60	10.0	9.8	41.3	~100	W
54b			24.5	117	151	
55a			8.8	15.0	323	
56a			70%	20.1	0%	
57b			84.5	90.2	19.1	
58a			5%	1%	1%	
58b			3%	0%	6%	
59a	I-30	I-30	~100	21%	−10%	W
59b	I-30	I-30	6%	4%	16%	W
60a	I-30	I-30	25%[e]	2%	23%	C
60b	9.2	3.8	40.0	24.0	750	W/C
61a	22.5	16.2	50%[e]	19%	14%	W
61b	27.2	0.44	7.4	1.25	32.1	S
62a	~25	6.2	258	40.8	863	W
62b	8.4	1.6	28.5	8.1	292	W
63a	>30	>30	22%	~100	−3%	W/C
63b	~3	1.2	26%	30.7	6%	W
64a			~100	~100	21%	W
64b	6.8	1.5	7.6	3.8	68.0	W
65a	>60	I-60	3%	0%	3%	W
65b	~30	3.3	17%	62%	15%	W
66b	I-30	I-30	0%	4%	12%	W
67a	I-30	I-30	31%[e]	0%	0%	W
67b	6.4	1.9	604	81.0	145	W
68a			15%	~100	−3%	
68b	I-3	I-3	19%	69%	32%	
69a	~30	~3	36%[e]	11%	−9%	W
69b	>30	0.87	0%	7%	−17%	W
70	>60	I-60	0%	4%	4%	W/C
71	I-10	I-10	15%[e]	6%	2%	W
72	I-30	I-30	18%[e]	1%	−10%	W/C
73a	I-60	I-60	33%	0%	4%	W
73b	I-30	I-30	17%[e]	3%	9%	C
74a	~40	~40	19%	13%	6%	W
74b	~35	17.4	36%	~100	5%	W
75a			~1000	27%	11%	W
75b	>30	>30	>1000	13.7	415	W
76a	I-60	I-60	>1000	2%	4%	C
76b	I-30	I-30	36.4	10.5	15%	W
77a	I-10	I-10	1620	866	2190	
77b	~2	1.25	81.6	6.3	428	
78a			6%	20%	6%	
78b	>3	I-3	9%	35%	9%	
79a	I-10	I-10	10%	34%	28%	D
79b	~5	0.79	5.2	1.4	37.9	S
80a	I-30	I-30	30%	23%	2%	D
80b	~24	~30	39.8	14.6	43.3	W
81a	>30	>30	0%	8%	6%	W
81b	2.4	~0.75	9.8	7.5	111	W
82a	I-30	I-30	0%	7%	−21%	D
82b	1.07	0.30	2.9	2.3	186	S
88	~10	~10	36.4	5.6	170	W
89	~10	~10	4%	38%	4%	W
nomifensine (**4**)	0.18	0.11	79.0	3.8	874	W
imipramine (**1**)	1.15	0.78	>10000	12.0	41.8	
mianserin	>30	9.7	>10000	26.0	>1000	
DMI	0.07[g]	0.05[g]	6530	0.65	182	
sertraline (**91**)			78.3	159	0.85	
diclofensine (**5**)			10.9	8.8	10.3	
amfonelic acid			7.2	41.1	879	

Footnotes to Table IV

[a] Ninety-five percent confidence ranges are presented in the supplementary material. DMI = desmethylimipramine. [b] Tetrabenazine (TBZ) antagonism measured in mice, via intraperitoneal administration unless noted otherwise. Data for two parameters, motor activity (MA) and ptosis, are presented. For relatively inactive compounds, the maximum dose tested, which may have been limited by toxicity, is presented. Thus, for example, a compound that is weakly active (≥10% and ≤30% antagonism) at 30 mg/kg is represented as ">30" and a compound that is inactive (<10% antagonism) at 30 mg/kg is represented as "I-30". Dosage is expressed in terms of the free base. [c] Inhibition of monoamine uptake measured in rat brain synaptosomes. K_i values are reported unless activity was fairly weak, in which case values for percent inhibition at 0.100 μM are given, except in a few instances, so noted. [d] Gross behavioral effects ascertained in mice (see Experimental Section). W = weak stimulant or depressant activity of little significance; S = significant stimulant properties; D = significant depressant properties; C = overt convulsant. [e] Tested at 1.00 μM. [f] Apparent stimulant properties at high dosage levels (>10 times the TBZ ED_{50}). [g] Administered by subcutaneous route.

weak activity in the TBZ and/or uptake tests, namely, 3′,4′,5′-trimethoxy (**20b**), 10-chloro (**27b**), 2′,3′,4′,5′,6′-pentafluorophenyl (**34b**), 2′-trifluoromethyl (**38b**), 3′-(trifluoromethyl)-7-chloro (**41b**), 3′,5′-bis(trifluoromethyl) (**42b**), 4′-*n*-butyl (**44b**), 2′-cyano (**47b**), 4′-methylsulfonyl (**50b**), 2′-carboxy (**58b**), and 2′,7-ethano (**59b**). Also, some compounds in this series are exceedingly potent: **7b**, **10b–12b**, **33b**, and **51b-53b** antagonize TBZ-induced ptosis with an ED_{50} of less than 0.10 mg/kg; **7b**, **22b**, **23b**, **25b**, **29b**, **33b**, and **52b** inhibit the uptake of NE with a K_i of less than 0.7 nM; **22b**, **23b**, **25b**, **29b**, **45b**, and **52b** inhibit the uptake of DA with a K_i of less than 3 nM; and **10b**, **22b**, **28b**, **29b**, **45b**, and **48b** inhibit the uptake of 5-HT with a K_i of less than 3 nM. Indeed, the 4′-chloro (**22b**, McN-5292) and 4′-amino (**52b**, McN-5908) derivatives are more potent antagonists of NE uptake than desmethylimipramine (DMI), the 3′,4′-dichloro (**29b**, McN-5532) and 4′-amino (**52b**) derivatives are more potent inhibitors of DA uptake than amfonelic acid, and the 4′-methylthio derivative (**48b**, McN-5652-Z) is a more potent inhibitor of 5-HT uptake than sertraline (see Table IV).[21] Acetamide **53b** is exceedingly potent in the TBZ assay, yet it does not show exceptional neurochemical activity; thus, **53b** may be a prodrug for **52b**.

It is interesting to note that although monochloro substitution at positions 4′ (**22b**), 3′ (**23b**), 2′ (**24b**), and 9 (**25b**) leads to potent activity, substitution at position 7 (**26b**) results in some attenuation, and substitution at position 10 (**27b**) strongly reduces activity. The negative effect of chloro substitution at positions 7 and 10 may be connected with steric (peri) interactions. 2′-Chloro (**24b**) and 2′-bromo (**35b**) substitution give virtually identical, decent activity. For other substituents in the 2′-position: methoxy (**14b**) shows strong activity; methyl (**43b**), methylthio (**49b**), cyano (**47b**), and hydroxy (**15b**) show moderate reduction of activity; and trifluoromethyl (**38b**) shows weak activity, at best. By contrast, trifluoromethyl substitution at positions 3′ (**37b**), 4′ (**36b**), or 9 (**39b**) affords good activity. Dihalo substitution gives variable results: in vitro activity is diminished for 2′,4′ (**30b**) and 2′,6′ (**31b**) substitution; only in vivo activity is diminished for 4′,9′-dichloro substitution (**28b**), but 4′,9-difluoro substitution (**33b**) retains high potency, as does 3′,4′-dichloro substitution (**29b**). Although a 4′-nitro (**51b**) or cyano (**46b**) group shows substantial activity, the methylsulfonyl (**50b**) group does not. Considering also that a 4′-butyl (**44b**) group leads to relatively weak activity, while a 4′-ethynyl (**45b**) or 4′-methylthio (**48b**) group leads to strong activity, there may be a steric sensitivity at this portion of the molecule. Another possible steric effect may relate to substitution of both sides of the pendant phenyl ring, in that 3′,4′,5′-trimethoxy (**20b**), 3′,5′-bis(trifluoromethyl) (**42b**), pentafluoro (**34b**), and 2′-chloro-6′-fluoro (**31b**) compounds exhibit greatly reduced activity.

The pattern of aromatic substitution can have a dramatic impact on neurotransmitter uptake. Referring to Table IV, high selectivity (>9-fold) for NE uptake inhibition vs. DA and 5-HT inhibition obtains with **13b**, **15b**, **19b**, **22b**, and **37b**; moderate selectivity (>3-fold) for DA vs. NE and 5-HT uptake is obtained with **8b**, **54a**, and **54b**; and moderate selectivity (>3-fold) for 5-HT vs. NE and DA uptake is obtained with **48a**, **48b**, and **57b**.

Although these selectivities in vitro are reasonably significant, they are not especially exciting. Much greater differentiation between uptake sites (>50-fold selectivity) is seen with known drugs, e.g., desmethylimipramine (for NE), amfonelic acid (for DA), and sertraline (for 5-HT). Given the high affinity, but modest selectivity, of **48b** for 5-HT uptake sites, we have examined **48b** and a collection of closely related derivatives for potentiation of serotonin in vivo. This subject will be discussed more deeply in a separate paper.[22]

Meaningful in vitro activity is not confined to the trans isomers, as appreciated for example from **10a**, **17a**, **19a**, **48a**, **50a**, **52a**, **54a**, and **62a**. Compound **54a** (McN-5847) deserves special recognition because the cis isomer is actually more robust in blocking DA and NE uptake than the trans isomer (**54b**). This cis isomer also has the distinction of being one of the few potent monoamine uptake inhibitors selective for the DA carrier.

Powerful stimulant activity appears to be associated with the presence of unsubstituted aromatic rings (viz. **7b**), and such activity is evidenced by molecules with hydroxy or methoxy groups in certain positions on either aromatic ring (viz. **8b**, **9b**, **11b**, **13b**, and **19b**) or with chloro, amino, or ethynyl groups at the para and/or meta position of the pendant phenyl ring (viz. **22b**, **23b**, **29b**, **52b**, and **45b**).[23] However, derivatives bearing a chloro, hydroxy, or methoxy group at the ortho position of the pendant phenyl lack stimulant properties (viz. **24b**, **15b**, and **14b**). Stimulant activity is also attenuated when a 3′-methoxy (but not a 3′-hydroxy) group is present (viz. **12b**, **18b**, **20b**, and **21a/b**). Other substitution offers an effective separation of antidepressant activity and stimulant activity (e.g., viz. **37b**, **48b**, and **51b**).

During the early phase of our studies, we had an impression that stimulant properties might be associated with compounds that are powerful inhibitors of DA uptake,

(21) Some of our potent inhibitors of DA uptake counteract the neurotoxicity induced by 1-methyl-4-phenyltetrahydropyridine (MPTP); see: Mayer, R. A.; Kindt, M. V.; Heikkila, R. E. *J. Neurochem.* **1986**, *47*, 1073.

(22) Maryanoff, B. E.; McComsey, D. F.; Vaught, J. L.; Shank, R. P.; Gardocki, J. F.; Costanzo, M. J.; Nortey, S. O., manuscript in preparation.

(23) The stimulant character of **7b** has been studied in greater detail by Prof. K. Moore; see: Neilsen, J. A.; Duda, N. J.; Mokler, D. J.; Moore, K. E. *Pharmacol. Biochem. Behav.* **1984**, *20*, 227.

relative to NE and/or 5-HT uptake. However, inspection of the data in Table IV reveals that there is no viable correlation in this regard. Some compounds were tested for induction of stereotypy in the rat to evaluate stimulant activity. The following data were obtained for references (ED_{50}, mg/kg): *d*-amphetamine 2.0 (ip), apomorphine 0.79 (sc), and nomifensine 13.7 (ip); and for selected pyrroloisoquinolines (percent induction at 10 mg/kg, sc): **7b** 60%, **12b** 75%, **24b** 0%, **28b** <10%, **32b** 71%, **33b** 45%, **37b** 0%, **48b** <2%, **52b** ca. 90%, and **53a** 25%. These data suggest that **7b**, **12b**, **32b**, **33b**, and **52b** are stimulant in nature, whereas **24b**, **28b**, **37b**, and **48b** are not disposed to this liability.[23,24]

Methyl substitution on the aliphatic network was examined. Analogues with a methyl group at position 10b (**60b**) or 6 (**61b**) show appreciable activity, albeit less than **7b**; however, methyl substitution at position 5 significantly depletes (**65b**) or abolishes (**66b**) activity. Compound **61b** still possesses stimulant activity. A 6-hydroxy (**62b**) or 6-fluoro (**63b**) group diminishes activity somewhat more than a 6-methyl group (**61b**). The cis isomers of the 6-methyl (**61a**) and 6-hydroxy (**62a**) demonstrate modest activity.

Compounds **69a** and **69b**, in which the pendant phenyl ring is moved to the 5-position, exhibit in vivo activity, but lack influence on neurotransmitter uptake. Placement of the phenyl group at the 10b-position (**70**) abolishes activity, as does elimination of the pendant phenyl altogether (viz. **71** and **72**). Replacement of the phenyl substituent with a related aliphatic group, cyclohexyl (**67b**) or benzyl (**68b**), provides modest activity.

Expansion of the C (pyrrolidine) ring to a six- or seven-membered ring substantially diminished activity, cf. **7b**, **75b**, and **74b**, as did expansion of the B ring by insertion of a methylene group, cf. **7b** and **78b**. Azeto[2,1-*a*]isoquinoline **77b** showed moderate activity in vitro and in vivo. Loss of activity occurs with ring-opened analogue **89**, but activity is demonstrated by **88**, which structurally resembles nomifensine and diclofensine.

Replacing the A ring with a heterocycle gives compounds that retain activity, but **79b** and **82b** still evince stimulant characteristics. Bis-thienyl compound **80b** shows much less activity.

The 3-one precursors to **7a** and **7b** (viz. Ia and Ib, appropriately substituted) were inactive in the TBZ assay at 30 mg/kg.

Thus, the antidepressant-like activity is optimized in amine derivatives with the pyrroloisoquinoline (6,6,5) ring system, having a suitably substituted phenyl ring linked to the 6-position, and otherwise unsubstituted on rings B and C.

As mentioned earlier, enantioselectivity is another important aspect of the biological activity for our series. The (+) enantiomers of the acid-addition salts of **7b**, **24b**, **37b**, and **48b** are considerably more potent than the corresponding (−) enantiomers (by 40–1500 times, depending on the particular compound and in vitro assay). These four trans enantiomers possess the same absolute geometry, that with the 10b*R* configuration (vide supra). Some reports on antidepressant structural classes showing high enantioselectivity have appeared;[1a,25] enantioselectivity was reported for the following uptake inhibitors/antidepressants: oxaprotiline,[25,26] YM-08054-1,[27] mianserin,[25] sertraline (**90**) and some of its congeners,[28] nomifensine (**4**),[19] diclofensine (**5**),[18] Lu-19-055 (**91**) and some congeners,[29] tandamine,[25] and viloxazine.[25]

Other Biological Testing. Certain derivatives in Table I were assayed for their ability to bind to various CNS receptors (see Table V). We examined interaction with dopamine D_1 and D_2, adrenergic α_1 and α_2, serotonin S_1 and S_2, and muscarinic cholinergic receptors in synaptic membrane preparations.[30]

We were particularly interested in determining the affinities of analogues with a catecholamine substructure for the dopamine receptors. The data for **9a**, **9b**, **19a**, and **19b** indicate weak binding to the D_2 receptor; however, **9a** and **9b** have significant, but modest, affinity for the D_1 receptor. Compound **33b** also has modest affinity for the D_1 site, as well as the D_2 site. Dopaminergic agonist activity, selective for D_1 receptors, has been reported for the 3′,4′-dihydroxy derivative of nomefensine,[9a] as well as for a related tetrahydro-3-benzazepine.[31]

Generally, the analogues investigated in Table V were just weakly active (i.e., $K_i > 200$) in the battery of tests. A notable exception is the intense activity of **24b** and **33b** in the S_2 receptor assay, with K_i values of 8.6 and 7.4 nM, respectively, in analogy to mianserin and clomipramine. That **24b** is a central serotonin antagonist was demonstrated by its ability to counteract L-5-hydroxytryptophan-induced head twitches in mice, with an ID_{50} of 7.3 mg/kg, ip (data not shown). Thus, strangely enough, **24b** could, at once, enhance and attenuate the function of endogenous 5-HT by inhibition of uptake and receptor blockade. However, these disparate activities may be applied in distinct and separate brain regions. Interestingly, the cis isomers **24a**, **37a**, and **52a** exhibit a strong affinity for the S_2 site, although they show no evidence of antidepressant properties, as indicated by the TBZ or neurochemical uptake tests.

It is important to note that **24b**, **37b**, and **48b** have very little effect on the uptake of GABA. Inhibition at an elevated concentration of 0.01 mM was found to be 16%, 16%, and 10%, respectively. Consequently, the pyrroloisoquinolines are not nonspecific inhibitors of neurotransmitter uptake.

Derivatives from this series generally lack anticholinergic properties in vivo or in vitro. This can be appreciated by the absence of affinity for the muscarinic cholinergic receptor (Table V) and by their detailed pharmacology, the latter of which will be published in a different forum.

Related Antidepressants. Structure and Stereochemistry. As mentioned earlier, the trans (Ar vs. H)

(24) Extensive motor activity studies have been performed on selected analogues; these data will be reported elsewhere in due course. Compound **24b** was devoid of stereotypic behavior in rats at 10 mg/kg (ip) and 300 mg/kg (po).

(25) Waldmeier, P. C. *Trends Pharmacol Sci.* **1983**, *448*.

(26) Delini-Stula, A.; Hauser, K.; Baumann, P.; Olpe, H.-R.; Waldemeier, P.; Storni, A. In *Typical and Atypical Antidepressants: Molecular Mechanisms*; Costa, E., Racagni, G., Eds.; Raven: New York, 1982; pp 265–275.

(27) Tachikawa, S.; Harada, M.; Maeno, H. *Arch. Int. Pharmacodyn.* **1979**, *238*, 81.

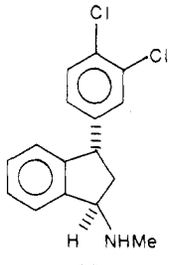
(28) (a) Koe, B. K.; Weissman, A.; Welch, W. M.; Browne, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (b) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508.

(29) (a) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (b) Hyttel, J.; Larsen, J.-J. *J. Neurochem.* **1985**, *44*, 1615. (c) Bogeso, K. P. *J. Med. Chem.* **1983**, *26*, 935. (d) Bogeso, K. P.; Hyttel, J.; Christensen, A. V.; Arnt, J. In *Innovative Approaches to Drug Research*; Harms, A. F., Ed.; Elsevier: Amsterdam, 1986; pp 371–392.

(30) Experimental details and literature precedent are referred to in the Experimental Section.

(31) Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Bass, L. S.; Clardy, J. *J. Med. Chem.* **1982**, *25*, 697.

relative stereochemistry of the pyrroloisoquinolines is principally responsible for robust antidepressant activity. The absolute stereochemistry of four active enantiomers in our series is consistent; it is 6*S*,10b*R* (in the absence of a change due to atom priority assignments[15]). The pyrroloisoquinoline antidepressants structurally resemble a number of reported CNS agents. Of course, there is a particular analogy to nomifensine (**4**) and diclofensine (**5**),[32] as already indicated. These embody the 4-phenyltetrahydroisoquinoline subunit,[33] and it is the 4*S* enantiomers that manifest the antidepressant activity.[18,19] Butaclamol (**92**) is an interesting antipsychotic agent that also contains



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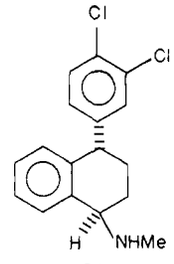

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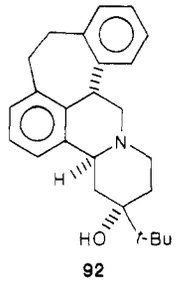

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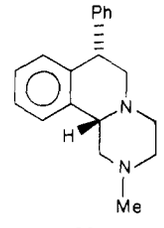


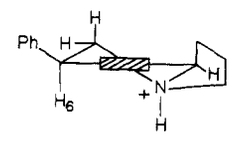
93

this subunit; but it is the 4a*S*,13b*S* (cis Ar vs. H, not trans) stereoisomer that is biologically active.[34] The atypical pyrazino[2,1-*a*]isoquinoline antidepressant **93** bears a structural resemblance to our compounds, and biological activity mainly resides with the 7*S*,11b*S*-cis stereoisomer,[35] analogous to our case (there is a reversal of priority at position 11b[15b]). However, it should be noted that the antidepressant properties of **93** do not appear to be similar to those found for our series, in that **93** does not inhibit DA or NE uptake and binds to the muscarinic cholinergic receptor.[35]

The pyrroloisoquinolines and the 4-phenyltetrahydroisoquinolines also bear a structural likeness to 1-amino-3-phenylindan (e.g., **90**)[29] and 1-amino-4-phenyltetralin (e.g., **91**)[28] antidepressants, a comparison that has been effectively discussed by Bogeso et al.[29a] Suffice it to say that compounds with both the cis and trans relative stereochemistry in these latter series show some antidepressant-like character, although there are some differences in selectivity for neurotransmitter uptake sites. Nevertheless, for biological activity the absolute stereochemistry at the center linked to the appended aryl group is invariably *S* (i.e., 4*S* or 3*S*, respectively). Thus, the absolute spatial arrangement at the aryl-bearing site corresponds across all of these compound classes. Given this pattern, Bogeso et al. have attempted to formulate a model for designing DA, NE, and 5-HT uptake inhibitors and for mapping the uptake sites.[29a] Bogeso and co-workers suggested that the topography of the three uptake sites must be similar; also, they proposed a general definition for interaction at the sites based on stereochemistry of the pendant aryl group and on appropriate substructural units.[29d] Our extensive exploration of substitution of the appended aryl group of the pyrroloisoquinolines affords some added insight to their general idea. As discussed above in the SAR section, certain minor substitution differences lead to a separation or disappearance of affinity for the three uptake sites. E.g., compare the 3′-trifluoromethyl compound **37b** with **7b** (parent), **38b** (2′-trifluoromethyl), and **42b** (3′,5′-bis(trifluoromethyl)). In the same vein, one might compare **24b** (2′-chloro) with **31b** (2′-chloro-6′-fluoro), **30b** (2′,4′-dichloro), **29b** (3′,4′-dichloro), and **22b** (4′-chloro); or **32b** (4′-fluoro) with **34b** (2′,3′,4′,5′,6′-pentafluoro); or **10b** (4′-methoxy) with **14b** (2′-methoxy), **18b** (3′,4′-dimethoxy), and **20b** (3′,4′,5′-trimethoxy). A steric bulk factor in substitution at the 4′-position was important in determining biological activity. There was also a critical dependence on specific methyl substitution on the aliphatic network, which may reflect steric interference with interaction of the nitrogen center, and on the size of the C ring, which may relate to subtle conformational effects.

We have studied hydrogen bromide salts of certain pyrroloisoquinolines and C-ring-modified analogues in the solid state by X-ray crystallography and in $CDCl_3$ solution by 360-MHz ^1H NMR.[36] Because of space limitations, we cannot report extensive details of this work herein; however, it is apropos to divulge some of the highlights in the context of our SAR discussion.[36] Although compounds **7a**, **7b**, **75a**, and **75b** adopt a trans junction between the B and C rings in solution, the picture on protonation is quite different. Since the protonated version of the active molecule has relevance to the in vivo situation, where the ambient pH is 7.3, we ascribe considerable importance to the subsequent findings.[37]

By analyzing vicinal proton–proton coupling constants between the NH and adjacent CH groups,[38] it was possible to determine the configurational disposition of the ring fusion in the salts. Thus, **7b**·HBr assumes a cis B "conformation" (**94**) to the extent of at least 90%, whereas



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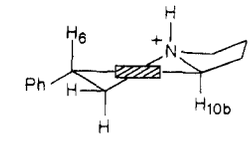

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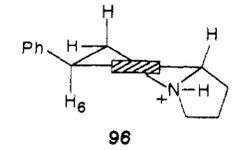

96

(32) Thieno[2,3-*c*]pyridine analogues of nomifensine have been reported to have antidepressant activity; see: Schneider, C. S.; Weber, K. H.; Daniel, H.; Bechtel, W. D.; Boeke-Kuhn, K. *J. Med. Chem.* **1984**, *27*, 1150.

(33) (a) This subunit is present in some natural products, such as cherylline and latifine, which possess the 4*S* configuration.[33b] (b) Takano, S.; Akiyama, M.; Ogaswara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2447. Brossi, A.; Grethe, G.; Teitel, S.; Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1970**, *35*, 1100.

(34) Humber, L. G.; Bruderlein, F. T.; Voith, K. *Mol. Pharmacol.* **1975**, *11*, 833.

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(36) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Olofson, R. A., manuscript in preparation.

(37) (a) The pK_a of **7b** is 9.1,[37b] which means that it would be at least 95% protonated at physiological pH. (b) Chrzanowski, F. A.; McGrogan, B. A.; Maryanoff, B. E. *J. Med. Chem.* **1985**, *28*, 399.

(38) There is a Karplus-type relationship for this vicinal coupling; see: (a) Fraser, R. R.; Renaud, R. N.; Saunders, J. K.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 2433. (b) Crowley, P. J.; Morris, G. A.; Robinson, M. J. T. *Tetrahedron Lett.* **1976**, 3375.

Table V. Receptor Binding Properties of Selected Compounds[a]

compd	D_1	D_2	α_1	α_2	musc	S_1	S_2
7b	35%	875	172	750	0%[b]	>10000	
(+)-**7b**		40%	83	64%			
(−)-**7b**		14%	262				58%
8a	452	400					
8b		6%					
9a	64	19%					
9b	106	20%	87	21%	0%		46%
11a		59%					
11b	27%	65%	252	70%	3%		
12b	40%	27%	87%	37%	1%		
13a		4%					
14b						45%	74%
18b		−1%	58%	15%	−1%		
19a	>1000	6%					
19b	>1000	5%	675	26%	0%		
20a			90%				88%
20b		17%	29			31%	2%
22b		35%	61%	35%	0%		59%
23b							49
24a		54%	41				10
24b[c]		415	163	12%	6%	1680	8.6
(+)-**24b**			150			9200	6.4
(−)-**24b**			620			2700	406
28b		55%	20%	10%		11%	
29b		37%	33%	990	9%	465	24%
32b	56%						
33a		48%				−9%	5%
33b	183	241	536	25%	0%	−6%	7.4
37a			86				29
37b[c]	17%	2220	213	7%	1%		602
(+)-**37b**			48%				44%
(−)-**37b**		9%	30			58%	45%
48a		28%	43%		0%		
48b[d]	24%	4%	314			1030	208
(+)-**48b**		1030	274			31%	142
(−)-**48b**		5%	213			775	939
52a		16%	69%			36%	29
54a							54
fluoxetine		12%	5260			13%	>1000
mianserin		828	99	62		580	1.1
clomipramine		56	75	51		5000	8.3
haloperidol	24	0.75	24	14%	>10000	58%	4.2
imipramine		63%	220	4900		15%	23
Sch-23390	0.14	53%	65%			75%	13
diclofensine	38%	27%	−6%			33%	37

[a] Receptor affinity is represented in terms of K_i, with nM units, or as percent inhibition at 1.0 μM, unless specified otherwise. See Table VI for further details on the binding assays. [b] At 10 μM. [c] Inhibition of GABA uptake: 16% at 1.0 μM. [d] Inhibition of GABA uptake: 10% at 1.0 μM.

7a·HBr assumes on initial dissolution a fleeting trans conformation (**95**; ca. 80%), reflective of a structure imposed by the solid state, and then converts on standing to a cis A form (**96**; >90%). Clearly, cis ring junctions of the salts are favored relative to the trans junctions. The X-ray crystal structure of **24b**·HBr (Figure 1) illustrates the cis B form in the solid state. Examination of **66b**·HBr mustered support for the proposed behavior of **7b**·HBr. On dissolution of this salt in $CDCl_3$, the ^1H NMR spectrum indicated ca. 90% trans species, which on standing slowly converted to the corresponding cis A form (>90%). Incontrovertible evidence for this phenomenon was gleaned by monitoring the two species over the time course for their interconversion. To confirm the solid-state structure, we performed an X-ray analysis on **66b**·HBr and found the trans structure with pseudoequatorial methyl and phenyl substituents.[8] The HBr salt of desphenyl analogue **72** first showed a mixture of trans and cis B forms (30:70) on dissolution, which rapidly shifted to the cis B form, and the HBr salts of benzoquinolizidines **75a** and **75b** assumed the trans and cis B forms, respectively.[39]

(39) X-ray analyses on **61a** and **61b** (to be published elsewhere) depicted the cis A conformation.

It is apparent that the protonated trans diastereomers, of which **7b** is a prototype, will exhibit a propensity to adopt the cis B disposition in solution. The significance of this in regard to their mode of interaction with uptake sites is self-evident.[40]

Conclusion

A structure–activity study has been conducted on a series of pyrrolo[2,1-*a*]isoquinoline derivatives with antidepressant properties. Activity principally resides in the trans diastereomeric class and also is associated with just one set of enantiomers. Compounds from this series represent some of the most potent agents yet reported for inhibition of TBZ-induced ptosis and uptake of DA, NE, or 5-HT. On the basis of this body of information, compounds **24b** (McN-5707) and **48b** (McN-5652-Z) were investigated pharmacologically in some detail.[41a] Thus, we were excited to discover that these two agents are effective

(40) From our discussion of conformational behavior, it should be clear that the pyrroloisoquinoline derivatives are not "very rigid because of the 5–6 ring system", as stated in ref 29d in an attempt to rationalize the high enantioselectivity for the biological activity of **7b**.

in down-regulating β adrenergic receptors in the CNS,[41b] a property associated with clinical antidepressant activity.[41c] Additionally, **48b** potently enhanced the ability of L-5-hydroxytryptophan to induce head twitches in mice and the "serotonin behavioral syndrome" in rats.[22,42] Both of these compounds were selected for advanced development as antidepressants.

Experimental Section

General Information and Procedures. Proton NMR spectra were recorded on a Varian EM-390 (90 MHz), Varian EM-360 (60 MHz), or Bruker AM-360 (360 MHz) spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard, unless otherwise indicated. Carbon-13 NMR spectra were recorded on a JEOL FX60Q spectrometer (15.0 MHz) in $CDCl_3$ with Me_4Si as an internal reference. NMR abbreviations used are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = d of d of d, m = multiplet, q = quartet, br = broad. IR spectra were obtained on a variety of spectrophotometers in KBr pellets. Mass spectra were obtained on a VG Micro Mass 7035 or Finnigan GC-MS-DS Model 9500-3300-1600 instrument. GLC analyses were performed on a Perkin-Elmer 3920B instrument (flame-ionization detector) equipped with a Hewlett-Packard Model 3352 data system and 18652A A/D converter, using a glass column ($^1/_8$ in. × 6 ft) with 3% SE-30 on Chromosorb Q packing or with 1.35% OV-17 on Chromosorb W AW/DMS packing or on a Hewlett-Packard 5890 instrument (FID) equipped with a Hewlett-Packard Model 3393A data system, using fused-silica capillary columns (0.2 mm × 25 m) with 5% phenyl methyl silicone. TLC separations were conducted on 250-μm silica gel plates with visualization by UV fluorescence and iodine staining. Melting points are corrected; melting ranges may be preceded by softening ranges, in parentheses. Preparative high-performance LC separations were conducted on a Waters Prep LC/System 500 or 500A instrument using silica gel columns. Enantiomeric purity, in some cases, was assayed with a Waters analytical HPLC instrument equipped with a UV detector (254 nm) and a Hewlett-Packard Model 3390A integrator, using a Chiralpak (OT(+) column from Daicel Industries, Ltd. Optical rotations (589 nm) were determined by using a Perkin-Elmer 241 polarmeter. X-ray diffraction analysis of (+)-**24b**·HBr was performed by Oneida Research Service. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA, Scandanavian Labs, Herlev, Denmark, or Galbraith Laboratories, Inc., Knoxville, TN.

Materials. Commercially available reagents were used without further purification unless warranted. 4-Methoxy- and 4-chloromandelic acids were prepared according to literature procedure.[43] The following mandelic acids were prepared by a modification of that procedure (see below): 4-SMe [mp 138–140 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.45 (s, 1 H), 4.98 (s, 3 H), 7.1–7.5 (m, 4 H)]; 3,4-$(OMe)_2$[44] [mp 108–110 °C; ^{1}H NMR δ 3.7 (s, 6 H), 5.1 (s, 1 H), 6.2–8.6 (m, 5 H)]; 2-SMe [^{1}H NMR δ 2.3 (s, 3 H), 5.5 (s, 1 H), 7.1–7.5 (m, 4 H)]; 3,4,5-$(OMe)_3$[45] [^{1}H NMR δ 3.7 (s, 9 H), 5.1 (s, 1 H), 6.4–8.3 (m, 4 H, 2 exch)].

The following 2-arylpyrrolidines were prepared from *N*-vinyl-2-pyrrolidinone[46a] (see below): phenyl [^{1}H NMR (60 MHz) δ 1.6–2.3 (m, 4 H), 2.5 (br s, NH), 2.8–3.4 (m, 2 H), 4.1 (dd, 1 H, J = 7 Hz)]; 3-(trifluoromethyl)phenyl [^{1}H NMR (90 MHz) δ 1.5–2.3 (m, 5 H), 2.8–3.3 (m, 2 H), 4.1 (dd, 1 H), 7.5 (m, 4 H)]; 3-chlorophenyl; 2-chlorophenyl [^{1}H NMR δ 1.3–1.8 (m, 4 H), 2.0–2.4 (m, 1 H), 2.8–3.2 (m, 2 H), 4.5 (t, 1 H), 7.0–7.6 (m, 4 H, arom)]. 2-(3-Methoxyphenyl)pyrrolidine was synthesized by reaction of 2-methoxy-1-pyrroline with (3-methoxyphenyl)magnesium bromide (82% yield),[46b] followed by reduction of the intermediate pyrroline with $NaBH_4$ (97% yield).

Substituted styrene oxides were prepared according to several literature procedures. The following were prepared by using the method of Corey et al.[47] (trimethylsulfoxonium iodide/NaH) and distilled by Kugelrohr: 3-CF_3;[48] 3-Cl;[49] 3,5-$(CF_3)_2$ [^{1}H NMR δ 2.7 (dd, 1 H, J = 3, 6 Hz), 3.2 (dd, 1 H, J = 4.5, 6 Hz), 3.9 (dd, 1 H, J = 3, 4.5 Hz), 7.6–8.0 (m, 3 H, arom)]; 4-n-C_4H_9 [^{1}H NMR δ 0.7–2.0 (m, 7 H, aliph), 2.3–2.7 (m, 3 H), 3.0 (dd, 1 H, J = 4.5, 6 Hz), 3.7 (dd, 1 H, J = 3, 4.5 Hz), 7.1 (br s, 4 H, arom)]; 2-Cl, 6-F [^{1}H NMR δ 2.8–3.3 (m, 2 H), 3.9 (dd, 1 H, J = 4 Hz), 6.5–7.4 (m, 3 H, arom)]; 4-CF_3 [^{1}H NMR δ 2.7 (dd, 1 H, J = 3.0, 6 Hz), 3.1 (dd, 1 H, J = 4.5, 6 Hz), 3.8 (dd, 1 H, J = 4.5, 3.0 Hz), 7.3 (d, 2 H, J = 9 Hz), 7.5 (d, 2 H, J = 9 Hz)]. The following styrene oxides were prepared by using trimethylsulfonium iodide[50] (potassium *tert*-butoxide/Me_2SO) and distilled by Kugelrohr: 2-Me;[51] 2,4-Cl_2.[52] The following styrene oxides were prepared by using the phase-transfer method of Merz[53] (trimethylsulfonium iodide/aqueous NaOH) and distilled by Kugelrohr: 2-Cl[54] [^{1}H NMR δ 2.63 (dd, 1 H, J = 3, 6 Hz), 3.15 (dd, 1 H, J = 4, 6 Hz), 4.20 (dd, 1 H, J = 3, 4 Hz), 7.1–7.5 (m, 4 H)]; 2-Br;[55] 2-CF_3 [^{1}H NMR δ 2.6 (m, 1 H), 3.2 (m, 1 H), 4.1 (m, 1 H), 7.3–7.7 (m, 4 H, arom)]. The C_6F_5-bearing styrene oxide was prepared from the corresponding alkene by using MCPBA in $ClCH_2CH_2Cl$.[56] The 4-NO_2 compound was prepared by reduction of the corresponding 4-nitrophenacyl bromide with $NaBH_4$ in methanol, following by treatment with 3 N NaOH (88% yield).[57]

The following benzaldehydes were prepared: 2-MeS;[58] 3,5-$(CF_3)_2$[59] [^{1}H NMR δ 8.1 (s, 1 H), 8.4 (s, 2 H), 10.2 (s, 1 H, CHO); 4-I (from 4-bromobenzaldehyde and KI under Pd(0) catalysis).[60]

Several bis(aryl)ethylamines were prepared by using a modification of Quelet's procedure[61] (see below and ref 2): 2,2-bis-(2-thienyl)ethylamine [fumarate salt: mp 174–177 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.35 (d, 2 H, J = 8 Hz), 4.84 (t, 1 H, J = 8 Hz), 6.47 (s, 2 H), 6.9–7.6 (m, 6 H, arom)]; 2,2-bis(4-fluorophenyl)ethylamine (see below).

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-methanamine, used for the synthesis of **59a** and **59b**, was prepared by reacting 5-chlorodibenzosuberane with AgCN and then reducing the intermediate nitrile with borane–THF (75% overall yield).[62] The

(41) (a) For details on the pharmacology of **24b**, see: Shank, R. P.; Gardocki, J. F.; Schneider, C. R.; Vaught, J. L.; Setler, P. E.; Maryanoff, B. E.; McComsey, D. F. *J. Pharmacol. Exp. Ther.*, in press. (b) Details will be published in due course. We are grateful to Prof. Alan Frazer (University of Pennsylvania) for these data. (c) Sulser, F. *Trends Pharmacol. Sci.* **1979**, *1*, 92.

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material was characterized as a fluffy, white HCl salt, mp (250–270 °C, darkened) 270–280 °C dec (from ethyl acetate/methanol; lit.[62b] mp >295 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.14 (m, 4 H, CH_2CH_2), 3.48 (d, 2 H, CH_2N^+, J = 6 Hz), 4.71 (t, 1 H, J = 6 Hz), 7.19 (m, 8, arom), 8.26 (br s, 3 H, NH_3^+).

α-Methyl-β-phenylbenzeneethanamine, used to prepare **65a**, **65b**, and **66b**, was obtained by reduction of crude 1,1-diphenylacetone oxime with Raney nickel aluminum alloy.[2,63a]

Mononitration of **7a** and **7b** was conducted according to a literature description.[35]

Preparation of Mandelic Acids from Benzaldehydes. General Procedure. This is an adaptation of a procedure described previously.[43] To a mixture of lithium bromide (0.5 mol) in 200 g of ice was added potassium hydroxide (85% assay, 66 g, 1.0 mol). The mixture was stirred at 5 °C until all of the solids had dissolved, and 200 mL of dioxane was added. The aromatic aldehyde (0.25 mol) was added, followed by bromoform (0.25 mol). The resultant mixture was stirred at 0 °C for 18 h and then at 23 °C for 24 h. After extraction with ether (2 × 100 mL), 200 g of ice was added to the aqueous phase and it was acidified with 6 N HCl to pH 1. This was extracted with ether (3 × 100 mL) and the combined organic extract was dried ($MgSO_4$) and evaporated in vacuo to give the mandelic acid (60–80% yield).

Example. Lithium bromide (174 g, 2.0 mol), KOH (85% assay, 267 g, 4.0 mol), 4-(methylthio)benzaldehyde (152 g, 1 mol), and bromoform (264 g, 1 mol) were combined in 1600 mL of water and 1600 mL of dioxane according to the general procedure. Upon workup, a yellow solid was isolated (192 g, 97%), which still contained some dioxane. A portion (20 g) was recrystallized from acetonitrile to give white crystals (7.6 g): mp 138–140 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.45 (s, 3 H), 4.98 (s, 1 H), 7.1–7.5 (m, 4 H, arom); IR δ_{max} 3449 (OH), 1714 cm^{-1} (C=O). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.88; H, 5.08.

Preparation of 2-Arylpyrrolidines. General Procedure. 2-Arylpyrrolines were prepared from a benzoate ester and *N*-vinyl-2-pyrrolidinone, as described previously.[46a] A mixture of *N*-vinyl-2-pyrrolidinone (60.26 g, 0.54 mol) and an ethyl or methyl benzoate (0.46 mol) in THF (150 mL) was added to a slurry of sodium hydride (30.68 g of 50% dispersion in mineral oil, 0.63 mol, washed with anhydrous ether) in 420 mL of THF. The reaction mixture was stirred for 5–10 min under nitrogen, whence an exothermic reaction with vigorous evolution of gas commenced. The mixture was refluxed for 1 h, cooled to room temperature, treated with a solution of 76 mL of concentrated HCl in 128 mL of water, and stirred for 5 min. The THF was evaporated, additional concentrated HCl (128 mL) and water (200 mL) were added, and the mixture was refluxed for 15 h. The solution was basified with 50% NaOH (ice-bath cooling) and extracted with anhydrous ether (2 × 200 mL). The organic extracts were combined, washed with water, washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude pyrroline as a syrup (further purification of pyrroline may be accomplished via Kugelrohr distillation). Sodium borohydride (16.06 g, 0.42 mol) was added portionwise to a mixture of pyrroline (89.63 g, 0.42 mol) in absolute ethanol (340 mL). The reaction was stirred several hours, treated with 100 mL of 1 N HCl (at 0–10 °C), and then acidified to pH 1 by addition of 3 N HCl. (Treatment with HCl is necessary to effect thorough imine reduction.) The ice bath was removed and the mixture was stirred for 45 min. It was then basified with cold 25% NaOH to pH 11–12 and extracted with anhydrous ether (2 × 200 mL). The organic extracts were combined, washed once with water, washed once with brine, dried (K_2CO_3) quickly, and evaporated in vacuo to give the 2-arylpyrrolidine as a syrup in about 60–90% overall yield.

Example. 2-[3-(Trifluoromethyl)phenyl]pyrrolidine. *N*-Vinyl-2-pyrrolidinone (60.26 g, 0.54 mol), ethyl 3-(trifluoromethyl)benzoate (100 g, 0.46 mol), and sodium hydride (30.68 g, 0.63 mol) were combined according to the general procedure to give the pyrroline (90.4 g, 94%), which was reduced with sodium borohydride (16.06 g, 0.42 mol) to give pure 2-[3-(trifluoromethyl)phenyl]pyrrolidine (81.01 g, 90%): ^{1}H NMR δ 1.5–2.3 (m, 5 H, including NH), 2.8–3.3 (m, 2 H), 4.1 (t, 1 H), 7.5 (m, 4 H).

Preparation of Targets via the Styrene Oxide Route. General Procedure. The styrene oxide (0.10 mol) and 2-substituted pyrrolidine (0.10 mol) were combined in 200 mL of absolute ethanol, and the solution was refluxed for 4 h. The solvent was evaporated in vacuo to give the crude amino alcohols, which were combined with PPA (200 g). The reaction mixture was stirred on a steam bath for 4 h, poured into 1 L of ice water, made alkaline with 50% KOH, and extracted with methylene chloride. The organic layer was washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to give the crude amine product. The isomeric amines, usually in a ratio (α:β) of (2–4):1,[63b] were separated by preparative HPLC and generally purified as their acid-addition salts.

Example 1. *trans*-6-[3,5-Bis(trifluoromethyl)phenyl]-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (42b). 2-Phenylpyrrolidine (13.5 g, 0.092 mol) and 3,5-bis(trifluoromethyl)styrene oxide (37.5 g, 0.092 mol) were reacted according to the general procedure to yield a 2.3:1 mixture of cis (**42a**) and trans (**42b**) diastereomers (15.85 g, 47%). The isomers were separated via preparative HPLC (chloroform/ethyl acetate, 95:5) to afford **42a** (5.4 g) and **4b** (2.9 g), the slower eluting component. The latter HCl salt was recrystallized twice from acetonitrile/ether to give white crystals (2.1 g): mp 266–270 °C; ^{1}H NMR δ 2.2–2.4 (m, 3 H), 2.8–3.2 (m, 3 H), 3.6–3.8 (m, 1 H), 4.0–4.2 (m, 1 H), 4.8–5.0 (m, 1 H), 5.1 (dd, 1 H), 6.7 (d, 1 H), 7.1–7.4 (m, 3 H), 7.8 (s, 2 H), 7.9 (br s, 1 H), 13.8 (s, 1 H). Anal. C, H, N.

Example 2. 2,3,5,6,11,11a-Hexahydro-6-phenyl-1*H*-pyrrolo[2,1-*b*]-3-benzazepine (78a and 78b). Styrene oxide (13.7 g, 0.114 mol) and 2-benzylpyrrolidine[64] (18.37 g, 0.114 mol) were combined according to the general procedure to give a mixture (4:1, GLC) of amines **78a** and **78b** (20.7 g, 69%). This mixture was epimerized by heating in 100 mL of Me_2SO and 50 mL of 10 N NaOH at 110 °C for 3.5 h. The reaction mixture was cooled and partitioned between water and methylene chloride. The organic layer was washed three times with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to give amines **78a** and **78b** (58:42, GLC). The amines were separated by preparative HPLC (ethyl acetate/hexane, 1:1) to afford **78a** (6.7 g) and **78b** (5.4 g). Amine **78a** was purified as an HBr salt (ethanol) to give white crystals (6.5 g): mp 248–255 °C; IR ν_{max} 2573, 1454 cm^{-1}; ^{1}H NMR δ 1.9–3.4 (m, 8 H), 3.6–4.2 (m, 3 H), 5.2 (d, 1 H, J = 10 Hz), 6.45 (d, 1 H, J = 6 Hz, 6.8–7.4 (m, 8 H, arom). Anal. C, H, N. Likewise, **78b** was purified as an HBr salt (ethanol) to give white crystals (4.54 g): mp 285–290 °C; IR ν_{max} 2577, 1452 cm^{-1}; ^{1}H NMR δ 1.7–2.7 (m, 4 H), 2.7–3.9 (m, 6 H), 4.2 (m, 1 H), 5.1 (dd, J = 4.5, 10.5 Hz, H_{11a}), 6.7 (m, H_7), 6.9–7.3 (m, 8 H, arom). Anal. C, H, N.

Preparation of Targets via the Mandelic Acid Route. General Procedure. The mandelic acid (0.10 mol) and 2-arylpyrrolidine (0.10 mol) were combined in 300 mL of xylene. The reaction mixture was refluxed while the water produced was collected with a Dean–Stark trap. After 40 h, the solvent was evaporated in vacuo to give the crude amido alcohols (two diastereomers), which were combined with PPA (150 g). The reaction was stirred on a steam bath for 1 h, poured into 500 mL of water, and extracted with methylene chloride. The organic layer was washed once with water and once with saturated brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude lactams. The lactams may be separated by preparative HPLC or epimerized with K_2CO_3 in refluxing aqueous Me_2SO to enhance the ratio for trans isomer prior to reduction to amines. For reduction, the lactam (0.05 mol) in 20 mL of dry THF was added to 1 M borane–THF (0.125 mol) at 0 °C. The reaction was refluxed for 1 h, cooled with ice, quenched with 25 mL of water, and acidified with 40 mL of 12 N HCl. Most of the THF was distilled and the residual aqueous solution was refluxed for 15 min. The solution

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was cooled, made alkaline with 3 N NaOH, and extracted with methylene chloride. The organic layer was washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to yield crude amine. If an isomeric mixture of lactams was reduced, the resultant amines were separated by preparative HPLC.

Example 1. 1,2,3,4,6,10b-Hexahydro-6-(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline (10a and 10b). 4-Methoxymandelic acid (26 g, 0.143 mol) and 2-phenylpyrrolidine (21 g, 0.143 mol) were reacted according to the general procedure to give a mixture of lactams (34.5 g, 82%, α/β = ca. 3:1), which was separated by preparative HPLC. The faster eluting isomer (8.8 g, 0.03 mol) was reduced with borane–THF (75 mL, 0.075 mol) to give amine **10a**. This amine was purified as an HBr salt (methanol/2-propanol): white crystals (5.66 g), mp 202.5–204 °C; IR ν_{max} 1515, 1256 cm^{-1}; ^1H NMR δ 2.0–2.8 (m, 4 H), 3.3–4.3 (m, 4 H), 3.8 (s, 3 H, CH_3), 5.2 (m, H_{10b}), 6.8–7.3 (m, 8 H, arom). Anal. C, H, N. The slower eluting lactam (5.5 g, 0.019 mol) was reduced with borane–THF (50 mL, 0.050 mol) to furnish amine **10b** (4.5 g). The HBr salt was prepared and recrystallized (methanol/2-propanol) to give white crystals (3.0 g): mp 241–244 °C; IR ν_{max} 1512, 1244 cm^{-1}; ^1H NMR δ 2.1–2.4 (m, 3 H), 2.6–3.7 (m, 4 H), 3.8 (s, 3 H, CH_3), 4.05 (m, 1 H), 4.6–5.1 (m, 2 H), 6.7–7.3 (m, 8 H, arom). Anal. C, H, N.

Example 2. 1,2,3,5,6,10b-Hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinolin-6-ol (62a and 62b). Mandelic acid (25.85 g, 0.17 mol) and 2-phenylpyrrolidine were reacted according to the general procedure to give a mixture (α/β = 7:3, GLC) of lactams (45.3 g). A portion of this material (25 g, 0.085 mol) was dissolved in 500 mL of dry THF under an inert atmosphere and the solution was cooled to 5 °C. Sodium hexamethyldisilazide (33 g, 0.18 mol) was added. After 10 min, dry oxygen was passed through the solution for 30 min and stirring was continued for 1 h. The solution was evaporated in vacuo to an oil, which was partitioned between CH_2Cl_2 and aqueous sodium sulfite. The organic layer was washed once with water and once with brine, dried ($MgSO_4$), and evaporated in vacuo to give a mixture of crude hydroxy lactams, as an orange oil (26 g, 98%). This oil was crystallized slowly from ethyl acetate to give a single hydroxy lactam (3.9 g, 0.014 mol), which was reduced with borane–THF (55 mL, 0.055 mol). Methanol was used to work up this reduction because various acidic workups led to dehydration or decomposition of the product. Methanol (50 mL) was added to the cold borane reaction mixture. After 30 min of stirring at 23 °C, the solution was evaporated in vacuo to give crude solid **62b**. This was converted to a fumarate salt and recrystallized (ethanol) to give white crystals (3.0 g): mp 178.5–181 °C; IR ν_{max} 3400, 1600 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.7–2.1 (m, 3 H), 2.5–3.5 (m, 5 H), 3.80 (m, 1 H, H_{10b}), 6.55 (s, 2 H), 6.9–7.5 (m, 9 H, arom). Anal. C, H, N. The filtrate from the ethyl acetate crystallization was evaporated in vacuo to an oil, which was separated by preparative HPLC (ethyl acetate/hexane, 1:1). The other isomeric hydroxy lactam (faster eluting, 10 g) was reduced with borane–THF and worked up (methanol), as above. The crude amine **62a** was converted to an HBr salt (2-propanol), which was then washed once with ethyl acetate and recrystallized (methanol) to give white crystals (3.4 g): mp 211.5–212 °C; IR ν_{max} 3335, 1448 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.0–3.0 (m, 4 H), 3.6–4.0 (m, 4 H), 4.95 (m, 1 H, H_{10b}), 6.9–7.5 (m, 9 H, arom). Anal. C, H, N.

1,2,3,5,6,10b-Hexahydro-6-fluoro-6-phenylpyrrolo[2,1-*a*]isoquinoline (63a and 63b). The mixture of crude hydroxy lactams (39 g, 0.14 mol), prepared above, in 100 mL of dry methylene chloride was added slowly (45 min) to (diethylamino)sulfur trifluoride (22.5 g, 0.14 mol) in 70 mL of dry methylene chloride at −75 °C under an inert atmosphere. The reaction mixture was allowed to warm to 0 °C, whereupon water (200 mL) was added with ice-bath cooling. The organic layer was separated and washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to give crude solid fluoro lactams (38 g, 98%). This solid was recrystallized from ethyl acetate (100 mL) to give only one fluoro lactam (7.9 g). This lactam (6.4 g, 23 mmol) was reduced with borane–THF (95 mL, 95 mmol) and worked up with 100 mL of methanol (reflux for 15 min). The solvent was evaporated in vacuo to an oil, which was partitioned between ether and 1 N HCl. The aqueous solution was made alkaline with 3 N NaOH and extracted with methylene chloride. The organic phase was washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to give crude oily amine **63b** (4.7 g, 77%). The product was converted to an HCl salt (ether) and recrystallized (2-propanol) to give white crystals (2.4 g): mp 192–193 °C; IR ν_{max} 1450 cm^{-1}; ^1H NMR (360 MHz; free base) δ 1.75–1.99 (m, 3 H), 2.42 (m, 1 H), 2.62 (dd, 1 H, J = 8, 17 Hz), 3.0 (m, 1 H), 3.09 (dd, H_{5a}, J = 11.2, J_{HF} = 13.3 Hz), 3.44 (dd, H_{5e}, J = 11.2, J_{HF} = 7.0 Hz), 3.56 (m, 1 H), 7.2–7.44 (m, 9 H, arom). Anal. ($C_{18}H_{18}FN$·HCl·0.3C_3H_8O) C, H, N. The filtrate from the ethyl acetate recrystallization (above) was separated by preparative HPLC (ethyl acetate/hexane, 1:2) to give the second fluoro lactam. This lactam (3.0 g, 10.6 mmol) was reduced with borane–THF (50 mL, 0.05 mol) and worked up with methanol (as above) to give crude amine **63a** (2.1 g). The material was purified by preparative HPLC (ethyl acetate/hexane, 1:6) and the product was converted to an HCl salt (2-propanol/ether). The salt was recrystallized again to give a white powdery solid (0.92 g): mp 180–181 °C; IR ν_{max} 1451 cm^{-1}; ^1H NMR (360 MHz; free base) δ 1.9–2.07 (m, 3 H), 2.42–2.51 (m, 2 H), 2.82 (dd, H_{5a}, J = 13.2, J_{HF} = 33.8 Hz), 3.27 (m, 1 H), 3.36 (m, 1 H), 3.67 (dd, H_{5e}, J = 13.2, J_{HF} = 18.4 Hz), 7.06–7.37 (m, 9 H, arom). The large $^3J_{HF}$ value of 33.8 Hz is connected with an anti H–F orientation, indicative of structure **63a** with equatorial phenyl and axial fluoro groups. Anal. C, H, N.

Mercuric Acetate Oxidation Route. General Procedure. The appropriate isomeric mixture of hexahydropyrrolo[2,1-*a*]isoquinolines (40 mmol) was dissolved in 150 mL of 5% acetic acid and a solution of mercuric acetate (62 g, 0.195 mol) in 400 mL of 5% acetic acid was added with stirring. The reaction mixture was placed on a steam bath, stirred for 2 h, and cooled in an ice bath. A tan solid was filtered and discarded. To the filtrate was added thioacetamide (25.7 g, 0.34 mol) and the mixture was placed on a steam bath for 45 min (**CAUTION**: H_2S is generated). The reaction mixture was cooled in ice, filtered to remove the mercuric sulfide, and treated with 35 mL of 48% hydriodic acid. After the mixture was allowed to stand at 0 °C for 1–2 days, the iminium iodide was filtered and dried in air.

Example 1. 6-(4-Chlorophenyl)-1,2,3,5,6,10b-hexahydro-10b-methylpyrrolo[2,1-*a*]isoquinoline (64a and 64b). A mixture of amines **22a** and **22b** (19.5 g, 0.069 mol), prepared according to the mandelic acid procedure, was slurried in 300 mL of 5% acetic acid and mercuric acetate (111 g, 0.35 mol) in 700 mL of 5% acetic acid was added. The solution was stirred at 100 °C for 2 h, cooled in an ice bath, and filtered. Thioacetamide (45 g, 0.60 mol) was added to the filtrate and the mixture was heated at 100 °C for 45 min (H_2S!). The mixture was cooled in an ice bath, filtered, and treated with 50 mL of 48% HI. After the mixture was allowed to stand at 0 °C for 48 h, the yellow solid, iminium iodide salt (16.1 g, 58%) was collected and dried. This salt was suspended in 400 mL of dry THF at −70 °C and methylmagnesium bromide in ether (2.85 M, 18 mL, 0.050 mol) was added. The solution was stirred at −70 °C for 1 h and then stirred at ambient temperature for 3 h. The reaction mixture was poured into 200 mL of cold 5% H_2SO_4, made alkaline with 10% NaOH, and extracted with methylene chloride. The organic layer was washed once with water and once with brine NaCl, dried (K_2CO_3), and evaporated in vacuo to furnish crude **64a** and **64b** (11.2 g, 95%, ca. 1:1). After preparative HPLC failed to separate these isomers, amine **64b** was selectively crystallized as a fumarate salt from 2-propanol. Recrystallization (2-propanol) afforded pure **64b** fumarate salt (6.0 g): mp 145–150 °C; IR ν_{max} 1707 (C=O), 1568 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.36 (s, CH_3), 1.8–2.5 and 2.7–3.5 (m, 8 H, aliph), 4.32 (dd, H_6, J = 3.5, 9 Hz), 6.58 (s, 2 H), 6.6–7.5 (m, 8 H, arom). Anal. ($C_{19}H_{20}NCl$·$C_4H_4O_4$·0.3C_3H_8O) C, H, N. The filtrates from the fumarate salt isolation were combined and basified. Amine **64a** was isolated and purified as a perchlorate salt (2-propanol). Recrystallization (methanol) gave pure **64a** perchlorate (2.63 g): mp 244–246 °C; IR ν_{max} 1495, 1115 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.82 (s, CH_3), 1.5–2.5 (m, 4 H), 3.2–3.8 (m, 4 H), 4.73 (dd, H_6, J = 8 Hz), 6.76 (dd, H_7), 7.0–7.7 (m, 7 H, arom). Anal. C, H, N.

Example 2. *trans*-1,2,3,5,6,10b-Hexahydro-5-phenylpyrrolo[2,1-*a*]isoquinoline (69b). According to the general procedure, highly enriched *cis*-1,2,3,5,6,10b-hexahydro-5-phenylpyrrolo[2,1-*a*]isoquinoline (10.5 g, 42 mmol, **69a**, prepared via the acyliminium route[6]) was reacted with mercuric acetate (62 g, 0.19 mol). Workup gave the iminium iodide (6.8 g), a portion

of which (6.2 g) was converted to enamine (probably a mixture of positional isomers) by treatment with methylene chloride and 20% NaOH at 0 °C. The organic layer was dried (K_2CO_3) and evaporated in vacuo to give a brown oil (5.0 g), which was dissolved in 25 mL of ethanol and 5 mL of triethylamine. This solution was shaken with platinum (freshly prepared from 0.25 g of platinum dioxide under a hydrogen atmosphere) at 45 psig of hydrogen on a Parr apparatus for 4 h. The platinum was filtered and the filtrate was evaporated in vacuo to give a brown oil (3.6 g). The HBr salt was prepared from 2-propanol and 48% HBr and was recrystallized from methanol/2-propanol to give analytically pure white crystals of **69b**·HBr (3.55 g): mp 264–268 °C; IR ν_{max} 2573, 1460 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6–3.6 (m, 8 H), 4.7–5.4 (m, 2 H, H_5 and H_{10b}), 7.2–7.8 (m, 9 H, arom), 10.7 (br s, 1 H, NH^+). Anal. C, H, N.

Preparation of Phenols by Demethylation. Method A. Boron Tribromide. General Procedure. The methyl ether (0.10 mol) in methylene chloride was cooled to −70 °C (dry ice/acetone) and 1 M boron tribromide in methylene chloride (0.125 mol) was added slowly. The solution was stirred at −70 °C for 1 h and then at room temperature for 3 h. With ice-bath cooling, 50 mL of 2-propanol was added, which precipitated a solid. This HBr salt of the product amine was filtered and purified by recrystallization.

Example. *trans*-4-(1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)phenol (11b). *trans*-1,2,3,5,6,10b-Hexahydro-6-(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline hydrobromide (**10b**·HBr, 3.5 g, 9.7 mmol) was suspended in 25 mL of methylene chloride and treated with the boron tribromide solution (12.5 mL, 12.5 mmol), according to the general procedure. Workup gave crude **11b**·HBr (3.28 g, 97%), which was recrystallized from methanol to furnish pure white crystals (2.7 g): mp 257–260 °C; IR ν_{max} 3284, 1515 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.90–2.30 (m, 3 H), 2.7 (m, 1 H), 3.1–3.9 (m, 4 H), 4.38 (dd, H_6, J = 6, 12 Hz), 4.83 (m, H_{10b}, 1 H), 6.6–7.4 (m, 8 H, arom), 9.42 (s, 1 H), 10.8 (br s, 1 H, NH^+). Anal. C, H, N.

Method B. Hydrobromic Acid. General Procedure. The aryl methyl ether hydrobromide salt (0.010 mol) was combined with 40% hydrobromic acid (2.82 mL, 0.025 mol) in 75 mL of glacial acetic acid and heated at reflux for about 4 h with stirring under nitrogen. After cooling, the phenol product (as the HBr salt) crystallized either directly or following dilution with ether.

Example. 1-(*trans*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzene-3,4-diol (19b). *trans*-1,2,3,5,6,10b-Hexahydro-6-(3,4-dimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline hydrobromide (**18b**·HBr, 5.10 g, 0.013 mol) was combined with 48% hydrobromic acid (3.66 mL, 0.033 mol) in 100 mL of glacial acetic acid and the mixture was heated at reflux for 26 h with stirring under nitrogen. After cooling, the reaction was diluted with ca. 300 mL of ether, causing the diol product, **19b**·HBr, to crystallize. The salt was twice recrystallized (methanol/*tert*-butyl alcohol) to afford light gray crystals (2.85 g, 61%): mp 244–248 °C; IR ν_{max} 3300 (OH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.8–4.1 (m, 8 H), 4.2–4.5 (m, 1 H), 4.6–5.0 (m, 1 H), 6.4–7.5 (m, 7 H), 8.9 (s, 1 H). Anal. C, H, N.

1,4,5,9b-Tetrahydro-5-phenyl-2*H*-azeto[2,1-*a*]isoquinoline (77a and 77b). A mixture of the monoethyl ester of malonic acid (8.6 g, 0.06 mol) and 3,4-dihydro-4-phenylisoquinoline[65] (10 g, 0.05 mol) was stirred in a preheated oil bath (120 °C) for 45 min to give the ethyl 1-acetate derivative (14.0 g, 0.05 mol, 99%), as a pale yellow syrup.[66a] To a suspension of $LiAlH_4$ (5.4 g, 0.14 mol) in dry ether (140 mL) was added to solution of this product in 90 mL of ether. The reaction mixture was stirred for 45 min and cautiously hydrolyzed with water (5.4 mL), 15% sodium hydroxide (10.8 mL), and water (10.8 mL). The solids were filtered, and the filtrate was washed with 3 N NaOH, dried ($MgSO_4$), and concentrated. The pale yellow syrup was purified by chromatography (Waters prep HPLC, ethyl acetate/hexane/methanol, 8:2:1) to give the corresponding amino alcohol (7.2 g, 60%), as a syrup that crystallized slowly on standing to soft waxy solid. Part of the material was converted to an HBr salt (2.8 g, 0.008 mol), which was combined with triphenylphosphine (2.24 g, 0.008 mol) in benzene (30 mL) and dimethylformamide (60 mL) and then treated dropwise with diethyl azodicarboxylate (1.4 g, 0.008 mol).[66b] The mixture was stirred for 3.5 h under argon and concentrated in vacuo. The resultant syrup was treated with 3 N NaOH and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The syrup was chromatographed (preparative HPLC, ethyl acetate/hexane/methanol, 8:2:1) to give cis and trans diastereomeric azetidines, **77a** and **77b**, in a 1:2 ratio (0.22 g of **77a** and 0.39 g of **77b**; 34% yield):[67] ^1H NMR (90 MHz, **77a**) δ 1.9 (m, 1 H), 2.9–3.0 (m, 3 H), 3.5 (m, 2 H), 4.3 (dd, J = 5.3, 10.8 Hz), 4.9 (dd, J = 4, 8 Hz), 6.7–7.3 (m, 9 H, arom); ^1H NMR (90 MHz, **77b**) δ 2.4 (m, 1 H), 2.7–3.5 (m, 4 H) 3.6–3.8 (m, 1 H), 4.0 (dd, 1 H, J = 4.0, 10.4 Hz), 5.1 (dd, 1 H, J = 6, 7 Hz), 6.6–7.4 (m, 9 H, arom.). Both compounds were purified as fumaric acid salts, each of which was recrystallized from 2-propanol: mp (**77a** salt) 145–146 °C, mp (**77b** salt) 163–164 °C. Anal. (salts of **77a** and **77b**) C, H, N.

4-(*trans*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzonitrile (46b). A 4:1 mixture of *cis*- and *trans*-6-(4-bromophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (from the styrene oxide route; 35.2 g, 0.107 mol), copper(I) cyanide (19.2 g, 0.215 mol), and tetrakis(triphenylphosphine)palladium(0) (1.00 g, 0.87 mmol) were combined in 107 mL of *N*,*N*-dimethylacetamide and heated at reflux for 17 h with stirring under argon. After cooling to 23 °C, the reaction mixture was poured into 1 L of concentrated ammonium hydroxide and extracted four times with 250 mL of ether. The combined ethereal extracts were washed three times with 250 mL of brine, dried (K_2CO_3), and concentrated in vacuo to give a mixture of crude cis and trans benzonitriles, as a dark brown oil (22.6 g, 77%). The isomers were separated via preparative HPLC ($CHCl_3$) to yield the cis (**46a**, 7.19 g) and trans compounds (**46b**, 3.50, slower eluting component). The HCl salt of the trans isomer (**46b**) was recrystallized twice (methanol) to afford off-white crystals (2.31 g): mp 271–276 °C. IR ν_{max} 2228 (CN) cm^{-1}; ^1H NMR (CD_3OD) δ 2.2–2.4 (m, 3 H), 2.8–3.0 (m, 1 H), 3.4–3.6 (m, 2 H), 3.6–3.8 (m, 1 H), 3.8–4.0 (m, 1 H), 4.6 (dd, 1 H), 6.75 (d, 1 H), 7.2–7.9 (m, 7 H). Anal. C, H, N.

2-(*trans*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzonitrile (47b). A 6:1 mixture of *cis*- and *trans*-6-(2-bromophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**35a** and **35b**; from the styrene oxide route; 20.1 g, 0.061 mol), copper(I) cyanide (21.9 g, 0.244 mol), and tetrakis(triphenylphosphine)palladium(0) (3.68 g, 0.0032 mol) were combined in 80 mL of DMF and heated at 100 °C for 2 days and 120 °C for 2 days, with stirring under argon. The reaction was worked up as described above to give a mixture of crude cis and trans benzonitriles, as a dark brown oil. The isomers were separated via preparative HPLC (hexanes/ethyl acetate, 70:30) to give the cis (**47a**, 2.74 g) and trans (**47b**, 0.55 g, faster eluting component) isomers. The HCl salt of the trans isomer (**47b**) was recrystallized once from THF and once from acetonitrile to afford 0.227 g of light gray crystals: mp 216–220 °C; IR ν_{max} 2208 (CN) cm^{-1}; ^1H NMR δ 2.1–4.9 (m, 9 H), 5.1 (dd, 1 H), 6.7 (d, 1 H), 7.2–7.9 (m, 7 H), 13.6 (s, 1 H). Anal. C, H, N.

4-(*trans*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzamide (57b). 4-(*cis*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzonitrile (**46a**) (7.18 g, 0.026 mol) and finely ground potassium hydroxide (5.43 g, 0.082 mol, 85% assay) in 75 mL of *tert*-butyl alcohol and were heated at reflux for 45 min with stirring. After cooling to 23 °C, the reaction mixture was diluted with 500 mL of brine and extracted three

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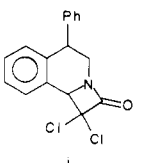
(66) (a) Cava, M. P.; Pelletier, J. C. *Tetrahedron Lett.* **1985**, *26*, 1259. (b) Sammes, P. G.; Smith, S. *J. Chem. Soc., Perkin Trans. 1*, **1984**, *2415*.

(67) We also tried to prepare **77** via β-lactam i; however, double dechlorination could not be effected with Zn in acetic acid or with n-Bu_3SnH.



i

times with 200 mL of chloroform. The combined chloroform extracts were washed twice with 200 mL of brine, dried (K_2CO_3), and concentrated in vacuo to provide the crude cis benzamide (**57a**), as a bluish-green foam (7.02 g, 92%). This material was combined with K_2CO_3 (20.6 g, 0.149 M) in 100 mL of Me_2SO and 10 mL of water and heated at reflux for 1.5 h with stirring under argon. After cooling, the reaction mixture was diluted with 600 mL of water and extracted three times with 200 mL of methylene chloride. The combined extracts were washed three times with water, dried (K_2CO_3), and concentrated in vacuo to yield a mixture of crude cis and trans benzamides, as a yellowish-brown solid (6.50 g, 95%). The isomers were separated via preparative HPLC (chloroform/methanol, 98:2) to afford the cis (57a, 31.2 g) and trans isomer (**57b**, 1.82 g, slower eluting component). The latter was converted to a fumarate salt and recrystallized twice (methanol/2-propanol) to give of white crystals (1.6 g): mp 191–196 °C; IR ν_{max} 1669 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6–2.0 (m, 3 H), 2.3–2.6 (m, 2 H), 2.8–3.1 (m, 3 H), 3.4–3.5 (m, 1 H), 4.3 (dd, 1 H), 6.6 (s, 1 H), 6.8 (d, 1 H), 7.0–8.0 (m, 9 H). Anal. ($C_{19}H_{20}N_2O$·0.5$C_4H_4O_4$·0.12H_2O) C, H, N, H_2O.

2-(1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzoic Acid (58a and 58b). 2-(*cis*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzamide (from nitrile **47a**; 0.730 g, 2.5 mmol) was combined with 25 mL of 6 N HCl and heated at reflux for 4 h with stirring under argon. The hydrochloride salt of **58a** formed on standing at 23 °C for 18 h. The salt was filtered and recrystallized (acetonitrile/water) to give beige crystals (0.74 g, 87%): mp 165–168 °C; IR ν_{max} 1706 (C=O) cm^{-1}; ^1H NMR δ 1.8–5.4 (m, 10 H), 5.5–5.7 (m, 1 H), 6.8 (d, 1 H), 6.9 (d, 1 H), 7.1–7.5 (m, 5 H), 8.1 (d, 1 H), 12.2 (s, 1 H, NH^+). Anal. ($C_{19}H_{19}NO_2$·HCl·0.67H_2O·0.1C_2H_3N) C, H, N, H_2O. Likewise, 2-(*trans*-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzamide (from nitrile **47b**; 0.410 g, 1.4 mmol) was treated as described above and recrystallized from water to give the hydrochloride salt of **58b** (0.358 g, 77%), as white crystals: mp 250–260 °C dec; IR ν_{max} 1702 (C=O) cm^{-1}; ^1H NMR δ 1.9–5.4 (m, 8 H), 5.6–5.9 (m, 1 H), 6.6–8.3 (m, 8 H), 12.4–13.2 (m, 2 H). Anal. C, H, N.

***trans*-1,2,3,5,6,10b-Hexahydro-6-[4-(methylsulfonyl)phenyl]pyrrolo[2,1-*a*]isoquinoline (50b).** *trans*-1,2,3,10b-Tetrahydro-6-[4-(methylthio)phenyl]pyrrolo[2,1-*a*]isoquinolin-5(6*H*)-one (2.1 g, 7 mmol; prepared via the mandelic acid route and purified by preparative HPLC) in 25 mL of methylene chloride was added dropwise to a mixture of *m*-chloroperbenzoic acid (2.4 g, 14 mmol) and 50 mL of methylene chloride at 0 °C and stirred for 4 h. The solution was washed once with 1 N NaOH, dried ($MgSO_4$), and evaporated in vacuo to an oily sulfonyl lactam (2.77 g). This oil in 100 mL of dry THF was added to 30 mL of BH_3·THF (1 M, 30 mmol) at 0 °C and the reaction mixture was stirred at 23 °C for 4 h. The reaction mixture was quenched by addition of 25 mL of water, followed by 30 mL of 12 N HCl; then it was heated on a steam bath for 15 min. The solution was cooled in an ice bath, made alkaline with 3 N NaOH, and extracted with methylene chloride. The organic layer was dried (K_2CO_3) and evaporated in vacuo to an oil (4.67 g). The HCl salt was recrystallized (2-propanol) to give pure solid **50b**·HCl (0.95 g): mp 283–290 °C; IR ν_{max} 1615, 1372, 1277 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.9–2.8 (m, 4 H), 3.26 (s, 3 H), 3.0–3.8 (m, 4 H), 4.5–5.0 (m, 2 H), 6.6–8.0 (m, 8 H, arom). Anal. ($C_{19}H_{21}NO_2S$·HCl·0.12C_3H_8O) C, H, N.

***N*-[4-(*cis*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)phenyl]-*N'*-(4-methoxyphenyl)urea (55a).** 4-(*cis*-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)-benzenamine, **52a** (350 mg, 1.325 mmol, prepared from 4-nitrostyrene oxide and 2-phenylpyrrolidine, then standard H_2/PtO_2 reduction of the nitro group), and 4-methoxyphenyl isocyanate (207 mg, 1.39 mmol) were combined in 7 mL of methylene chloride under argon and stirred for 24 h. The solution was evaporated in vacuo to a solid (650 mg), which was chromatographed on a column of Silicar CC-7 (20 g) using ethyl acetate/methanol (10:1). The white solid (350 mg) was recrystallized (ethanol) to give pure **55a** (250 mg): mp 181–182 °C; IR ν_{max} 1661, 1651, 1602, 1514, 1235 cm^{-1}; ^1H NMR (360 MHz) δ 1.7–2.03 (m, 4 H), 2.34–2.54 (m, 2 H), 2.60 (dd, 1 H, J = 11 Hz), 3.10 (m, 1 H), 3.38 (dd, 1 H, J = 6.4, 11.7 Hz), 3.50 (dd, 1 H), 3.76 (s, 3 H), 4.32 (dd, H_6, J = 6.6, 10.3 Hz), 6.6–7.3 (m, 12 H, arom). Anal. C, H, N.

***trans*-6-(4-Ethynylphenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (45b).** 4-Iodobenzaldehyde (100.1 g, 0.432 mol) was converted to 4-iodostyrene oxide (71.2 g, 67%) according to the literature procedure,[53] but by using benzyltriethylammonium chloride (3.94 g, 0.017 mol) instead of tetrabutylammonium iodide. The crude residue was purified by Kugelrohr distillation (25–125 °C (0.15 torr)) to give 65.0 g (61%) of a white crystalline solid (mp 36–41 °C, 63% pure by ^1H NMR). This crude styrene oxide was reacted with 2-phenylpyrrolidine according to the general procedure to give 34.5 g (65%) of a 4.4:1 mixture of *cis*- and *trans*-1,2,3,5,6,10b-hexahydro-6-(4-iodophenyl)pyrrolo[2,1-*a*]isoquinolines, which was epimerized with NaOH in aqueous Me_2SO to provide 28.5 g (88%) of a 1.4:1 mixture of cis and trans diastereomers. The isomers were separated via preparative HPLC (chloroform/ethyl acetate, 85:15) to afford the cis (13.98 g) and trans isomer (8.53 g). The latter amine (0.0227 mol) was combined with copper(I) iodide (0.22 g, 1.14 mmol), tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol) and (trimethylsilyl)acetylene (3.85 mL, 0.027 mol) in 45 mL of degassed triethylamine and the reaction mixture was stirred under argon at 25 °C. After 18 h, the triethylamine was evaporated in vacuo and the residue was partitioned between methylene chloride and 1 N NaOH. The basic aqueous layer was extracted, and the combined extracts were washed twice with brine, dried (K_2CO_3), and concentrated in vacuo to yield 8.09 g (100%) of the Me_3Si-protected acetylene. This was combined with potassium carbonate (0.327 g, 0.0024 mol) in 50 mL of methanol and stirred for 40 h under argon at 25 °C. The methanol was evaporated in vacuo and the residue was dissolved in dichloromethane, washed twice with brine, dried (K_2CO_3), and concentrated in vacuo to give 6.27 g (97%) of crude **45b**, as a brown oil. The sample was purified via preparative HPLC (acetone) to give 2.74 g (43%) of an oil, the HCl salt of which was twice recrystallized (methanol) to afford beige crystals (1.9 g): mp 262–265 °C; IR ν_{max} 3191 (C–H), 2480 (C≡C) cm^{-1}; ^1H NMR δ 1.0–4.3 (m, 9 H), 4.7–5.0 (m, 2 H), 6.7–7.7 (m, 8 H), 13.4 (br s, 1 H). Anal. ($C_{20}H_{19}N$·HCl·0.08C_4H_4O·0.05H_2O) C, H, Cl, N, H_2O.

4-Fluoro-β-(4-fluorophenyl)benzeneethanamine.[61] Fluorobenzene (140 g, 2.5 mol) and aminoacetaldehyde diethyl acetal (69 g, 0.52 mol) were combined and cooled in an ice bath. Concentrated sulfuric acid (250 mL) was added, and the mixture was stirred at ambient temperature for 20 h, cooled to 0 °C, and poured into 2.5 L of ice. The solution was extracted once with ether and cooled in ice. Ten percent NaOH (1 L) was added with stirring followed by 250 mL of 50% NaOH to make the solution strongly alkaline. The solution was extracted twice with ether, and the combined extracts were washed once with brine, dried (K_2CO_3), and evaporated in vacuo to give an oily product (49.9 g, 42%). This material may be used for subsequent synthesis. A pure sample of an HCl salt was prepared (2-propanol): mp 236–238 °C; IR ν_{max} 1515 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.50 (d, 2 H, J = 8.0 Hz), 4.47 (t, 1 H, J = 8.0 Hz), 6.9–7.6 (m, 8 H, arom), 8.25 (br s, NH_3^+). Anal. Calcd for $C_{14}H_{13}F_2N$·HCl: C, 62.34; H, 5.23; N, 5.19. Found: C, 62.19; H, 5.19; N, 5.18.

Hexahydro-2-phenyl-1*H*-azepine. Caprolactam (228 g, 2 mol) in 660 mL of benzene was refluxed while dimethyl sulfate (252 g, 2 mol) was added slowly (2.5 h). After 16 h at reflux, the solution was cooled in an ice bath and potassium carbonate (4.41 g) in 400 mL of water was added slowly with stirring. The benzene solution was separated, dried (K_2CO_3), and evaporated in vacuo to an oil (125 g), which was distilled by Kugelrohr (45 °C (3.25 torr)) to give the methyl imidate (84.6 g). This material (81 g, 0.64 mol) was added at once to a solution of phenylmagnesium bromide (450 mL, 3.0 M in ether) under nitrogen at ambient temperature followed by addition of benzene (1 L). The ether was removed by distillation and the benzene solution was refluxed for 4 h. The solution was cooled in an ice batch and $LiAlH_4$ (16.4 g, 0.43 mol) was added portionwise. After 5 h at reflux, the mixture was cooled (ice bath), 100 mL of water was added slowly, and the resultant solution was poured slowly into 2 L of 0.5 N NaOH. The solution was extracted with ether and the organic layer was dried (K_2CO_3) and evaporated in vacuo to a yellow oil (123 g). This oil was distilled by Kugelrohr (75–80 °C (0.2 torr)) to give a clear oil (48 g), which was dissolved in 300 mL of 1 N HCl and washed with ether. The aqueous solution was made alkaline with 50% NaOH and extracted with ether. The organic layer was washed

once with brine, dried (K_2CO_3), and evaporated in vacuo to give hexahydro-2-phenyl-1*H*-azepine (41 g): EI-MS, *m/z* 175 ($M^{\cdot+}$); ^1H NMR δ 1.6–2.1 (m, 8 H), 2.9–3.2 (m, 2 H), 3.7–3.9 (m, 1 H), 7.2–7.4 (m, 5 H), arom).

1,2,3,5,6,10b-Hexahydro-6-(phenylmethyl)pyrrolo[2,1-*a*]isoquinoline (68a and 68b). According to a published procedure,[68] 70 g of lithium diisopropylamide in cyclohexane (23 g of LDA/100 g of solution; 16 g of LDA, 150 mmol) was diluted with 120 mL of dry THF, cooled to −70 °C, and treated with 17.6 g (150 mmol) of phenylacetonitrile in 50 mL of THF (under nitrogen; keeping the temperature at −60 °C with stirring). After 5 min of additional stirring, the orange solution was added via cannula to a solution of 20.2 g (160 mmol) of benzyl chloride in 40 mL of THF at −70 °C with stirring. Addition required 1 h, after which the mixture was stirred for 1 h at −78 °C and 1 h at 23 °C. Water was added, followed by 50 mL of dry ether. The organic layer was rinsed with brine, dried (Na_2SO_4), and concentrated to dryness. The brown residue was distilled by Kugelrohr. Some initial distillate, up to 100 °C (pot temperature) at 0.1 torr, was discarded (5 g of mainly $PhCH_2CN$). The major fraction, collected from 130–145 °C, crystallized to a cream solid (15.7 g, 51%), mp 50–52 °C (lit.[69] mp 57–58 °C; lit.[65] bp 145–145 °C (0.2 torr)). The nitrile (15.5 g, 75 mmol) was reduced with $LiAlH_4$ (6 g) in dry ether (250 mL) and the reaction was worked up in a conventional fashion, giving 15.8 g (~100%) of a light tan oil. The amine (15.0 g, 71 mmol) in 50 mL of methylene chloride was combined with 7.1 g (71 mmol) of succinic anhydride in 100 mL of same solvent. The solution was concentrated to dryness and the residue was treated with 200 mL of ethyl acetate and 15.6 g (140 mmol, 14.3 mL) of acetyl chloride. After gentle heating at reflux under a drying tube for 10 h, the reaction mixture was concentrated to dryness, giving 21 g (~100%) of a tan syrup. The crude imide was reduced with $NaBH_4$ (10.5 g, powder) and methanesulfonic acid in absolute ethanol to afford a tan oil (22 g), which was chromatographed on a dry column of silica gel (800 g; ethyl acetate/hexane, 3:2) to yield 9.2 g (38%) of oily ethoxypyrrolidinone (^1H NMR).[6,7] This material was heated in 150 g of PPA at 100 °C for 6 h with occasional stirring and then the mixture was poured into 600 mL of water.[6,7] The methylene chloride extract was rinsed with water, dried ($MgSO_4$), and concentrated to 7.4 g (93%) of tacky beige foam, an ca. 50:50 mixture of **68a** and **68b** by ^1H NMR [**68b**, δH_{5e} 4.18 (J = 12.0 Hz); **68a**, δH_{5e} 3.95 (J = 12, 6 Hz)]; GLC analysis (SE-30 column) gave an α/β ratio of 45:55 (β isomer eluted first), which is analogous to that obtained for an ethyl substituent.[7] The isomers were separated with difficulty by preparative HPLC (ethyl acetate/hexane, 2:1). Fractions enriched in each isomer were concentrated to dryness. Each residue was treated with dry ether, and solids were obtained. Those enriched (≥90% for β, ~70% for α) in one isomer were combined, providing 1.4 g of lactam precursor to **68b** and 1.5 g of precursor to **68a**. The isomers were reduced with borane–THF in the usual way,[6,7] affording **68a** and **68b**. For **68b**, the 1.25 g of off-white oil, which solidified on standing, was converted to a hydrobromide salt in 2-propanol. The product separated slowly to give 1.15 g of small white needles, mp (197–198) 199–200 °C; 99% diastereomerically pure by GLC. For **68a**, the 1.10 g of light tan oil was converted to a fumarate salt in 2-propanol. Recrystallization of the white crystals (0.75 g) from 90% 2-propanol gave 0.50 g of colorless leaflets, mp (188–190) 190–193.5 °C dec; ca. 70% diastereomerically enriched by GLC and ^1H NMR (360 MHz). ^1H NMR for **68b**·HBr (360 MHz) δ 1.9–2.2 (m, 3, 2 H_2 + H_1), 2.4–2.6 (m, 2; q for H_{5a} at δ 2.50, J = 11.6, 11.6, 11.6, Hz, collapsed to t on irradiation of NH^+; dd for one proton of $PhCH_2$ at δ 2.58, J = 10.0, 14.3 Hz), 2.65–2.85 (m, 2; H_1 centered at δ 2.72, H_{3a} centered at δ 2.79, on irradiation of NH^+ a small coupling (~4 Hz) was lost from H_{3a} to furnish a d of t centered at δ 2.80, J = 8.4, 12 Hz), 3.275 (d of t, H_{5e}, J = 3.6, 3.6, 11.6 Hz, the J = 3.6 Hz was lost on irradiation of NH^+), 3.57 (dd, one proton of $PhCH_2$, J = 5.7, 14.3 Hz), 3.80–3.95 (m, 2, H_{3e} + H_6, sharpened on decoupling of NH^+), 4.795 (d of t, H_{10b}, J = 6.8, 10.5 Hz, lost J = 6.8 Hz on irradiation of NH^+, indicating that $J \simeq$ 7.3 Hz is the residual coupling), 7.0–7.4 (m, 9, arom), 12.00 (br s, NH^+). Major structure present is the cis B form (viz., **94**). Anal. (salts of **68a** and **68b**) C, H, N.

1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinoline (72).[70a] 2-Phenethylamine (24.2 g, 200 mmol) and γ-butyrolactone (17.2 g, 200 mmol) were heated together at 100 °C for 30 min, then cooked in a pressure flask at ca. 290 °C, and maintained at that temperature (under nitrogen). After 16 h, the mixture was distilled by Kugelrohr at 0.1 torr. The major fraction, collected at a pot temperature of 135 °C, was a colorless liquid (26.0 g, 69%) (lit.[70b] bp ca. 130 °C (1 torr); the material crystallized on standing, mp ca. 40 °C). A flask charged with 60 g of P_2O_5 powder and 300 mL of 99% tetralin was stirred under nitrogen with a paddle and heated at reflux. The amide (24 g) was added, the reaction was continued for 30 min, and 100 g of P_2O_5 and 200 mL of tetralin were added. After 1 h, the cooled mixture was treated with crushed ice, then filtered, cooled, and basified with cold concentrated KOH (keep cold!). The alkaline mixture was extracted with ether and the extract was rinsed with brine, dried (Na_2SO_4), and concentrated to an orange oil (9.0 g, 38%). The oily enamine was dissolved in 100 mL of absolute ethanol and the solution was treated with 3 g of $NaBH_4$ at 0 °C. Glacial HOAc (2 mL) in 10 mL of ethanol was added slowly. After 10 h, water was added. The mixture was concentrated in vacuo, diluted with water, and extracted with methylene chloride twice. The combined extracts were rinsed with brine, dried (Na_2SO_4), and concentrated to 8.0 g (88%) of mobile liquid. The saccharinate salt was prepared in 50 mL of methanol by using 8.0 g of saccharin. A first crop of 7.1 g was obtained. Recrystallization from 75 mL of ethyl acetate/methanol (1:1) provided 5.65 g of pale tan prisms: mp 155–157 °C; ^1H NMR δ 1.9–4.2 (m, 11, 5 CH_2 + NH), 4.9–5.1 (pseudo t, 1, H_{10b}), 7.0–7.8 (m, 8, arom). Anal. C, H, N.

2-Ethyl-1,2,3,4-tetrahydro-4-phenylisoquinoline (88). 1,2,3,4-Tetrahydro-4-phenylisoquinoline hydrochloride[65] (3.7 g, 15 mmol) was reacted at 0 °C with acetyl chloride (1.26 g, 16 mmol) in the presence of triethylamine (3.25 g, 32 mmol). The crude amide (3.4 g) was reduced in a typical manner with lithium aluminum hydride (1.14 g, 30 mmol) in 50 mL of dry ether to afford 3.5 g of light tan oil. An HBr salt was prepared in 2-propanol (3.8 g) and recrystallization from methanol/ether (4:1) provided a fluffy white solid (3.1 g): mp (247–251) 251–252.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.34 (t, 3, J = 7 Hz), 3.2–3.6 (m, 3), 3.6–3.9 (m, 1, H_4), 4.4–4.8 (m, 3), 6.74 (d, 1, J = 7.5 Hz, H_5), 7.1–7.5 (m, 8, arom), 10.04 (br s, 1, NH^+); there appears to be axial and equatorial *N*-Et salts present. Anal. ($C_{17}H_{19}N$·HBr) C, H, Br.

2-Phenyl-1-(2-phenylethyl)pyrrolidine (89).[71] 2-Phenylpyrrolidine (2.92 g, 20 mmol) was reacted with phenylacetyl chloride in the presence of triethylamine. The crude amide (5.3 g) was reduced with lithium aluminum hydride (2.0 g) in 80 mL of dry ether to obtain 4.2 g of product. A salt was prepared with 2.0 g of fumaric acid in 100 mL of 2-propanol (4.4 g). Recrystallization from 2-propanol gave 3.5 g of off-white, fluffy powder: mp (108–114) 114–123 °C; ^1H NMR ($CDCl_3$/Me_2SO-d_6, 1:1) δ 1.03 (d, 2.5, CH_3 of 2-propanol), 1.5–1.6 (m, 1), 1.7–1.9 (m, 2), 2.05–2.15 (m, 1), 2.2–2.4 (m, 2), 2.5–2.8 (m, 3), 3.25–3.4 (m, 2), 3.78 (m, 0.5, CH of 2-propanol), 6.60 (5, 2, vinyl H), 7.0–7.3 (m, 10, arom). Anal. ($C_{18}H_{21}N$·$C_4H_4O_4$·0.5C_3H_8O·0.3H_2O) C, H, N [H_2O: calcd, 1.34; found, 0.38].

Resolution of *trans*-1,2,3,5,6,10b-Hexahydro-6-[4-(methylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline (48b). Highly diastereomerically enriched amine **48b** (17.7 g, 0.06 mol) and (+)-L-tartaric acid (9.0 g, 0.06 mol) were combined in 300 mL of absolute ethanol, filtered, concentrated to 200 mL, and let cool to ambient temperature. White crystalline solid was filtered (7.2 g), redissolved in 800 mL of hot acetonitrile, and let stand at ambient temperature for 7 days. The crystalline solid was filtered (4.42 g), dissolved in 275 mL of absolute ethanol, and let crystallize slowly at ambient temperature for 2 days to give 2.4 g of white crystals, $[\alpha]^{21}_D$ +54.9° (CH_3OH, *c* 0.244), which by ^1H NMR of the (+)-Mosher acid salt (C_6D_6) was shown to have an enantiomeric excess (ee) of 98%. This salt was converted to the free

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base by partitioning between methylene chloride and aqueous NaOH to give an oil (1.6 g), which was combined with perchloric acid in ethanol to afford crystalline perchlorate salt (1.63 g). One recrystallization from ethanol gave pure crystalline solid (+)-**48b**·$HClO_4$ (1.38 g): mp (186) 189–190 °C; $[\alpha]^{21}_D$ +52.0° (CH_3OH, *c* 0.244); >99% ee by ^1H NMR of the (+)-Mosher acid salt (C_6D_6); IR ν_{max} 1495, 1095 cm^{-1}; ^1H NMR δ 2.1–2.3 and 2.7–4.2 (m, 8 H, aliph), 2.47 (s, 3 H), 4.52 (dd, H_6, J = 4, 12 Hz), 4.95 (dd, H_{10b}), 6.7–7.4 (m, 8 H, arom). Anal. ($C_{19}H_{21}NS$·$HClO_4$) C, H, N. The filtrates from the acetonitrile and absolute ethanol recrystallizations were combined and evaporated in vacuo to a solid, which was partitioned between methylene chloride and aqueous NaOH. The organic layer was dried (K_2CO_3) and evaporated in vacuo to an oil (2.4 g), which was combined with (−)-D-tartaric acid (1.2 g), in 100 mL of absolute ethanol, and let crystallize slowly at ambient temperature for 6 days. Tan crystalline solid was filtered (1.3 g) and partitioned between methylene chloride and aqueous NaOH to afford the oily free base (0.93 g). The perchlorate salt was prepared from perchloric acid (0.44 g, 70%) in ethanol to give crystals (0.88 g). After one recrystallization from absolute ethanol, we obtained pure crystalline (−)-**48b**·$HClO_4$ (0.74 g): mp (180) 184–188 °C: >99% ee by optical rotation, $[\alpha]^{21}_D$ −52.3° (CH_3OH, *c* 0.237); IR ν_{max} 1492, 1301 cm^{-1}; ^1H NMR δ 2.1–2.4 and 2.7–4.3 (m, 8 H), 4.50 (dd, H_6, J = 4.5, 12 Hz), 4.9 (m, H_{10b}), 6.7–7.3 (m, 8 H, arom), 9.1 (br s, 1 H). Anal. ($C_{19}H_{21}NS$·$HClO_4$) C, H, N. (This resolution was also accomplished by recrystallization of the tartrate salt diastereomeric mixture from methanol.)

Resolution of *trans*-6-(2-Chlorophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (24b). Isomerically enriched amine **24b** (**24a**/**24b** = ca. 1:9; 17.0 g, 0.06 mol) and (+)-10-camphorsulfonic acid (13.9 g, 0.06 mol) were combined in 60 mL of hot absolute ethanol, filtered, and let stand at ambient temperature for 20 h. A white solid was filtered (10.3 g) and the filtrate gave a second crop (2.8 g) after being in an ice bath for 3 h. The first crop was recrystallized twice from ethanol to give white solid (4.3 g), mp 222–226 °C. This material was converted to the free base by partitioning between aqueous NaOH and methylene chloride, and evaporation in vacuo gave an oil (2.35 g). The HBr salt was prepared from 48% HBr (1.4 g) and 15 mL of 2-propanol to give pure white needles of (−)-**24b**·HBr (2.6 g): mp 256–259 °C; $[\alpha]^{20}_D$ −15.2° (CH_3OH, *c* 0.302); IR ν_{max} 2567 cm^{-1}; ^1H NMR (360 MHz) δ 2.1–2.4 (m, 3 H), 2.7–4.0 (m, 5 H), 4.7–4.9 (m, 1 H), 5.0 (m, 0.4 H, H_{10b} in conformation A) and 5.3 (m, 0.6 H, in H_{10b} conformation B), 6.7 (d, J = 7.5 Hz, H_7), 6.9–7.5 (m, 7 H, arom), 12.1/12.2 (2 br s, 1 H).[72] Anal. ($C_{18}H_{18}NCl$·HBr) C, H, N. The filtrate from the first crystallization above was evaporated in vacuo to a solid, which was partitioned between aqueous NaOH and methylene chloride. The dried (K_2CO_3) organic layer was evaporated in vacuo to give a solid (8.7 g), which was combined with (−)-10-camphorsulfonic acid (7.0 g, 30 mmol) in ethanol. White crystalline solid was filtered (8.1 g), recrystallized twice from ethanol (50 mL), and converted to free base by partitioning between aqueous NaOH and methylene chloride. The organic layer was dried (K_2CO_3) and evaporated in vacuo to an oil (2.6 g). This oil was combined with 48% HBr (1.55 g) in 15 mL of 2-propanol and kept at 0 °C for 24 h to give pure, white crystalline (+)-**24b**·HBr (3.0 g): mp 257–260 °C; $[\alpha]^{24}_D$ +14.85° (CH_3OH, *c* 0.303); IR ν_{max} 2568 cm^{-1}; ^1H NMR δ 2.1–2.3 (m, 3 H), 2.7–4.1 (m, 5 H), 4.9 (m, 1 H), 5.2 (m, 1 H, H_{10b}), 6.7 (d, J = 7 Hz, H_7), 6.9–7.5 (m, 7 H, arom). Anal. ($C_{18}H_{18}NCl$·HBr) C, H, N.

Resolution of *trans*-1,2,3,5,6,10b-Hexahydro-6-[3-(trifluoromethyl)phenyl]pyrrolo[2,1-*a*]isoquinoline (37b). The amine (7.0 g, 0.022 mol) and (+)-L-tartaric acid (3.31 g, 0.022 mol) were combined in 30 mL of hot ethanol, filtered, and let stand at ambient temperature. After 24 h, white solid was collected (3.6 g). The filtrate gave a second crop of crystals (0.73 g) after another 72 h. These two batches of crystal were combined and recrystallized twice from absolute ethanol (40 mL) to give white crystals (3.25 g) of constant optical rotation, $[\alpha]^{20}_D$ +25.3° (*c* 0.324, CH_3OH). This salt was partitioned between methylene chloride and dilute NaOH, and the organic solution was washed once with water, dried (K_2CO_3), and evaporated in vacuo to an oil (2.1 g). The HCl salt was prepared in methylene chloride by addition of ethereal HCl, and the solution was evaporated in vacuo to a solid. This solid was recrystallized (methylene chloride/ethyl acetate) to give pure, white crystalline (+)-**37b**·HCl (1.85 g): mp 205–208 °C; $[\alpha]^{21}_D$ +18.5° (*c* 0.303, CH_3OH); IR ν_{max} 1334 cm^{-1}; ^1H NMR δ 2.25 (m, 3 H), 2.8–3.1 (m, 3 H), 3.65 (ddd, 1 H), 4.05 (m, 1 H), 4.90 (m, 2 H), 6.7 (d, J = 7 Hz, H_7), 7.1–7.7 (m, 7 H, arom). Anal. ($C_{19}H_{18}NF_3$·HCl·0.25H_2O) C, H, H_2O. The filtrate of the original crystallization was evaporated in vacuo to an oil, which was partitioned between methylene chloride and dilute NaOH. The organic solution was washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to an oil (3.4 g). This oil was combined with (−)-D-tartaric acid (1.61 g, 10.7 mmol) in 15 mL of absolute ethanol. White crystals were filtered (3.88 g) after 2 h at 0 °C. This solid was recrystallized twice from 75 mL of absolute ethanol to afford white crystals (2.72 g) of constant optical rotation, $[\alpha]^{23}_D$ −27.6° (*c* 0.304, CH_3OH). This material was partitioned between methylene chloride and dilute NaOH, and the organic solution was washed once with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to an oil (1.76 g). The HCl salt was prepared from methylene chloride by addition of ethereal HCl, and the solution was evaporated in vacuo to give a white solid. This salt was recrystallized from 2-propanol to give pure, white crystalline (−)-**37b**·HCl (1.20 g): mp 207–209 °C; $[\alpha]^{25}_D$ −20.4° (*c* 0.318, CH_3OH); IR ν_{max} 1333 cm^{-1}; ^1H NMR δ 2.1–2.35 (m, 3 H), 2.75–3.13 (m, 3 H), 3.62 (ddd, 1 H), 3.9–4.1 (m, 1 H), 4.88 (m, 2 H), 6.7 (d, J = 8 Hz, H_7), 7.1–7.65 (m, 7 H, arom). Anal. ($C_{19}H_{18}NF_3$·HCl) C, H.

X-ray Crystallographic Analysis. Crystals of (+)-**24b**·HBr were grown from 2-propanol. A colorless needle, having the dimensions of 0.13 × 0.14 × 0.53 mm, was selected and mounted on a glass fiber with its longest axis parallel to the φ axis of the goniometer. Preliminary data collection was performed with CuKα radiation (λ = 1.541 84 Å) on an Enraf-Nonius CAD4 diffractometer, with a graphite monochromator. For $C_{18}H_{19}BrClN$, M_r 364.72, the orthorhombic cell parameters were established: a = 10.821 (1) Å, b = 11.643 (1) Å, c = 13.187 (2) Å, V = 1661.6 (6) Å^3; d_c = 1.46 g/cm^3 for Z = 4, space group $P2_12_12_1$. Data were collected at 22 °C by using the ω–θ scan technique. Of 1907 unique reflections collected up to 2θ = 156.0°, 1753 had $I > 2\sigma(I)$ and were used for structure analysis (data corrected for Lorentz and polarization factors, but not for absorption). The structure was solved by using the Patterson heavy-atom method, which revealed the position of the Br atom. The remaining atoms were located from subsequent difference Fourier maps. Hydrogen atoms were located and their positions were refined by least-squares analysis (B_{iso} = 5.0 Å^2). Neutral atom scattering factors were taken from Cromer and Weber.[73] Anomalous dispersion effects were included in F_c;[74] the values for f' and f'' were those of Cromer.[75] The absolute configuration was determined (6*R*,10b*R*) by convergence of each enantiomer by using a unit weighting scheme (solution 1: R/R_w = 0.0468/0.0416, ESD = 1.038; solution 2: R/R_w = 0.0385/0.0340, ESD = 0.0848), solution 2 being the proper choice. The final refinement cycle, including 247 variables, converged with $R_1 = \sum(||F_o| - |F_c||)/\sum|F_o|$ = 0.038 and $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum F_o^2]^{1/2}$ = 0.033, and the minimized function was $\sum w(|F_o| - |F_c|)^2$. All calculations were performed on a VAX-11/750 computer by using SDP-PLUS.[76] Various data are collected in the supplementary material.[16] The X-ray structure (Figure 1) shows (+)-**24b**·HBr with a cis fusion of the B and C rings, as pictorialized

(72) The conformations detected here are not due to cis/trans ring fusions, as trans molecules adopt the cis B form to the extent of at least 90%. These conformations are due to hindered rotation about the sp^2–sp^3 bond linking the pendant 2-chlorophenyl group to the isoquinoline network. This was verified by a brief variable temperature study. A rough estimate of the rotational barrier is 16–20 kcal/mol. 360-MHz ^1H NMR spectra of other 2′-substituted compounds also showed such behavior.

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in **94** (cis B arrangement). The 2-chlorophenyl group is in an equatorial position on the tetrahydroisoquinoline half-chair; the N–H is axial and the C_{10b} proton is pseudoequatorial.

Tetrabenazine Antagonism Assay.[77] The effect of the test compound on TBZ-induced decrease in motor activity (sedation) and ptosis was determined in mice. Nonfasted male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18–24 g, were used in this assay. The test compound was administered intraperitoneally 30 min prior to the injection of 32 mg/kg, ip, of TBZ. Control mice were injected with saline 30 min prior to the administration of TBZ. Thirty minutes later, the mice were individually placed in the center of a 12-in. × 24-in. screen raised 6 in. above the bench top and observed for 10 s for the presence of exploratory activity and the degree of bilateral eyelid closure. The presence of normal locomotor activity or exploratory head movements and less than 50% eyelid closure indicated a block of TBZ sedation and ptosis, respectively. Ten mice were used per dosage level of the test compound and in the control group. When the response, sedation, and/or ptosis to TBZ was 90% or less in the control group, the response in the drug treated group was corrected by using Abbott's formula.[78] Four to five dosage levels of the test compounds were used in obtaining an ED_{50} value. ED_{50}'s and 95% confidence limits were calculated by probit analysis.

General Behavioral Effects. The general behavioral effects of selected compounds were observed in mice following intraperitoneal doses of 1, 3, 10, 30, 100, and 300 mg/kg. The mice were held for 4 days following administration of the test compounds. (An estimated LD_{50} range based on lethality count was made on day 4.) Three male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18–24 g, were used per dosage level of compound administered.

Synaptosomal Uptake of NE, DA, and 5-HT. For each experiment, one or more rats (male, albino Wistar) were killed by cervical dislocation. The brain was excised, and the hypothalamus, striatum cerebral cortex, and/or other specified areas were isolated, weighed, and homogenized in either 10 volumes of 0.32 M sucrose or 20 volumes of 0.30 M sucrose buffered to pH 7.6 at 4 °C with 5 mM NaHEPES. A P_2 fraction for each of the brain areas was obtained by the procedure of Gray and Whittaker[79] and was washed once by resuspending it in the previously specified volume of homogenizing fluid. After resedimentation (centrifugation at 11000*g* for 20 min), each P_2 fraction was resuspended in 20–50 volumes of medium comprised as follows: 134 mM NaCl, 4.1 mM KCl, 1.1 mM KH_2PO_4, 1.2 mM $MgCl_2$, 5.5 mM (+)-glucose, 23.6 mM Tris base, 1.3 mM $CaCl_2$, 0.03 mM EDTA–Na_2, 0.1 mM ascorbic acid, and 0.01 mM nialamide. The pH was adjusted to 7.4 at 37 °C with 12 N HCl. In some experiments HEPES (20 mM) was substituted for Tris base, in which case the pH was adjusted to 7.4 at 37 °C with 5 N NaOH.

For each sample, 0.7 mL of either buffered medium described above, 0.1 mL of the test compound solution diluted to 10^{-5} M or less with either the Tris or HEPES buffered medium (or 0.1 mL of medium for control samples), and 0.1 mL of synaptosomal suspension (P_2 fraction) from hypothalamus (NE), striatum (DA), cerebral cortex (5-HT), or other specified region were added to a glass tube immersed in an ice bath. The sample was then gently mixed and transferred to a 37 °C shaking water bath for a 10-min preincubation period (in some experiments the preincubation period was 30 min and in some it was omitted). To initiate the incubation process, 0.1 mL of acidified saline (0.15 M NaCl and 0.01 N HCl) containing 100–300 nM (–)-[^{3}H]norepinephrine, 50–300 nM [^{3}H]dopamine, or 100–200 nM [^{3}H]serotonin was mixed into each sample. Samples were incubated for 3 min (DA), 6 min (NE and 5-Ht), or 10 min (NE). Blank samples were the same as controls except they were incubated in ice water. Incubation was terminated by the addition of 4 mL of ice-cold 0.9% aqueous NaCl. Synaptosomal material was separated from the incubation fluid by suction filtration (Millipore filters, 0.45 or 0.65 μm) and washed once with 4 mL of ice-cold 0.9% saline. Each filter was transferred to a scintillation vial, and tritium levels were measured by standard liquid scintillation counting procedures.

Table VI. Tissue, Ligand, and Agent for Determining Nonspecific Binding in Receptor Binding Assays

receptor	tissue	ligand (concn, nM)[a]	nonspecific determinant (concn, μM)
α_1 adrenergic	cerebral cortex	[^{3}H]WB4104 (0.4)	(–)-NE (100)
α_2 adrenergic	cerebral cortex	[^{3}H]clonidine (0.4)	(–)-NE (10)
dopamine D_1	striatum	[^{3}H]Sch-23390 (0.1)	Sch-23390 (1)
dopamine D_2	striatum	[^{3}H]spiperone (0.05)	(+)-butaclamol (1)
serotonin S_1	cerebral cortex	[^{3}H]serotonin (1)	serotonin (10)
serotonin S_2	cerebral cortex	[^{3}H]ketanserin (0.2)	mianserin (1)
muscarinic	whole cerebrum	[^{3}H]QNB (0.5)[b]	atropine (1)

[a] From New England Nuclear. [b] QNB = quinuclidinyl benzilate.

Binding Assays for Adrenergic α_1, Dopamine D_2, Dopamine D_1, Serotonin S_1, and Serotonin S_2 Receptors. For these assays, a P_2 fraction was prepared from the corpus striatum or cerebral cortex (Table VI). The tissue was homogenized in 20 volumes of cold NaHEPES (20 mM, pH 7.5 at 22 °C) buffered sucrose (0.3 M) solution. To obtain the P_2 fraction, the homogenate was first centrifuged (4–6 °C) at 1000*g* for 10 min and then the resulting supernatant was centrifuged at 48000*g* for 10 min. The pellet (P_2 fraction) was resuspended in 20 volumes of a NaHEPES (20 mM) solution (approximate osmolarity of 30 mosm/L, pH 7.5 at 37 °C) and, except for the adrenergic assay, incubated for 15 min at 37 °C. Particulate material was sedimented by centrifuging for 10 min at 48000*g*. For all assays, the "crude synaptic membrane" fraction was then suspended in the 20 mM NaHEPES solution (no sucrose) such that the volume was 30–100 times the initial tissue weight. For each sample, 2.2 mL of 20 mM NaHEPES (pH 7.5 at 37 °C), 0.1 mL of ^{3}H-ligand (Table VI), 0.1 mL of test compound solution diluted to 10^{-5} M or less in water (for control samples 0.1 mL of water was used), and 0.1 mL of water or other specified solution were placed in polystyrene test tubes. For determination of nonspecific binding, 0.1 mL of a specific binding inhibitor (Table VI) was substituted for 0.1 mL of water. For the 5-HT_1 assay, 0.1 mL of 30 mM glutathione and 0.1 mL of 75 mM $MgCl_2$ were added to each sample. The binding reactin was initiated by adding 0.5 mL of the "synaptic membrane" suspension, mixing the contents, and placing the sample in a 25 °C (adrenergic) or a 37 °C water bath. The samples were incubated for 45 min (D_2 and 5-S_2 assays), 20 min (5-S_1 assay), or 30 min (adrenergic assay). Particulate matter was separated from the incubation fluid via suction filtration through Whatman GF/B glass microfiber filters mounted on either a Millipore 1225 sampling manifold or a Brandel cell harvester. Filters were presoaked in water 0.01% BSA (adernergic assay only). At the end of the incubation period, samples were filtered, immediately followed by two 6-mL washes with ice-cold NaHEPES solution (Brandel cell harvester), or diluted with 10 mL of ice-cold NaHEPES solution, filtered, and then washed once with 10 mL of the same solution (Millipore 1225 manifold). The total time that the synaptic membranes were exposed to the wash solution was less than 20 s. The tritium retained by the filter was subsequently measured by standard liquid scintillation procedures. In some experiments, conditions used in the α_1 assay were similar to the α_2 assay conditions described below.

α_2 Adrenergic Receptor Binding Assay.[16] This assay is a modified version of the procedure used by U'Prichard and Snyder.[80]

Muscarinic Cholinergic Receptor Binding.[16] This assay is based on that of Yamamura and Snyder.[81]

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Analysis of in Vitro and ex Vivo Data. Where concentration–inhibition curves were generated, four to ten concentrations of test compound were employed, each done in duplicate. The percent inhibition of control uptake or specific binding was calculated for each concentration of test compound, and the IC_{50} was determined from a linear least-squares analysis of data transformed into a logit vs. log concentration format. Since IC_{50} values are dependent on radioisotope concentration, we obtained an apparent K_i by using the Cheng–Prusoff equation.[82] Confidence limits were calculated by using Fieller's theorem.

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Supplementary Material Available: Table of 95% confidence limits for data in Tables IV; tables of bond distances, bond angles, torsional angles, and positional and thermal parameters for (+)-**24b**·HBr; a stereoview of (+)-**24b**·HBr and a figure showing the atom numbering scheme; experimental procedures for GABA uptake, α_2 receptor binding, and muscarinic cholinergic receptor binding (17 pages). Ordering information is given on any current masthead page.

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Specific Dopamine D-1 and DA_1 Properties of 4-(Mono- and -dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline and Its Tetrahydrothieno[2,3-*c*]pyridine Analogue

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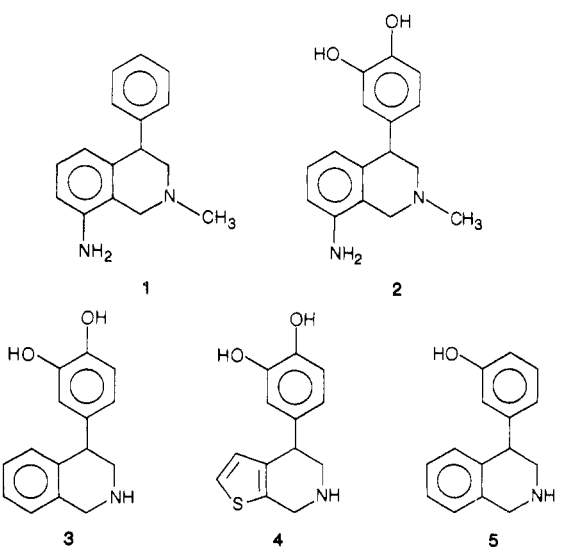
The title compounds were prepared and examined to elucidate further the structure–activity relationships of dopamine agonists related to nomifensine. Two of the compounds, 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline and 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine, have been reported in the patent literature. In stimulation of rat retinal adenylate cyclase, a measure of dopamine D-1 agonist activity, the tetrahydroisoquinoline was about equipotent to dopamine. The thienyl isostere had nearly twice the potency. Both compounds were potent vasodilators in the canine renal artery, producing dilation through stimulation of DA_1 type peripheral dopamine receptors. A monohydroxy analogue, 4-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline, had only slight activity in the cyclase assay and was inactive in the canine renal artery. These results, combined with those from an earlier study, demonstrate that N-alkylation decreases both dopamine D-1 and DA-1 agonist potency, with activity ordered as H > methyl > ethyl > propyl. The results also demonstrate the necessity for the catechol function in this series.

Nomifensine (1) is an antidepressant agent with weak in vivo dopaminergic activity. This action has been attributed to its ability to inhibit dopamine uptake into neuron terminals.[1] Poat et al.[2] showed that, while nomifensine and its 4-hydroxy derivative were devoid of direct dopamine agonist activity, 3′,4′-dihydroxynomifensine (2) exhibited direct dopamine-like agonist properties. Also, 2 shows significant DA_1 agonist activity in the canine renal artery.[3]

It was previously shown[4] that the 8-amino of 2 is not required for dopamine DA_1 agonist activity. The 8-desamino compound (the *N*-methyl derivative of 3) was equipotent to 2. Surprisingly, it was discovered that activity decreased in the *N*-ethyl and *N*-*n*-propyl derivatives. Nichols[5] subsequently proposed that the longer *N*-alkyl group might adopt a pseudoequatorial conformation, forcing the nitrogen lone-pair electrons into a pseudoaxial orientation and out of the position proposed to be necessary for optimum receptor activation.

It was decided to complete the 8-desamino series by the synthesis of the nor compound 3. The corresponding 4-(3′,4′-dihydroxyphenyl)-1,2,3,4-tetrahydrothieno[2,3-*c*]-pyridine (4) and the 3′-monohydroxy compound 5 were set as targets to evaluate the bioisosteric effect of the thienyl and to examine the necessity for the catechol function in this series of agonists, respectively. Compounds 3 and 4 have been reported in the patent literature, but no bio-



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