Dopaminergic and Serotonergic Activities of Imidazoquinolinones and Related Compounds

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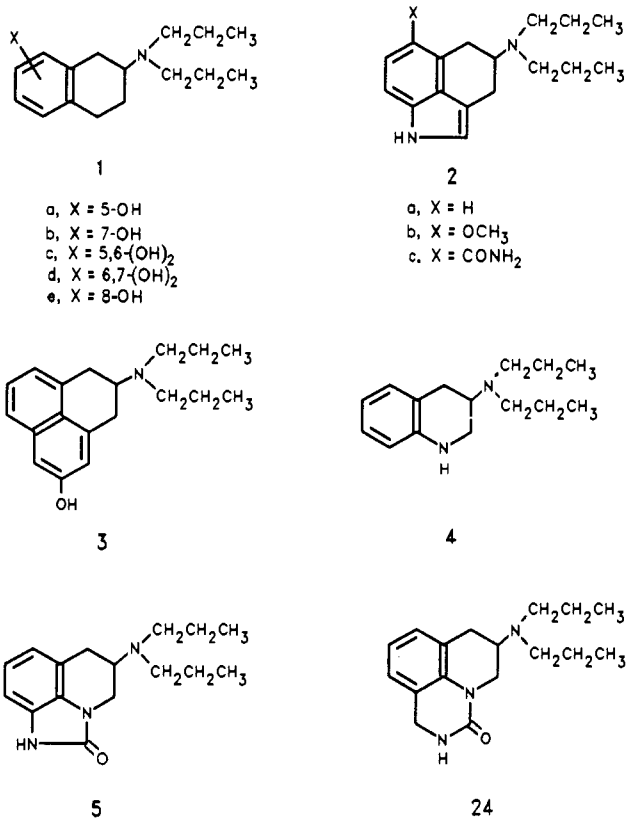
The synthesis of 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (**5**), a potent dopamine D2 agonist showing high dopamine/serotonin ($5HT_{1A}$) selectivity, is described. Dopaminergic activity is associated with the (*R*)-enantiomer of **5**; the (*S*)-enantiomer shows no dopaminergic activity. A series of analogues where the imidazolone ring was modified to various 5- or 6-membered heterocyclic rings were prepared. Some of these compounds showed a combination of dopaminergic and serotonergic activity, while one compound, 6-(dipropylamino)-1,2,6,7-tetrahydro-3*H*,5*H*-pyrido[3,2,1-*ij*]quinazolin-3-one (**24**), was a selective serotonergic agonist. Various analogues of **5** where the dipropylamine substituent was modified were prepared. Most of these showed reduced dopaminergic activity, while several were as potent as **5** at the serotonin $5HT_{1A}$ receptor. Orientations for the new compounds at dopamine and serotonin receptors are proposed and compared with those of other tricyclic ligands known to have high affinity at these receptors.

Introduction

Various cyclic amines which incorporate a phenethylamine structure show dopaminergic and serotonergic activities. These include aminotetralins of structure **1**[1-5] and related tricyclic structures, for example, the benzindoles of structure **2**[6-9] and dihydrophenalenes related to **3**.[10,11] In the case of the aminotetralins, the position of the hydroxyl substituent in the benzene ring has a major effect on activity; compounds **1a-d** (Chart I) show primarily dopaminergic activity,[1-4] whereas **1e** is a selective serotonin agonist.[5] These compounds have played a significant role in the development of dopamine and serotonin receptor models.[12-14] The aminotetrahydroquinoline **4** has been prepared and shows no serotonergic activity,[15] while related 1-acylated products have been reported to possess cardiovascular activity.[16] As part of a program to discover compounds which would be useful as antipsychotic or anxiolytic drugs, we have prepared various tricyclic analogues of **4**, including **5**,[17] a potent dopamine D2 agonist showing high dopamine/serotonin ($5HT_{1A}$) selectivity. In this report, we describe the synthesis of **5** and a series of analogues (Tables I and II) and report their dopaminergic and serotonergic activities as determined with receptor binding assays. We have further characterized active compounds as agonists by determining their effects on catechol and indolamine synthesis and by their effects on firing rates of dopaminergic neurons in the substantia nigra pars compacta and serotonergic neurons in the dorsal raphe nucleus. Several analogues of **5** showed a combination of dopaminergic and serotonergic activities, while one of the compounds (**24**, Chart I) was a selective serotonergic agonist. Orientations of the new compounds at dopamine and serotonin receptors are proposed and compared with those of other tricyclic ligands known to have high affinity at these receptors.

Chart I



Chemical Synthesis

Compound **5** and related imidazoquinolinones were prepared as outlined in Scheme I. Formylation of 3-aminoquinoline with formic acetic anhydride gave **26**. This was reduced using a platinum catalyst to the tetrahydroquinoline and the crude reduction product[18] was formylated to **27**. We were unable to selectively nitrate **27** at the 8-position; direct nitration of **27** gave a 1:1 mixture of the

† Department of Medicinal Chemistry.
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§ Department of CNS Research.

(1) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. Synthesis and Pharmacology of Some 2-Aminotetralins. *J. Med. Chem.* **1975**, *18*, 362-367.
(2) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. Synthesis and Dopaminergic Activity of (±), (+), and (-)-2-Dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. *J. Med. Chem.* **1976**, *19*, 547-549.
(3) Cannon, J. G.; Kim, J. C.; Aleem, M. A.; Long, J. P. Centrally Acting Emetics. 6. Derivatives of β-Naphthylamine and 2-Indanamine. *J. Med. Chem.* **1972**, *15*, 348-350.
(4) Cannon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. J. Cerebral Dopamine Agonist Properties of Some 2-Aminotetralin Derivatives after Peripheral and Intracerebral Administration. *J. Med. Chem.* **1977**, *20*, 1111-1116.

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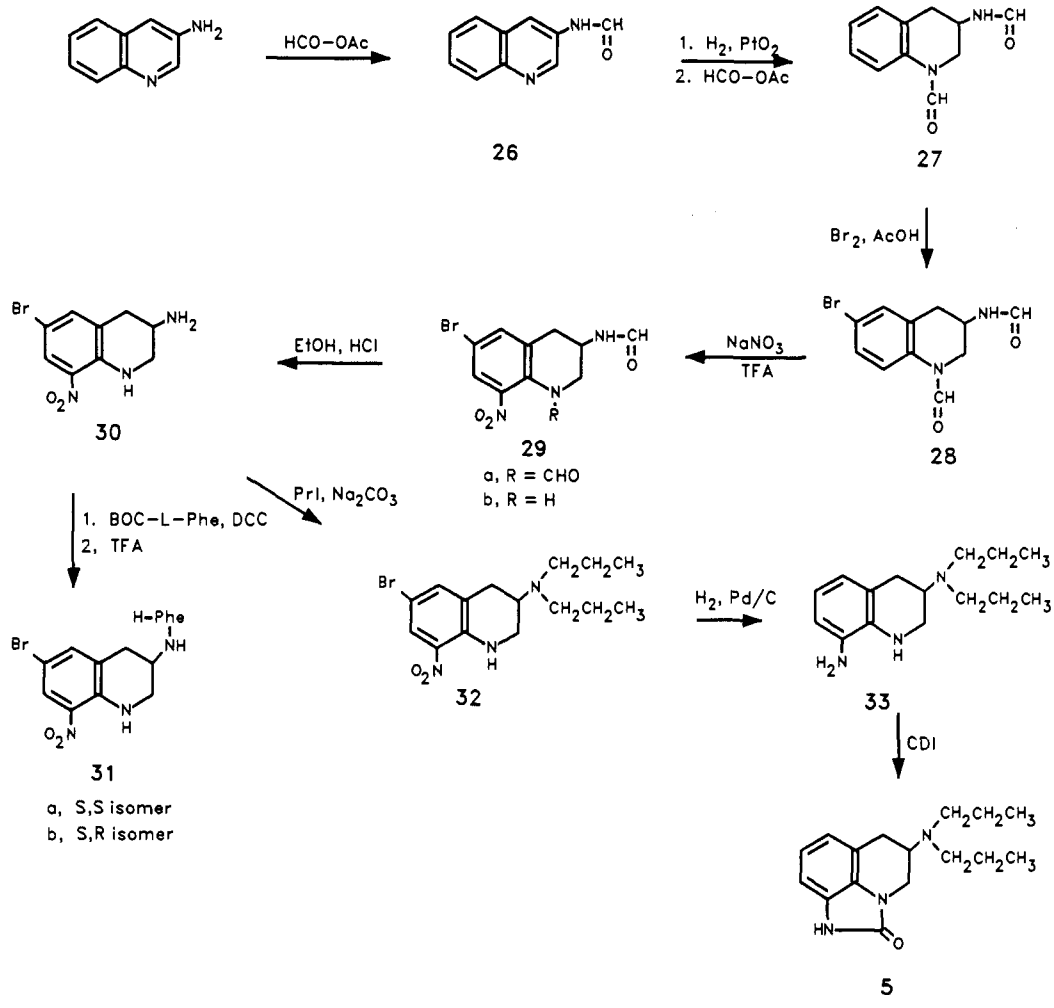
Scheme I



6- and 8-nitro-substituted products which could be separated with difficulty only after removal of the formyl protecting groups. Halogen protection at the 6-position before nitration seemed a probable way of directing nitration to the 8-position. While attempts to selectively monochlorinate **27** were unsuccessful, giving a mixture of products which included isomeric monochlorinated and dichlorinated species,[19] bromination of **27** gave an excellent

(5) Arvidsson, L. E.; Hacksel, U.; Nilson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. 8-Hydroxy-2(di-*n*-propylamino)tetralin, a New Centrally Acting 5-Hydroxytryptamine Receptor Agonist. *J. Med. Chem.* 1981, *24*, 921–923.

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(7) Boissier, J. R.; Nedelac, L.; Oberlander, C.; Labrie, F. Simplified Ergolines as New Dopamine Agonists. *Acta Pharm. Suec. Suppl. 2* 1983, 120–131.

(8) Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. 6-Substituted 1,3,4,5-Tetrahydrobenz[*cd*]indol-4-amines: Potent Serotonin Agonists. *J. Med. Chem.* 1988, *31*, 1746–1753.

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(10) VonVoigtlander, P. F.; Althaus, J. S.; Ochoa, M. C.; Neff, G. L. Dopamine Receptor Agonist Activity of U-66444B and its Enantiomers. *Drug Dev. Res.* 1989, *17*, 71–81.

(11) Tang, A.; Franklin, S. R.; Code, R. A.; Althaus, J. S.; VonVoigtlander, P. F.; Darlington, W. H.; Szmuszkovicz, J. In Vivo Dopamine Agonist and Antagonist Activities of a Series of Substituted Dihydrophenalenes. *Drug Dev. Res.* 1990, *21*, 53–62.

(12) McDermed, J. D.; Freeman, H. S. Stereochemistry of Dopamine Receptor Agonists. *Adv. Biosci.* 1982, *39*, 179–187.

(13) Hibert, M.; Middlemiss, D. N.; Fozard, J. R. The Central $5HT_{1A}$ Receptor: Graphics Computer-Aided Mapping of the Agonist Site. In *Brain $5HT_{1A}$ Receptors* (Series in Biomedicine); Dourish, C. T., Ahlenius, S., Hutson, P. H., Eds.; Ellis Horwood Ltd: Chichester, England, 1987; Chapter 3.

(14) Froimowitz, M.; Baldessarini, R. J. A Stereochemical and Conformational Model of Dopaminergic Agonist and Antagonist Activity; Further Evaluation. *J. Pharm. Sci.* 1987, *76*, 557–564.

(15) Glennon, R. A.; Jacyno, J. M.; Salley, J. J., Jr. 2,3-Dihydro and Carbocyclic Analogues of Tryptamines: Interaction with Serotonin Receptors. *J. Med. Chem.* 1982, *26*, 68–70.

(16) Vecchietti, V.; Mussini, E.; Ferrari, G. 1-Acyl-3-amino-1,2,3,4-tetrahydroquinoline Derivatives Useful as Cardiotonic Agents With Low Toxicity. European Pat. Appl. 82200959.3 Feb 16, 1983.

(17) Lahti, R. A.; Evans, D. L.; Figur, L. M.; Huff, R. M.; Moon, M. W. Pre- and Postsynaptic Dopaminergic Activities of U-86170F. *Naunyn. Schmied. Arch. Pharm.* 1991, *344*, 509–513.

(18) Partial rearrangement of the formyl group occurred during the reduction and the crude product contained a mixture of *N*-(1,2,3,4-tetrahydro-3-quinolyl)formamide and 1-formyl-1,2,3,4-tetrahydro-3-quinolinamine which could be separated by silica gel chromatography; direct reduction of 3-aminoquinoline in acetic acid with a platinum catalyst did not afford 1,2,3,4-tetrahydro-3-quinolinamine.

Table I. Structures and Activities of Various Tricyclic Dipropylamines

R-N($CH_2CH_2CH_3$)$_2$

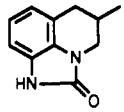
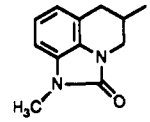
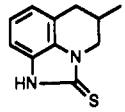
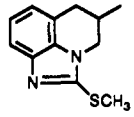
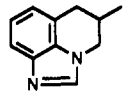
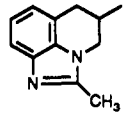
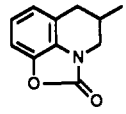
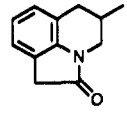
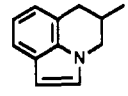
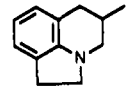
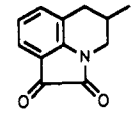
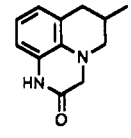
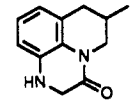
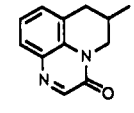
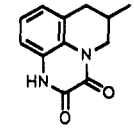
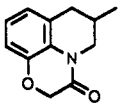
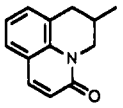
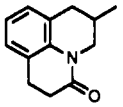
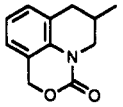
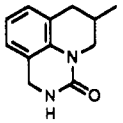
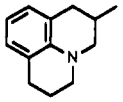
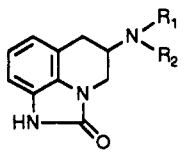
compd	R	formula[a]	mp, °C	binding data[b] D2: K_i, nM	binding data[b] 5HT$_{1A}$: K_i, nM	amine synthesis data[c] (% change from control at 1.0 mg/kg) DOPA	amine synthesis data[c] (% change from control at 1.0 mg/kg) 5-HTP
5[d]		$C_{16}H_{23}N_3O$·HCl	221–224	207	102	−34**[e]	12[e]
(*R*)-**5**[f]		$C_{16}H_{23}N_3O$·HBr·H_2O	198–200[g]	68	92	−50*[h]	−1.2
(*S*)-**5**		$C_{16}H_{23}N_3O$·HCl·0.25H_2O	120[i]	>1000	569	0.3	6.4
6		$C_{17}H_{25}N_3O$	83–85	924	124		
7		$C_{16}H_{23}N_3S$	150–151	40	90	−38*	−7
8		$C_{17}H_{25}N_3S$	49–52	>1000	173		
9		$C_{16}H_{23}N_3$	95–98	>1000	827	−12[j]	−7
10		$C_{17}H_{25}N_3$·2HCl·H_2O	202–205	>1000	4493		
11		$C_{16}H_{22}N_2O_2$·$C_7H_8O_3S$	192–194	899	>1000	−27	−6
12		$C_{17}H_{24}N_2O$	86–88	1082	108	−53*	−11
13		$C_{17}H_{24}N_2$·$C_4H_4O_4$	139–140	210	252	−29	−14
14		$C_{17}H_{26}N_2$·$C_4H_4O_4$	114–115	>1000	12.5	−33*	−13
15		$C_{17}H_{22}N_2O_2$	110–112	>1000	687	−46*	−7
16		$C_{17}H_{25}N_3O$·HCl	250–255[k]	30	304	−52*	−16
17		$C_{17}H_{25}N_3O$	97–99	80	49	−37*[l]	−32*
18		$C_{17}H_{23}N_3O$·$C_7H_8O_3S$	188–190	>1000	933		
19		$C_{17}H_{23}N_3O_2$·HCl	295[k]	150	>1000	−37*	6

Table I (Continued)

compd	R	formula[a]	mp, °C	binding data[b] D2: K_i, nM	binding data[b] $5HT_{1A}$: K_i, nM	amine synthesis data[c] (% change from control at 1.0 mg/kg) DOPA	amine synthesis data[c] (% change from control at 1.0 mg/kg) 5-HTP
20		$C_{17}H_{24}N_2O_2 \cdot C_4H_4O_4$	124–127	1348	12	-18	-12
21		$C_{18}H_{24}N_2O$	82–84	315	17	-40*	-18
22		$C_{18}H_{26}N_2O$	44–46	83	2.4	-41*	-48*
23		$C_{17}H_{24}N_2O_2 \cdot HCl$	192–195	292	31	-36*	-13
24		$C_{17}H_{25}N_3O$	116–119	>1000	3.2	-13	-45*
25		$C_{18}H_{28}N_2 \cdot C_4H_4O_4$[m]	112–116	35	105		
	quinpirole[n]			54			
	apomorphine			46	534	-55*	4
	buspirone[p]				6.6	115*	-46*

[a] $C_7H_8O_3S$ indicates *p*-toluenesulfonate salt; $C_4H_4O_4$ indicates maleate salt unless otherwise indicated; satisfactory elemental analyses (±0.4%) for all elements (C, H, N, and S or halogen when present) were obtained for all compounds except 16 [C 63.04 (62.39)]. [b] For K_i determination, each drug was investigated in triplicate at four concentrations; standard error was <5%. [c] The asterisk (*) indicates statistically significant at 0.05 level. [d] Compound also available as the free base, mp 179–181 °C. [e] Also active at 0.1 mg/kg (-54% change in DOPA level); compound shows serotonergic activity at 10 mg/kg (-37% change in 5-HTP level). [f] Compound also available as the free base, mp 119–121 °C. [g] Compound dehydrates before melting. [h] Also active at 0.1 mg/kg (-51% change in DOPA level). [i] Melts over range starting at 120 °C. [j] Compound active at 10 mg/kg (-40% change in DOPA level; -39% change in 5-HTP level). [k] Melts with decomposition. [l] Also active at 0.1 mg/kg (-29% change in DOPA level). [m] Fumarate salt. [n] (4a*R-trans*)-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1*H*-pyrazolo-[3,4-*g*]quinoline hydrochlorlde. [p] 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

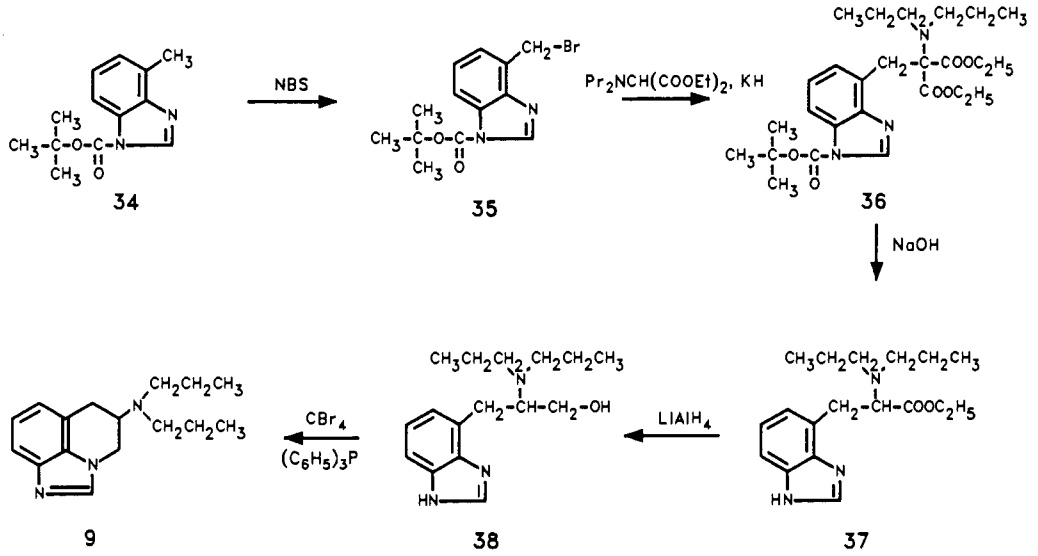
Table II. Structures and Activities of Various Substituted 5-Amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-ones



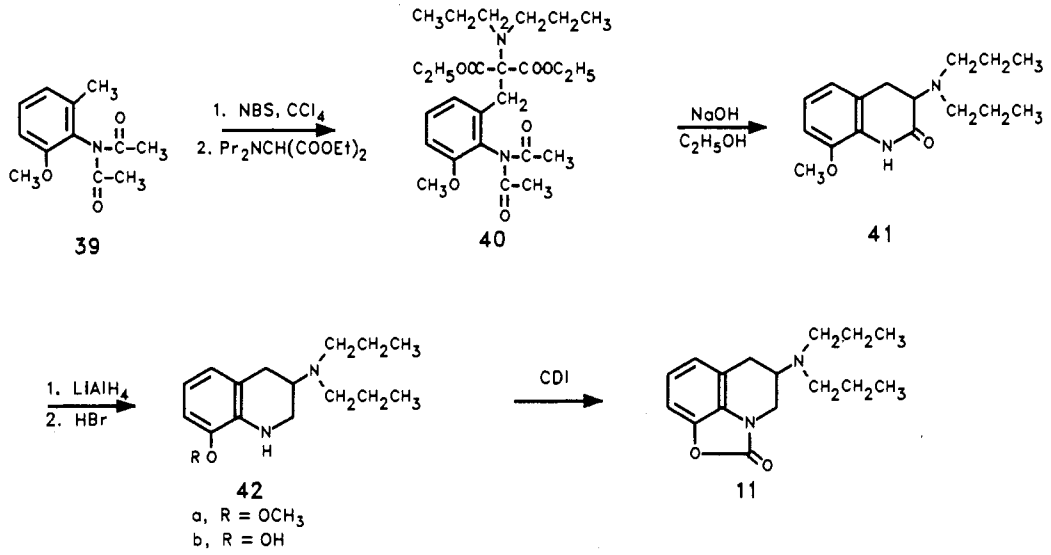
compd	R_1	R_2	structure[a]	mp, °C	binding data[b] D2: K_i, nM	binding data[b] $5HT_{1A}$: K_i, nM
56	H	H	$C_{10}H_{11}N_3O \cdot HCl$	>300	>10000	44
57	H	$CH_2CH_2CH_3$	$C_{13}H_{17}N_3O \cdot HCl$	>300	1037	94
58	H	$CH_2CH{=}CH_2$	$C_{13}H_{15}N_3O \cdot HCl$	260[c]	363	109
59	H		$C_{14}H_{17}N_3O \cdot HCl$	309[c]	3996	84
60	H	$CH_2CH_2CH_2CH_3$	$C_{14}H_{19}N_3O$	145–148	>10000	>1000
61	CH_3	CH_3	$C_{12}H_{15}N_3O \cdot HCl$	220–223	>10000	350
5	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	$C_{16}H_{23}N_3O \cdot HCl$	221–224	207	102
62	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$C_{16}H_{19}N_3O$	150–152	>10000	>1000
63	$CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	$C_{17}H_{25}N_3O$	156–158	167	171
64	$CH_2CH_2CH_3$	CH_2-C_6H_5	$C_{20}H_{23}N_3O$	115–119	1914	>1000
65			$C_{18}H_{23}N_3O$	152–154	7730	95
66	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	$C_{18}H_{27}N_3O$	166–169	>10000	

[a] Satisfactory elemental analyses (±0.4%) for all elements (C, H, N, and halogen when present) were obtained for all compounds. [b] For K_i determination, each drug was investigated in triplicate at four concentrations; standard error was <5%. [c] Compound melts with decomposition. [d] Compound also available as the free base, mp 129–131 °C, from ethyl acetate/hexane.

Scheme II



Scheme III



yield of the monobrominated product **28**. Nitration of **28** using concentrated nitric acid or acetyl nitrate afforded a mixture of products,[20] while nitration using sodium nitrate in trifluoroacetic acid[21] gave a single product, **29a**. Compound **29a** was rather susceptible to hydrolysis during workup and was more conveniently isolated as the monoformyl derivative **29b**. Hydrolysis of **29a** or **29b** in refluxing ethanolic hydrogen chloride gave **30**, which was resolved as outlined in Scheme I. Compound **30** was coupled to (*tert*-butoxycarbonyl)-L-phenylalanine and hydrolyzed with TFA to give diastereoisomers **31a** and **31b** which were separated by chromatography. The separated diastereoisomers were subjected to Edman degradation[22] to remove the phenylalanine resolving agent and give the (*R*)- and (*S*)-isomers of **30**. This degradation involved treating **31a** or **31b** with phenyl isothiocyanate to generate a thiourea intermediate which decomposed on treatment with trifluoroacetic acid to the enantiomers of amine **30** and 2-anilino-4-benzyl-2-thiazol-5-one. The amine was readily separated from the thiazolone byproduct by precipitation as the trifluoroacetate salt.

Alkylation of racemic **30** with propyl iodide gave **32**. Hydrogenation of **32** reduced the nitro group and removed the bromine protecting group to give **33**. This was reacted with 1,1'-carbonyldiimidazole to give **5**. The enantiomers of **30** were converted to the (*R*)- and (*S*)-enantiomers of

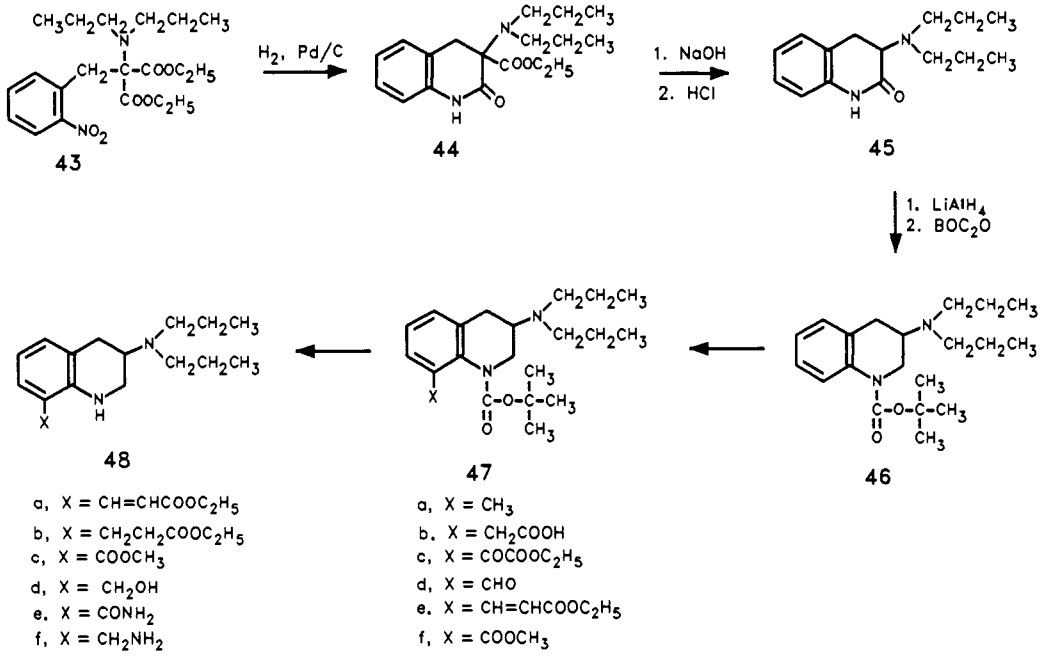
(19) Separation of these mixtures into their components was possible by gas chromatography or by analytical HPLC, but could not be accomplished on a preparative scale. Similar mixtures were obtained on chlorination of the model compound methyl 1,2,3,4-tetrahydroquinoline-1-carboxylate.

(20) Studies with the model compound methyl 6-bromo-1,2,3,4-tetrahydroquinoline-1-carboxylate showed that displacement of the bromine during nitration was a problem. In addition to the desired product (methyl 6-bromo-1,2,3,4-tetrahydro-8-nitroquinoline-1-carboxylate), products formed include the related 6,8-dibromo, 6-nitro and 6,8-dinitro substituted products.

(21) Uemura, S.; Toshimitsu, A.; Okano, M. Nitration of Aromatic Hydrocarbons and *ipso*-Nitrosodemetallation of Arylmetal Compounds in Sodium Nitrite-Trifluoroacetic Acid. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1076–1079.

(22) Edman, P. A Method for Determination of the Amino Acid Sequence in Peptides. *Acta Chem. Scand.* **1950**, *4*, 283. Fairwell, T.; Lovins, R. E. Quantitative Protein Sequencing Using Mass Spectrometry: Mass Spectral Analysis of 2-Anilino-5-thiazolinone Derivatives of Amino Acids Without Prior Conversion to the Phenyl Thiohydantoins. *Biochem. Biophys. Res. Comm.* **1971**, *43*, 1280–1289.

Scheme IV



5 by using the same three-step procedure, and the absolute stereochemistry of (*R*)-5 was determined by X-ray methods.

Alkylation of 5 with methyl iodide/potassium hydride afforded 6 (Table I). Various analogues of 5 were prepared from triamine 33. Reaction of 33 with di-2-pyridyl thionocarbonate[23] gave 7, which was alkylated with methyl iodide to 8. Triamine 33 was reacted with chloroacetic anhydride, ethyl bromoacetate, butyl glyoxylate, and ethyl oxalyl chloride to give the pyridoquinoxalinones 16–19, respectively.

The imidazoquinoline 9 was prepared as outlined in Scheme II. 4-Methylbenzimidazole[24] was converted to the *tert*-butoxycarbonyl derivative 34 which was brominated with *N*-bromosuccinimide to 35.[25] This was reacted with the potassium salt of diethyl (dipropylamino)malonate to give 36. Alkaline hydrolysis of 36 rapidly removed the *tert*-butoxycarbonyl protecting group and more slowly cleaved one of the ethoxycarbonyl groups to give 37. Compound 37 was reduced to the alcohol 38 and this was treated with carbon tetrabromide/triphenylphosphine to give the corresponding primary bromide which cyclized to 9 under the reaction conditions.

Oxazoloquinoline 11 was prepared in seven steps as outlined in Scheme III. 2-Methoxy-6-methylbenzenamine was acetylated to 39. This product was brominated with *N*-bromosuccinimide and then reacted with the potassium salt of diethyl (dipropylamino)malonate to give 40. Hydrolysis of 40 accomplished deacetylation, cyclization, ester hydrolysis, and decarboxylation[26] in a single step to give 41 in good yield (56%). Compound 41 was reduced with lithium aluminum hydride to give 42a. Treatment of 42a with hydrobromic acid cleaved the methyl ether, and the resulting phenol (42b) was cyclized to 11 with 1,1′-carbonyldiimidazole. The related oxazinoquinoline analogue 20 was prepared by reaction of the sodium salt of 42b with methyl chloroacetate.

Compounds 12–15 and 21–24 (Table I) were prepared as outlined in Scheme IV. 2-Nitrobenzyl chloride was reacted with the sodium salt of diethyl (dipropylamino)-malonate to give 43. Catalytic reduction of the nitro group afforded the corresponding aniline which cyclized to 44 when refluxed in ethanol. Hydrolysis of 44 gave the corresponding acid which decarboxylated to 45 upon acidification. Reduction of 45 with lithium aluminum hydride followed by treatment with di-*tert*-butyl dicarbonate afforded 46. Metalation of 46 ortho to the *tert*-butoxycarbonyl group with *sec*-butyllithium[27] gave the anion at the 8-position in the quinoline ring, and this anion was reacted with methyl iodide to give 47a. Compound 47a was again converted to an anion with *sec*-butyllithium and this was reacted with carbon dioxide to give 47b. Reaction of 47b with trifluoroacetic acid gave 12 (Table I). Reduction of 12 with lithium aluminum hydride gave a mixture of 13 and 14 which was readily separated into its components by chromatography on silica gel. The anion of 46 reacted with diethyl oxalate to give 47c which cyclized to 15 when treated with trifluoroacetic acid. The anion of 46 was reacted with ethyl formate to give 47d and this intermediate was treated with trimethyl phosphonoacetate to give 47e. Trifluoroacetic acid converted 47e to 48a which was refluxed in ethanol in presence of *p*-toluenesulfonic acid to effect cyclization to 21. Catalytic hydrogenation of 48a gave 48b which cyclized to 22 when refluxed in ethanol. Compound 47f was prepared by re-

(23) Kim, S.; Yi, K. Y. Di-2-pyridyl Thionocarbonate. A New Reagent for the Preparation of Isothiocyanates and Carbodiimides. *Tetrahedron Lett.* 1985, *26*, 1661–1664.

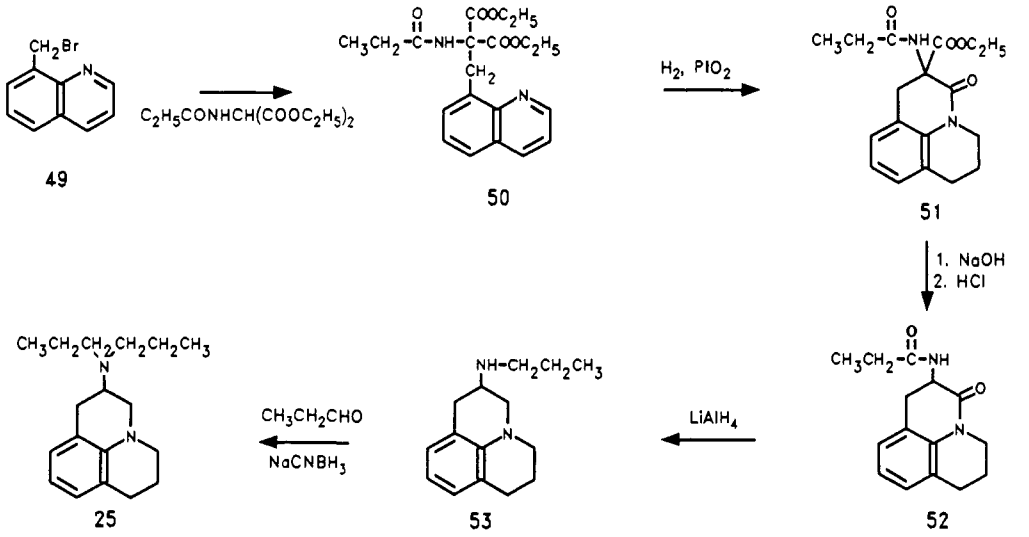
(24) Gabriel, S.; Thieme, A. Zur Kenntnis der Nitro-toluylsäure. *Chem. Ber.* 1919, *52*, 1079–1092.

(25) Small amounts of the dibromomethylated product are formed in this and related brominations and can often be separated by crystallization or chromatography of the crude product. Separation is not essential as the dibromomethyl compound does not react with the sodium salt of the malonate in the next step of the reaction sequence. In related bromination reactions, some of which require prolonged reaction times, we have found dibromantin a more efficient brominating reagent.

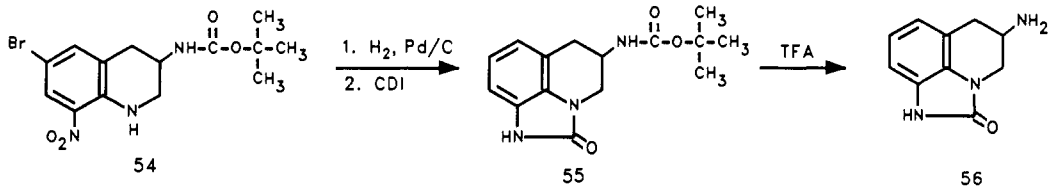
(26) The reaction proceeds by initial loss of an acetyl group to give diethyl (dipropylamino)[[2-(acetylamino)-3-methoxyphenyl]-methyl]propanedioate which has been isolated in crystalline form (mp 96–99 °C) at short reaction times.

(27) For a review of related metallation reactions, see: Snieckus, V. Directed Ortho-Litiation of Aromatic Compounds. New Methodologies and Applications in Organic Synthesis. *Bull. Soc. Chim. Fr.* 1988, 67–78.

Scheme V



Scheme VI



acting the anion of **46** with methyl chloroformate. The *tert*-butoxycarbonyl protecting group was removed with trifluoroacetic acid, and the resulting product (**48c**) was reduced to alcohol **48d** with lithium aluminum hydride. Treating **48d** with 1,1′-carbonyldiimidazole gave **23**. Compound **48c** was converted to the amide **48e** by treatment with phosgene followed by ammonia. Reduction of **48e** with lithium aluminum hydride gave the amine **48f** and this was cyclized to **24** with 1,1′-carbonyldiimidazole.

Compound **25** was prepared in five steps from 8-(bromomethyl)quinoline[28] (**49**) as outlined in Scheme V. Reaction of **49** with the sodium salt of diethyl propionamidomalonate gave **50**. Hydrogenation of **50** in the presence of a platinum catalyst gave the corresponding tetrahydroquinoline which cyclized under the reaction conditions to **51**. Hydrolysis of **51** gave **52** which was reduced to **53** and alkylated to give **25**.

The primary amine analogue of **5** (**56**) was prepared as outlined in Scheme VI. 6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (**30**, Scheme I) was converted to the *tert*-butoxycarbonyl derivative **54**. This was reduced, cyclized to **55** with 1,1′-carbonyldiimidazole, and hydrolyzed to the primary amine **56**. Reductive alkylation of **56** with the appropriate aldehyde and sodium cyanoborohydride, or alkylation with the appropriate alkyl halide gave the secondary and tertiary amines **57–66** (Table II).

Many of the products of Tables I and II were converted to crystalline, water-soluble salts before biological evaluation; analytical data for the compounds are presented in Tables I and II.

X-ray Crystallography

The crystal structure and absolute configuration of (*R*)-**5** as the hydrobromide salt monohydrate was determined. Details of the structure determination are in the Experimental Section, and the conformation found in the crystalline state is shown in Figure 1.

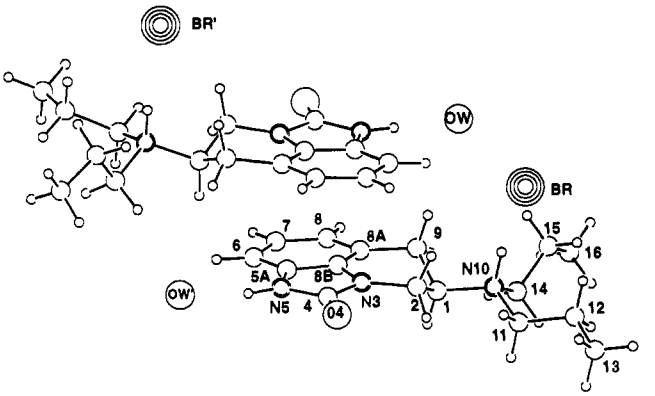


Figure 1. Conformation and numbering in the crystal structure of (*R*)-**5**. The two symmetry-independent molecules are related by an approximate 2_1 axis, with the bromine atoms and the propyl chain atoms deviating most from the pseudosymmetry. The two molecules are very similar in conformation and form similar hydrogen bonds with the corresponding bromines and water molecules. In each molecule, the tertiary amine nitrogen is protonated and hydrogen bonded to a bromine (N–Br distances are 3.340 (6) and 3.252 (5) Å). The secondary amine hydrogens in the imidazolone rings form hydrogen bonds with the water oxygens. Each water donates one hydrogen to an imidazolone carbonyl oxygen and the other hydrogen to a bromine. N–water oxygen distances are 2.775 (9) and 2.854 (8) Å, water oxygen–carbonyl oxygen distances are 2.724 (9) and 2.764 (9) Å, and water oxygen–bromine distances are 3.305 (6) and 3.354 (6) Å. The distance between the nitrogen atoms of the dipropylamine residue and the ring NH is 5.9 Å.

Biological Methods

Inhibition constants were determined using the dopamine D2 antagonist ligand [^{3}H]raclopride (*methoxy*-[^{3}H]3,5-dichloro-2-hydroxy-6-methoxy-*N*-(1-ethyl-1-pyrrolidinylmethyl)benzamide) in membranes prepared from rat striatal homogenates[29] and the serotonin $5HT_{1A}$

(28) Buu-Hoi, Ng. Ph. Several New Halogenations with *N*-Bromo and *N*-Chlorosuccinimides. *Rec. Trav. Chim. Pays-Bas* **1954**, *73*, 197–202.

Table III. Electrophysiological Data for Various Compounds

compd	ED_{50}, μg/kg DA cells[a]	ED_{50}, μg/kg $5HT_{1A}$ cells[a]
5	5.0 ± 1.4 (5)	340 ± 60 (5)
(R)-5	1.4 ± 0.2 (5)	107 ± 32 (5)
(S)-5	>1000 (4)	
9	219 ± 47 (4)	
13	83 ± 30 (4)	
16	39 ± 22 (5)	
19	88 ± 38 (5)	
24	212 ± 54 (4)	3.4 ± 0.8 (5)
57	36 ± 7 (4)	650 ± 180 (4)

[a] Dose to reduce neuronal firing by 50% (mean ± standard error); numbers in parentheses represent number of cells tested with each compound.

agonist ligand [^{3}H]DPAT ([^{3}H]8-hydroxy-DPAT, [^{3}H]7-(dipropylamino)-5,6,7,8-tetrahydro-1-naphthalenol) in membranes prepared from homogenates of bovine hippocampus.[30] Effects on synthesis of catechol and indolamines in the brain were determined following subcutaneous administration and HPLC procedures with electrochemical detection were used to determine 3,4-dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5-HTP) levels.[10] Firing rates of dopaminergic neurons in the substantia nigra pars compacta and serotonergic neurons in the dorsal raphe nucleus were determined following subcutaneous injection of the test compounds. Procedures for these assays are presented in the Experimental Section.

Results and Discussion

The activity of 5 in binding assays is shown in Table I. The compound displaces both the tritiated dopamine (D2) antagonist ligand [^{3}H]raclopride and the $5HT_{1A}$ agonist ligand [^{3}H]DPAT from brain membrane preparations. The K_i for raclopride (200 nM) is comparable with that found for the potent dopamine agonists quinpirole and apomorphine (54 and 46 nM, respectively), while the K_i for displacement of the agonist ligand [^{3}H]DPAT (102 nM) is considerably higher than that found for potent serotonin agents, for example buspirone (K_i 6.6 nM), as is shown in Table I. Agonist drugs interact efficiently at the high affinity state of the receptor, but less effectively with the low affinity, antagonist, form of the receptor and are less effective in displacing antagonist ligands.[31] Thus, while the absolute K_i values for the D2 and $5HT_{1A}$ receptors using the chosen ligands (antagonist and agonist, respectively) are similar, these values are consistent with the fact that 5 shows significant dopamine selectivity. This selectivity is further evident when the amine synthesis data is examined. Compound 5 shows a statistically significant reduction in brain levels of the dopamine precursor 3,4-dihydroxyphenylalanine (DOPA) following subcutaneous injection at 1.0 and 0.1 mg/kg, effects characteristic of a dopamine agonist.[10] In this test, serotonin agonists produce a decrease in levels of the serotonin precursor 5-hydroxytryptophan (5-HTP).[10] Compound 5 had no effect on 5-HTP levels at the above-mentioned doses; a dose of 10 mg/kg was needed to affect 5-HTP levels. The dopamine selectivity of 5 was further indicated by the electrophysiological data shown in Table III. Compound 5 showed an agonist effect on dopamine neurons at 5 μg/kg, while a 70-fold higher dose (340 μg/kg) was required to elicit an agonist response at serotonin neurons. As is shown in Tables I and III, the activity of 5 resides in the (R)-enantiomer, which is about twice as active as the racemate; the (S)-enantiomer shows no dopaminergic activity and only weak serotonergic activity.

A series of compounds where the imidazolone ring was modified to other 5-membered rings were prepared (compounds 6–15, Table I). N-Methylation of 5 gave 6, a compound with reduced activity at both receptors. The thione 7 had comparable activity to 5 in the binding assays, while S-methylation of this compound significantly reduced activity. The related imidazole 9 showed low activity in the binding assays and showed dopaminergic activity in the other assays only at higher doses (amine synthesis at 10 mg/kg and electrophysiologically at 219 μg/kg); the 2-methyl analogue of 9, compound 10, also showed low activity. Analogues of 5 where the NH was changed to O (11) or CH_2 (12) had reduced activity. Pyrrole 13 showed good activity on D2 binding, but was inactive in the amine metabolism and electrophysiological studies. Reduction of the double bond in 13 gave a compound (14) with weaker dopaminergic activity, but improved serotonergic activity. Dicarbonyl analogue 15 had low activity. Of these analogues with a 5-membered heterocyclic ring (compounds 6–15), only 7 showed comparable dopaminergic potency to 5, and only 14 was superior in serotonergic activity.

A series of analogues was prepared where the imidazolidinone ring was modified to a 6-membered ring (compounds 16–25, Table I); several of these compounds (16–19, and 24) showed good activity. Compound 16, with the carbonyl moved away from the tertiary ring nitrogen, was primarily a dopaminergic compound while 17, with the carbonyl group adjacent to this nitrogen atom, showed a combination of dopaminergic and serotonergic activities. The unsaturated analogue of 17, compound 18, was less active, while the dicarbonyl analogue 19 showed only dopaminergic activity. Several of these compounds with a carbonyl group adjacent to the tertiary ring nitrogen (20–24) showed good serotonergic activity; compounds 20–23 showed a combination of serotonergic and dopaminergic activity, while 24 was a selective serotonin agonist.

In view of the excellent activity found for 5, we investigated the effect that modifying the amine substituent had on activity. In addition to the primary amine 56, a series of secondary amines (57–60) and tertiary amines (61–66) were prepared. Of the secondary amines, only 57 and 58 showed significant dopaminergic activity but were less active than 5, while of the tertiary amine analogues only 63 showed good dopaminergic activity. While few compounds compared to 5 in dopaminergic activity, several showed comparable serotonin K_i's, suggesting that the size of the substituents attached to the amine nitrogen is not as critical for activity at the serotonin receptor. A similar observation has been made for aminotetralins showing serotonergic activity.[3,32]

Comparison of 5 and Its Analogues with Other Structurally Similar D2 Ligands. In order to deter-

(29) Kohler, C.; Hall, H.; Ögren, S. V.; Gawell, G. Specific *In Vitro* and *In Vivo* Binding of ^{3}H-Raclopride. A Potent Substituted Benzamide Drug with High Affinity For Dopamine D-2 Receptors in the Rat Brain. *Biochem. Pharmacol.* 1985, *34*, 2251–2259.

(30) Gozlan, H.; El Mestikawy, S.; Pichat, L. Glowinski, J.; Hamon, M. Identification of Presynaptic Serotonin Autoreceptors Using a New Ligand: ^{3}H-PAT. *Nature* 1983, *305*, 140–142.

(31) For comparative data on dopamine D2 binding using agonist and antagonist ligands, see e.g.: Martin, G. E.; Williams, M.; Haubrich, D. R. A. Pharmacological Comparison of 6,7-Dihydroxy-2-Dimethylaminotetralin (TL-99) and N-*n*-Propyl-3-(3-Hydroxyphenyl)Piperidine with (3-PPP) Selected Dopamine Agonists. *J. Pharmacol. Exp. Ther.* 1982, *223*, 298–303.

(32) Naiman, N.; Lyon, R. A.; Bullock, A. E.; Rydelek, L. T.; Titeler, M.; Glennon, R. A. 2-(Alkylamino)tetralin Derivatives: Interaction with 5-HT_{1A} Serotonin Binding Sites. *J. Med. Chem.* 1989, *32*, 253–256.

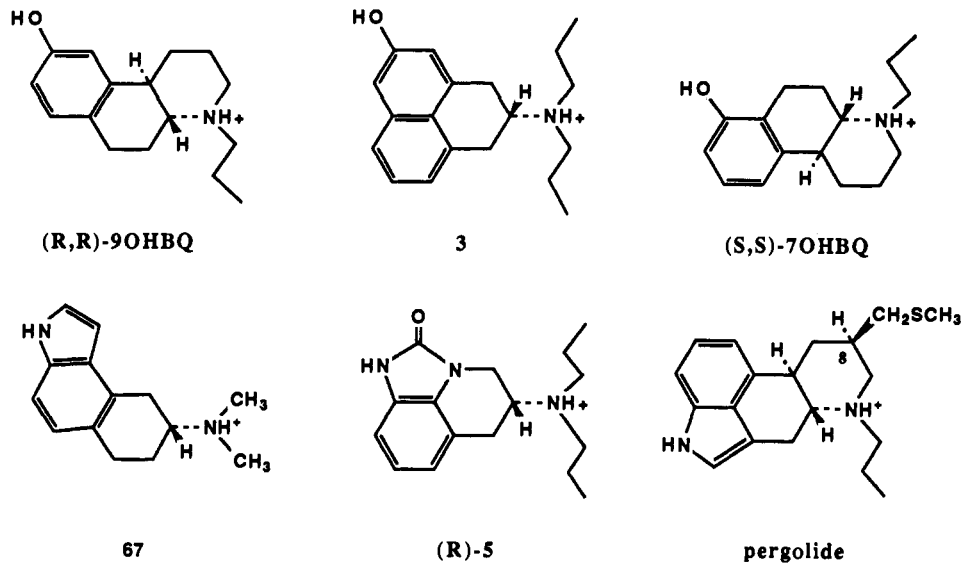


Figure 2. Comparison of orientation of (*R*)-**5** at the dopamine receptor with those of other dopamine agonists. In all molecules, the protonated nitrogen lies above the plane of the aromatic ring with its proton pointing downward toward the receptor.

mine the structural features necessary for activity at the dopamine receptor, we have compared **5** to other tri- and tetracyclic dopamine agonists for which the dopamine D2 receptor has shown a strong enantiomeric preference. The structures in Figure 2 show the more active enantiomers for these compounds. Many D2 agonists have imbedded in their structure the phenylethylamine moiety present in dopamine itself, and the spatial relation that all these have in common is for the basic nitrogen to be above the plane of the aromatic portion when the molecules are drawn as in Figure 2. Note that the structural diagrams have the amine nitrogen *down*, but because the nitrogen is equatorial and the asymmetric carbon is above the plane of the aromatic ring, the nitrogen is also above this plane. Three of these molecules, *trans*-(4a*R*,10b*R*)-9-hydroxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline [(*R*,*R*)-9OH BQ], *trans*-(4a*R*,10b*R*)-7-hydroxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline [(*S*,*S*)-7OH BQ], and (*R*)-**3**, have a phenolic hydroxyl at the top left of the structure. The nitrogen to oxygen distance among these potent D2 agonists varies; the distance is about 7.4 Å for (*R*,*R*)-9OH BQ and for **3**,[33] and is about 6.5 Å for (*S*,*S*)-7OH BQ; apomorphine, not shown, also has an oxygen to nitrogen distance of about 6.5 Å. It has been suggested[34] that the indole ring nitrogen could substitute for the hydroxyl functionality, and in fact, Asselin and co-workers proposed this when they reported the dopamine agonist properties of racemic compound **67**.[35] When **67** was resolved and tested,[36] this prediction proved to be correct. This structure can be superimposed with (*R*,*R*)-9OH BQ with the NH of **67** occupying the same space as the OH of (*R*,*R*)-9OH BQ; the N–N distance in **67** is 7.4 Å. However, the enantiomeric preference of the ergolines is equally strong[37] and is known to be *S* for the natural ergolines[38] and for the semisynthetic ergoline pergolide (Figure 2)[39] which is a potent dopamine agonist. Assuming that the receptor prefers that the basic nitrogen be above the plane of the aromatic ring, as in all the other structures, then the ergoline NH cannot be superimposed with the hydroxyl or NH in **67**, but is at the bottom left side of the molecule, the side which is lipophilic in the other series. Because, except for the extra nitrogen and the carbonyl, **5** does have an ergoline-type structure, missing only a ring closing atom at top right, and because one of the resolved enantiomers is very much less active, it was important to determine the absolute configuration of **5**. The X-ray determination showed that the configuration is *R*, like that of the aminotetralins and with the ring heteroatoms on the same side of the molecule as (*R*,*R*)-9OH BQ, (*S*,*S*)-7OH BQ, **3**, and **67**, but opposite from the ergoline N–H. This prompts the obvious question: *why are the opposite configuration ergolines not more active*? The probable answer is given by a model for D2 receptor ligands proposed by Liljefors and Wikström in 1986[40] and further elucidated more recently.[41] According to this model, the receptor cannot accommodate a nitrogen substituent larger

(33) The crystal structure of (*R*)-**3** has been determined. Chidester, C. G. Unpublished results.

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(38) Stadler, P. A.; Hofmann, A.; Chemische Bestimmung der Absoluten Konfiguration der Lysergsäure. *Helv. Chim. Acta* 1961, *45*, 2005–2011.

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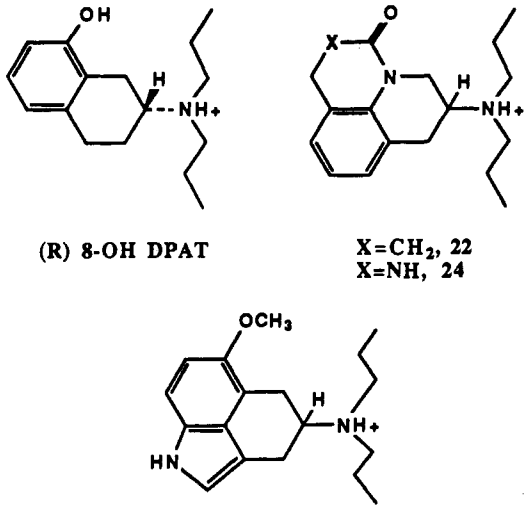

(R) 8-OH DPAT

X=CH$_2$, 22
X=NH, 24

2b

Figure 3. Comparison of orientation of **22** and **24** at the serotonin receptor with those of other serotonin agonists. In all molecules, the protonated nitrogen lies above the plane of the aromatic ring with its proton pointing downward toward the receptor.

than propyl at the bottom right side of the molecule when drawn as in Figure 2, but a larger substituent at nitrogen can fit if it is at the top right. This was first demonstrated using analogues of (*S*,*S*)-7OH BQ and (*R*,*R*)-9OH BQ.[42] The butyl analogue of (*S*,*S*)-7OH BQ is very active, but the butyl analogue of (*R*,*R*)-9OH BQ shows only very weak binding ability. Wikström and co-authors commented in this report that because the natural ergolines all have a large substituent at C-8, their opposite enantiomers cannot bind to the receptor when they are rotated 180° about a horizontal axis, because the receptor cannot accommodate a large substituent at bottom right. Examination of the binding data in Table II shows that, for **5** and its analogues, it is also important that one of the substituents is no larger than propyl for high dopaminergic activity. One of the propyl substituents in **5** can be changed to butyl (**63**) without affecting activity, while changing the substituent to benzyl (**64**) gives a compound with significantly reduced activity. Also, the monopropylamine **57** is about one-fifth as potent as **5**, while the butylamine analogue **60** showed no dopaminergic activity.

Considering the compounds in Table I, compounds with greatest affinity for the D2 receptor are (*R*)-**5**, **7**, **16**, **17**, **19**, **22**, and **25**. All of these except **22** and **25** have an NH in the heterocyclic ring adjacent to the benzene ring. None of the others with weaker affinity have this structural feature. This suggests that the dopamine D2 receptor prefers a hydrogen-bond donor in this location. This hypothesis is supported by the observation regarding aminotetralin structures that *O*-methyl analogues of potent hydroxy compounds have very much less affinity for the D2 receptor.[43,44] Hydroxyl groups can be either hydrogen-bond donors or acceptors, but methoxy groups can only be acceptors.

Comparison of 5 and Its Analogues with Structurally Similar 5HT$_{1A}$ Ligands. The 5HT$_{1A}$ receptor apparently has an enantiomeric preference similar to the dopamine D2 receptor. The most potent agonists, however, have a shorter basic nitrogen to oxygen distance, about 5.2 Å. Figure 3 shows some representative structures. Hibert et al.[45] suggested a model for the 5HT$_{1A}$ pharmacophore in which two features of each structure would be superimposed: the aromatic ring and the basic nitrogen. The basic nitrogen should be, as in the D2 pharmacophore, slightly above the plane of the aromatic ring when this substituent is at the top right. All compounds in Table I would fit this model, but in the case of (*R*)-**5**, the only resolved compound, it is the imidazolone ring which must overlay the aromatic ring rather than the benzene ring.

Closeness of fit with this Hibert model does not help to explain the large variation in affinities observed for the compounds in Table I. It is, however, possible to rationalize the varying affinities for the 5HT$_{1A}$ receptor if we assume that the 5HT$_{1A}$ receptor prefers a hydrogen-bond acceptor which can superimpose with the hydroxy, carbonyl, or methoxy oxygen in the Figure 3 structures. In contrast to dopamine ligands, methoxy analogues of 8-hydroxy aminotetralin ligands have affinities for the 5HT$_{1A}$ receptor not much less than their hydroxy counterparts.[46] Among the compounds in Table I, **14**, **17**, and **20–24** have the highest 5HT$_{1A}$ affinities. Of these, all except **14** have a 6-membered ring on the bottom with a carbonyl substituent ortho to the nitrogen. Compounds **18** and **19** also have 6-membered rings with ortho carbonyls and lack strong affinity, but this apparent contradiction can be explained by the fact that they both have other strong hydrogen-bond acceptors in close proximity which may interfere with the hydrogen-bond interaction desirable for binding. The analogous 5-membered ring structures with ortho carbonyls all have less affinity for the 5HT$_{1A}$ receptor. In the case of 5-membered rings, the carbonyl oxygen cannot be exactly superimposed with the oxygens in the other Figure 3 structures. Although the difference in position of the oxygen itself is not very great, the direction of the C–O bond is changed by about 23°, with the result that a hydrogen bond from a donor atom on the receptor to this carbonyl would be displaced significantly.

Conclusion

We have reported the synthesis of **5**, a potent dopamine agonist. Related compounds also show dopaminergic activity, including thio analogue **7** and pyridoquinoxalinone **16**. Several analogues (e.g., **17** and **22**) have a combination of D2 and 5HT$_{1A}$ activities, while **24** shows exclusively serotonergic activity. The activities of the compounds have been related to existing D2 and 5HT$_{1A}$ models. Compound

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(*R*)-5, U-86170, has recently been evaluated in additional tests,[17] and its dopaminergic agonist profile suggests that it may be of use in the treatment of Parkinson's disease. Also, preliminary studies suggest that the tritiated form of this compound which has recently been prepared will find use as an agonist ligand for dopamine receptor binding studies.[47]

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer; chemical shifts are recorded in δ units with $CDCl_3$ as solvent unless otherwise stated and tetramethylsilane as the internal standard (in NMR description s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). GC data were obtained on a Hewlett-Packard Model 5890A capillary gas chromatograph using an HP-1 methyl silicone column (5-m × 0.53-mm × 2.65-μm film thickness, column B) or a J and W Scientific Inc. DB-5 5% phenylmethyl silicone column (15-m × 0.53-mm × 1.5-μm film thickness, column A), a helium carrier gas (flow rate 100 mL/min), and a hydrogen flame ionization detector. Samples were injected at 100 °C and after 1 min the column temperature was raised 20 °C/min to a final temperature of 250 °C.

***N*-(3-Quinolyl)formamide (26).** A solution of acetic formic anhydride was prepared by slowly adding 95–97% formic acid (20.80 g, 17.05 mL, 0.45 mol) to acetic anhydride (40.84 g, 37.7 mL, 0.40 mol) at 0 °C. The solution was stirred at room temperature for 2 h, then added to a stirred solution of 3-aminoquinoline (28.84 g, 0.20 mol) in dry tetrahydrofuran (300 mL). After 15 min, the solution was evaporated, methanol (50 mL) was added, and the solution was stirred for an additional 30 min. The solution was then evaporated under reduced pressure, and the residual oil was triturated with ether. The resulting white solid was filtered to give 28.7 g (84%) of **26**, mp 157–160 °C. Anal. ($C_{10}H_8N_2O$) C, H, N.

***N*-(1-Formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (27).** A mixture of *N*-(3-quinolyl)formamide (**26**, 30.0 g, 0.175 mol), platinum oxide (2.0 g), and acetic acid (300 mL) was hydrogenated (50 lb initial hydrogen pressure) until 2 equiv of hydrogen had been consumed (reaction time 3 h). The mixture was filtered through Celite, the acetic acid was removed under reduced pressure, and the residual oil was dissolved in ethyl acetate which was washed with NaOH solution and water. Evaporation of the ethyl acetate gave 29.4 g of crude material.[18] This was dissolved in THF (200 mL), and acetic formic anhydride (prepared from 27.2 g of formic acid and 53.3 g of acetic anhydride) was added at 0 °C. After 15 min, the solution was allowed to warm to room temperature, and after an additional 15 min, methanol (60 mL) was added. The solution was evaporated, and the resulting oil was partitioned between ethyl acetate and 4 N sodium hydroxide solution. The sodium hydroxide solution was repeatedly extracted with ethyl acetate. The combined ethyl acetate extracts were evaporated, and the crude product was purified by chromatography on silica gel using 2.5% methanol/chloroform as eluant to give 23.55 g (69%) of **27** which was crystallized from methanol/ether (1:3), mp 125–128 °C. Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

***N*-(6-Bromo-1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (28).** Bromine (10.2 g, 0.064 mol) was added to a stirred solution of *N*-(1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (**27**, 14.0 g, 0.065 mol) and anhydrous sodium acetate (10.2 g, 0.12 mol) in acetic acid (70 mL). The solution was stirred for 30 min and water (500 mL) was added. The precipitate was filtered off and air dried to give 15.8 g (86%) of **28**, mp 174–178 °C. A sample was recrystallized from ethanol for analysis, mp 174–8 °C. Anal. ($C_{11}H_{11}BrN_2O_2$) C, H, N, Br: calcd, 28.23; found, 27.69.

***N*-(6-Bromo-1-formyl-1,2,3,4-tetrahydro-8-nitro-3-quinolyl)formamide (29a).** A mixture of *N*-(6-bromo-1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (**28**, 2.1 g), sodium nitrate (1.0 g, 11.8 mmol) and TFA (20 mL) was stirred at room temperature for 18 h. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate phase was washed with saturated sodium bicarbonate solution, 4 N sodium hydroxide solution, and water. The ethyl acetate was removed, and the residual solid was crystallized from ethyl acetate to give 1.8 g (74%) of **29a**, mp 168–71 °C. Anal. ($C_{11}H_{10}BrN_3O_4$) C, H, N, Br.

***N*-(6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolyl)formamide (29b).** A mixture of *N*-(6-bromo-1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (**28**, 35.9 g, 0.127 mol), sodium nitrate (21.56 g, 0.254 mol) and TFA (250 mL) was stirred at room temperature for 5 h. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and sodium hydroxide (4 N). The ethyl acetate was removed to give an orange solid (59.3 g), which was dissolved in methanol (1000 mL) containing triethylamine (18.29 g, 0.181 mol) and refluxed for 2 h. The reaction was cooled, concentrated, and filtered to give **29b** (32.9 g, 86%), mp 191–3 °C. Anal. ($C_{10}H_{10}BrN_3O_3$) C, H, Br, N.

6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (30). *N*-(6-Bromo-1-formyl-1,2,3,4-tetrahydro-8-nitro-3-quinolyl)formamide (**29a**, 14.6 g) was refluxed in ethanolic hydrogen chloride (100 mL of 4.0 N) for 1 h during which time the bulk of the product crystallized as the dihydrochloride salt. The solution was cooled, ether (200 mL) was added, and the precipitate was filtered off, washed with ether, and dried to give 12.8 g (82%) of **30** as the dihydrochloride salt, mp > 300 °C.

***N*-(6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)-phenylalaninamide (31a and 31b).** A mixture of (*tert*-butoxycarbonyl)-L-phenylalanine (29.0 g, 0.11 mol), 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride (**30**, 26.0 g, 0.075 mol), 1-hydroxybenzotriazole (15.0 g, 0.10 mol), triethylamine (20.0 g, 0.20 mol), and dicyclohexylcarbodiimide (40.0 g, 0.19 mol) in dimethylformamide (200 mL) was stirred at room temperature for 2 h. The solution was filtered to remove dicyclohexylurea, the DMF was removed under reduced pressure, and the residue was dissolved in trifluoroacetate (200 mL). After 2 h, the TFA was evaporated and the residual oil was partitioned between ethyl acetate (500 mL) and water (400 mL) containing sufficient sodium hydroxide (60 g) to render the aqueous phase basic. The ethyl acetate phase was washed with water, evaporated, and chromatographed to give, as the first product eluted from the column, 8.4 g (27%) of *N*-[(*S*)-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl]phenylalaninamide (**31a**) followed by 8.9 g (28%) of *N*-[(*R*)-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl]phenylalaninamide (**31b**).

(*R*)-6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine [(*R*)-30]. Phenyl isothiocyanate (2.9 g, 21.5 mmol) was added to a stirred solution of *N*-[(*R*)-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl]phenylalaninamide (**31b**, 8.6 g, 20.5 mmol) in THF (50 mL). After 1 h, the solvent was removed and the residual oil was chromatographed on silica gel using ethyl acetate/hexane (1:9) as the initial eluant. Fractions containing the desired compound were pooled, concentrated to a volume of 100 mL, and 9.8 g (88%) of the thiourea was filtered off: mp 208 °C; $[\alpha]_D$ = −73° (*c* = 1, THF). Anal. ($C_{25}H_{24}BrN_5O_3S$) C, H, Br, N, S.

The bulk of the product (8.6 g) was dissolved in TFA (30 mL). After the mixture was stirred for 1 h at room temperature, the bulk of the TFA was removed, ether was added, and the precipitate of (*R*)-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine trifluoroacetate (5.98 g) was filtered off. The product was partitioned between ethyl acetate and 4 N NaOH to give the free base which was crystallized from ethyl acetate to give 3.4 g of red solid (65% from **31b**): mp 165–8 °C; $[\alpha]_D$ = −133° (*c* = 1, MeOH). Anal. ($C_9H_{10}BrN_3O_2$) C, H, N, Br.

(*S*)-6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine [(*S*)-30]. This was prepared from **31a** following the procedure used to prepare (*R*)-**30**: mp 165–8 °C; $[\alpha]_D$ = +133° (*c* = 1, MeOH). Anal. ($C_9H_{10}BrN_3O_2$) C, H, N, Br.

6-Bromo-1,2,3,4-tetrahydro-8-nitro-*N*,*N*-dipropyl-3-quinolinamine (32). A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride (11.5 g, 0.033 mol), iodopropane (21 g, 0.12 mol), and anhydrous sodium carbonate (20 g, 0.19 mol) in dimethylformamide (100 mL) was stirred at 100 °C for 5 h. The solution was then evaporated and partitioned between ethyl acetate and water, and the ethyl acetate was evaporated to give a red oil. This was chromatographed on silica

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gel to give 8.2 g of **32**. The product was crystallized from ethyl acetate/hexane to give 7.6 g (65%) of product, mp 79–81 °C. Anal. ($C_{15}H_{22}BrN_3O_2$) C, H, Br, N. (*R*)-Enantiomer of **32**: mp 84–6 °C, $[\alpha]_D = -152°$ (c = 1, MeOH). Anal. ($C_{15}H_{22}BrN_3O_2$) C, H, Br, N. (*S*)-Enantiomer of **32**: mp 84–6 °C, $[\alpha]_D = +152°$ (c = 1, MeOH). Anal. ($C_{15}H_{22}BrN_3O_2$) C, H, Br, N.

5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (5). A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-*N*,*N*-dipropyl-3-quinolinamine (**32**, 8.8 g, 24.7 mmol) and 10% palladium charcoal (1.0 g) in ethanol (150 mL) was hydrogenated for 18 h. The solution was filtered and the ethanol evaporated. The residual oil was partitioned between ethyl acetate and sodium hydroxide solution and the ethyl acetate was evaporated to give 6.2 g of 1,2,3,4-tetrahydro-N^3,N^3-dipropyl-3,8-quinolinediamine (**33**) as an oil. This was dissolved in DMF (50 mL), 1,1′-carbonyldiimidazole (4.5 g, 28 mmol) was added, and the solution was stirred at 100 °C for 1 h. The DMF was evaporated under reduced pressure, and the residual oil was chromatographed on silica gel using ethyl acetate/hexane (1:9) as the initial eluant to give 6.2 g of product. The product was crystallized from ether/hexane to give 5.6 g (83%) of **5**: mp 155–7 °C; NMR δ 0.90 (t, 6 H), 1.47 (m, 4 H), 2.55 (m, 4 H), 2.88 (d of d, J = 10.0 and 16.0 Hz, 1 H, C(6)H_{ax}), 2.94 (d of d, J = 5.5 and 16.0 Hz, 1 H, C(6)H_{eq}) 3.30 (m, 1 H, C(5)H_{ax}), 3.47 (d of d, J = 11.1 and 11.7 Hz, 1 H, C(4)H_{ax}), 4.20 (d of d, J = 4.2 and 11.7 Hz, 1 H, C(4)H_{eq}), 6.94 (m, 3 H), and 10.00 (s, 1 H). Anal. ($C_{16}H_{23}N_3O$) C, H, N. The bulk of the product was converted to the hydrochloride salt, mp 221–4 °C, from methanol/ether. Anal. ($C_{16}H_{23}N_3O$·HCl) C, H, Cl, N. (*R*)-Enantiomer of **5**: Free base, mp 117–9 °C; $[\alpha]_D = -4.3°$ (c = 1, MeOH). Anal. ($C_{16}H_{23}N_3O$) C, H, N. Hydrobromide salt, mp 180–2 °C; $[\alpha]_D = -14.2°$ (c = 1, MeOH). Anal. ($C_{16}H_{23}N_3O$·HBr·H_2O) C, H, Br, N; Karl Fisher H_2O 4.97% (calcd 4.83%). (*S*)-Enantiomer of **5**: Hydrochloride salt, $[\alpha]_D = +16.5°$ (c = 1, MeOH). Anal. ($C_{16}H_{23}N_3O$·HCl·0.25H_2O) C, H, Cl, N; Karl Fisher H_2O 0.99% (calcd 1.43%).

5-(Dipropylamino)-5,6-dihydro-1-methyl-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (6). Potassium hydride (0.28 g of a 35% by weight mineral oil dispersion, washed with ether to remove oil, 2.7 mmol) in dry THF was added to a stirred solution of **5** (0.60 g, 2.2 mmol) in dry THF (25 mL). Methyl iodide (0.31 g, 2.2 mmol) in dry THF was then added. After the mixture was stirred at room temperature for 18 h, methanol was slowly added to the solution. The solvent was then removed under reduced pressure and the material dissolved in methanol/chloroform (1:1) and chromatographed on silica gel using chloroform as eluant to give 0.50 g (79%) of **6**. This was recrystallized twice from hexane to give 0.28 g of product, mp 83–5 °C. Anal. ($C_{17}H_{25}N_3O$) C, H, N.

5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline-2(1*H*)-thione (7). Di-2-pyridyl thionocarbonate (1.6 g, 7.2 mmol) was added to a stirred solution of 1,2,3,4-tetrahydro-N^3,N^3-dipropyl-3,8-quinolinediamine (**33**, 1.6 g, 6.7 mmol) in THF (50 mL). The solution was stirred for 1 h, evaporated, and partitioned between chloroform and water. The chloroform phase was evaporated and chromatographed on silica gel using ethyl acetate/hexane (1:9) as the initial eluant to give 1.6 g of product. Crystallization from cyclohexane gave 1.3 g (67%) of **7**, mp 150–1 °C. Anal. ($C_{16}H_{23}N_3S$) C, H, N, S.

5,6-Dihydro-2-(methylthio)-*N*,*N*-dipropyl-4*H*-imidazo[4,5,1-*ij*]quinolin-5-amine (8). Sodium methoxide in methanol (0.46 mL of 4.3 M, 2.0 mmol) was added to a stirred solution of **7** (0.60 g, 2.0 mmol) in dry THF (25 mL). Methyl iodide (0.71 g, 5 mmol) was added, and the solution was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the material dissolved in methanol/chloroform (1:1) and chromatographed on silica gel using chloroform as the eluant. The product was crystallized from hexane to give 0.34 g (56%) of **8**, mp 49–52 °C. Anal. ($C_{17}H_{25}N_3S$) C, H, N, S.

6-(Dipropylamino)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxalin-2(3*H*)-one (16). A mixture of chloracetic anhydride (0.51 g, 3.0 mmol) and **33** (0.60 g, 2.5 mmol) in THF (10 mL) was stirred at room temperature for 1 h. The solvent was evaporated, the product was partitioned between ethyl acetate and water, and the ethyl acetate was evaporated. The crude product was chromatographed using chloroform as the initial eluant to give 650 mg of 2-chloro-*N*-[3-(dipropylamino)-1,2,3,4-tetrahydroquinol-8-yl]acetamide. This was heated at 150 °C in DMF for 1 h, the DMF was evaporated, and the product was crystallized from methanol/ether to give 400 mg (49%) of the hydrochloride salt of **16**, mp 250–5 °C. Anal. ($C_{17}H_{25}N_3O$·HCl) H, Cl, N, C: calcd, 63.04; found, 62.39.

6-(Dipropylamino)-1,2,6,7-tetrahydro-3*H*,5*H*-pyrido[1,2,3-*de*]quinoxalin-3-one (17). A mixture of ethyl bromoacetate (0.51 g, 3.0 mmol) and **33** (0.62 g, 2.5 mmol) was refluxed in THF (15 mL) for 4 h. The solvent was evaporated, the product was partitioned between ethyl acetate and water, and the ethyl acetate was evaporated. The crude product was chromatographed to give, as the major product and first compound eluted from the column, 420 mg of compound **17**. The product was crystallized from ethyl acetate/hexane to give 280 mg of product, mp 97–9 °C. Anal. ($C_{17}H_{25}N_3O$) C, H, N. Continued elution of the column gave a small amount (22 mg) of **16**.

6-(Dipropylamino)-6,7-dihydro-3*H*,5*H*-pyrido[1,2,3-*de*]quinoxalin-3-one (18). A mixture of butyl glyoxylate (0.24 g, 1.8 mmol) and **33** (0.24 g, 1.0 mmol) was refluxed in dioxane (10 mL) for 2 h. The solvent was evaporated, the product partitioned between ethyl acetate and water, and the ethyl acetate was evaporated. The crude product was chromatographed using chloroform as the initial eluant to give 180 mg (63%) of compound **18**. The product was converted to the *p*-toluenesulfonate salt, mp 188–90 °C from methanol/ether. Anal. ($C_{17}H_{23}N_3O$·$C_7H_8O_3S$) C, H, N, S.

6-(Dipropylamino)-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-dione (19). A mixture of ethyl oxalyl chloride (0.40 g, 3.0 mmol) and **33** (0.60 g, 2.5 mmol) in THF (10 mL) was stirred at room temperature for 1 h and then refluxed for 1 h. The solvent was evaporated, the product was partitioned between ethyl acetate and NaOH solution, and the ethyl acetate was washed with water and evaporated. The residue was chromatographed using chloroform as the initial eluant and the purified product was crystallized from ethyl acetate/hexane to give 330 mg (44%) of **19**, mp 166–8 °C. Anal. ($C_{17}H_{23}N_3O_2$) C, H, N. The bulk of the product was converted to the hydrochloride salt which was crystallized from methanol/ether, mp 250–5 °C dec. Anal. ($C_{17}H_{23}N_3O_2$·HCl) C, H, Cl, N.

***tert*-Butyl 4-Methyl-1*H*-benzimidazole-1-carboxylate (34).** A mixture of 4-methyl-1*H*-benzimidazole (11.6 g, 0.088 mol) and di-*tert*-butyl dicarbonate (21.1 g, 0.097 mol) was heated at 80 °C in dioxane (200 mL) for 1 h. The solvent was removed under reduced pressure, and the residual oil (24.3 g) was chromatographed on silica gel using ethyl acetate/hexane as the eluant to give 18.7 g (92%) of **34** as an oil: NMR δ 1.70 (s, 9 H), 2.66 (s, 3 H), 7.16 (d, 1 H), 7.26 (t, 1 H), 7.81 (d, 1 H), and 8.42 (s, 1 H).

***tert*-Butyl 4-(Bromomethyl)-1*H*-benzimidazole-1-carboxylate (35).** A mixture of *tert*-butyl 4-methyl-1*H*-benzimidazole-1-carboxylate (**34**, 11.6 g, 0.05 mol), *N*-bromosuccinimide (8.9 g, 0.05 mol), and benzoyl peroxide (0.25 g) in carbon tetrachloride (100 mL) was stirred at reflux for 1 h. The solution was cooled and filtered to remove succinimide byproducts, and the solvent was removed. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:20) as the initial eluant to give, as the first major product eluted from the column, 1.6 g of *tert*-butyl 4-(dibromomethyl)-1*H*-benzimidazole-1-carboxylate. Recrystallization from hexane gave 1.04 g of product, mp 101–4 °C. Anal. ($C_{13}H_{14}Br_2N_2O_2$) C, H, Br, N. Continued elution of the column gave 10.4 g of **35** which was recrystallized from hexane to give 9.6 g (62%) of product, mp 87–9 °C. Anal. ($C_{13}H_{15}BrN_2O_2$) C, H, Br, N. Continued elution of the column gave 0.95 g of **34**.

Diethyl (Dipropylamino)malonate. Dipropylamine (22.3 g, 0.22 mol) was added to a stirred solution of diethyl bromomalonate (47.8 g, 0.20 mol) in THF (400 mL) and the solution was stirred for 18 h at room temperature. The precipitate of dipropylamine hydrobromide was filtered off and washed with THF. The THF phase was evaporated, and the residual oil was partitioned between ethyl acetate (200 mL) and sodium hydroxide solution (10 mL of 4 N). The ethyl acetate phase was separated and washed with water (2 × 10 mL), and the solvent was removed under reduced pressure. The residual oil was dissolved in an equal volume of hexane and was applied to a silica gel column (420 g) which was eluted initially with ethyl acetate/hexane (1:20). The concentration of ethyl acetate in the eluant was increased slowly until all the diethyl (dipropylamino)malonate was eluted from

the column. Fractions containing the compound as determined by TLC and GC were pooled, and the solvent was removed to give 44.0 g (85%) of diethyl (dipropylamino)malonate as an oil: NMR δ 0.87 (t, 6 H), 1.29 (t, 6 H), 1.46 (m, 4 H), 2.63 (m, 4 H), and 4.20 (m, 5 H).

Ethyl α-(Dipropylamino)-1*H*-benzimidazole-4-propanoate (37). Potassium hydride (3.3 g of 35% oil suspension, washed with ether to remove oil, 0.03 mol) was added to a stirred solution of diethyl (dipropylamino)malonate (10.2 g, 0.039 mol) in dry THF (100 mL). After 5 min, *tert*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate (**35**, 6.22 g, 0.02 mol) was added and the solution was refluxed for 6 h. The solvent was removed under reduced pressure, and the residual oil was partitioned between ethyl acetate and water. After evaporation of the ethyl acetate, the crude product was chromatographed on silica gel using ethyl acetate/hexane as the eluant to give 7.9 g (81%) of diethyl [[1-[(1,1-dimethylethoxy)carbonyl]-1*H*-benzimidazol-4-yl]-methyl](dipropylamino)propanedioate (**36**) as an oil: NMR δ 0.81 (t, 6 H), 1.12 (t, 6 H), 1.55 (m, 4 H), 1.68 (s, 9 H), 2.65 (m, 4 H), 3.87 (s, 2 H), 4.04 (m, 4 H), 7.26 (t, 1 H), 7.56 (d, 1 H), and 7.79 (d, 1 H).

Part of this product (3.4 g, 6.9 mmol) was dissolved in ethanol (50 mL) and treated with sodium ethoxide in ethanol (35 mL of 0.8 M, 4 equiv) and water (1.0 mL) and the reaction was refluxed for 4 h. The solution was then cooled, neutralized by addition of 15 mL of 2.2 N HCl in ethanol, and filtered to remove sodium chloride, and the solvent was removed under reduced pressure. The product was partitioned between ethyl acetate and water, the ethyl acetate was removed, and the crude product was chromatographed on silica gel using chloroform as the initial eluant. Elution of the column with 5% methanol/chloroform gave 1.60 g of **37** (64% from **35**). The product was crystallized from ethyl acetate/hexane; mp 78–80 °C. Anal. ($C_{18}H_{27}N_3O_2$) C, H, N.

5,6-Dihydro-*N*,*N*-dipropyl-4*H*-imidazo[4,5,1-*ij*]quinolin-5-amine (9). Lithium aluminum hydride (250 mg, 6.6 mmol) was added at 0 °C to a stirred solution of ethyl α-(dipropylamino)-1*H*-benzimidazole-4-propanoate (**37**, 1.5 g, 4.7 mmol) in dry THF (50 mL), and the solution was allowed to warm to room temperature. TLC in 10% methanol/chloroform showed that the reaction was complete in 15 min. Ethanol (5 mL) was added, and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave 1.3 g of β-(dipropylamino)-1*H*-benzimidazole-4-propanol (**38**): NMR δ 0.89 (t, 6 H), 1.49 (m, 4 H), 2.56 (m, 4 H), 2.87 (m, 1 H), 3.29 (m, 2 H), 3.40 (m, 1 H), 4.13 (m, 1 H), 7.05 (s, 1 H), 7.19 (t, 1 H), 7.40 (br d, 1 H), and 7.99 (s, 1 H).

Triphenylphosphine (625 mg, 2.4 mmol) was added to a stirred solution of **38** (600 mg, 2.18 mmol) in methylene chloride (12 mL). After solution was complete, carbon tetrabromide (940 mg, 2.8 mmol) was added and the solution was stirred for 30 min. Methylene chloride (20 mL) was added, and the solution was extracted with 1.0 N hydrochloric acid (25 mL). The methylene chloride was separated and reextracted with 1.0 N HCl (10 mL), and the combined aqueous extracts were made alkaline (20 mL of 4.0 N NaOH) and extracted with ethyl acetate. After the ethyl acetate was removed, the product was chromatographed on silica gel using chloroform as the initial eluant to give 380 mg of **9** (68% from **37**). A sample was crystallized from hexane for analysis, mp 95–8 °C. Anal. ($C_{18}H_{23}N_3$) C, H, N.

***N*-Acetyl-*N*-(2-methoxy-6-methylphenyl)acetamide (39).** 2-Methoxy-6-methylbenzenamine (13.8 g, 0.10 mol) was dissolved in acetic anhydride (100 mL), and the resulting solution was refluxed for 2 h. Part of the solvent (50 mL) was slowly removed over a 1-h period, and the remainder of the solvent was then removed under reduced pressure. The residual oil was crystallized from ethyl acetate/hexane (200 mL of 1:2) to give 20.5 g (93%) of **39**, mp 116–9 °C. Anal. ($C_{12}H_{15}NO_3$) C, H, N.

Diethyl (Dipropylamino)[[2-(diacetylamino)-3-methoxyphenyl]methyl]propanedioate (40). A mixture of *N*-acetyl-*N*-(2-methoxy-6-methylphenyl)acetamide (**39**, 25.0 g, 0.11 mol), *N*-bromosuccinimide (20.1 g, 0.11 mol), and benzoyl peroxide (4.5 g, 0.019 mol) in carbon tetrachloride (300 mL) was stirred under reflux for 3 h. The solution was cooled, filtered, and evaporated, and the residual solid was crystallized from ethyl acetate/hexane to give 21.0 g of *N*-acetyl-*N*-[2-(bromomethyl)-6-methoxyphenyl]acetamide, 95% pure by GC analysis: NMR δ 2.34 (s, 6 H), 3.83 (s, 3 H), 4.29 (s, 2 H), 6.96 (d, 1 H), 7.12 (d, 1 H), and 7.39 (t, 1 H).

Ten grams of this product was added to a stirred solution of diethyl (dipropylamino)malonate (34.6 g, 133 mmol) and potassium hydride (13.4 g of 35% in oil, 117 mmol) in THF (200 mL), and the solution was heated under reflux for 1 h. The solvent was evaporated, and the residual oil was partitioned between ethyl acetate and water. After evaporation of the ethyl acetate, the residue was chromatographed on silica gel using ethyl acetate/hexane (1:10) as the eluant to give 8.4 g (53%) of **40**. Crystallization from ethyl acetate/hexane gave 6.8 g of product, mp 72–5 °C. Anal. ($C_{25}H_{38}N_2O_7$) C, H, N.

3-(Dipropylamino)-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (41). Sodium ethoxide in ethanol (66 mL of 1.0 M) was added to a solution of **40** (6.34 g, 13 mmol) in ethanol (100 mL). After 20 min water (1 mL) was added and after 1 h the solution was heated under reflux; additional water was added to the reaction after 3 (2 mL), 4 (5 mL), and 5 h (10 mL). The solution was filtered to remove precipitated inorganic material, the solvents were removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The oil obtained after evaporation of the ethyl acetate was chromatographed on silica gel to give 3.3 g of **41**. The product was crystallized from pentane to give 2.02 g (56%) of product, mp 72–5 °C. Anal. ($C_{16}H_{24}N_2O_2$) C, H, N.

1,2,3,4-Tetrahydro-8-methoxy-*N*,*N*-dipropyl-3-quinolinamine (42a). Lithium aluminum hydride (3.53 g, 92 mmol) was added at 0 °C to a stirred solution of **41** (6.43 g, 23 mmol) in THF (50 mL), and the solution was then heated at 50 °C for 1 h. After cooling, ethyl acetate followed by methanol was added to destroy excess hydride, and the solvent was evaporated. The residue was partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave an oil which was chromatographed on silica gel to give 4.17 g (68%) of **42a** as an oil. Part of the product was converted to the hydrochloride salt, mp 179–84 °C from methanol/ether. Anal. ($C_{16}H_{26}N_2O\cdot HCl$) C, H, Cl, N.

5-(Dipropylamino)-5,6-dihydro-2*H*,4*H*-oxazolo[5,4,3-*ij*]-quinolin-2-one (11). A solution of 1,2,3,4-tetrahydro-8-methoxy-*N*,*N*-dipropyl-3-quinolinamine (**42a**, 0.98 g, 3.7 mmol) in hydrobromic acid (20 mL of 48%) was heated at 155 °C for 6 h. The solution was cooled, evaporated, and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous phase was re-extracted with ethyl acetate, and the combined organic phases were evaporated to give 0.88 g (95%) of 1,2,3,4-tetrahydro-8-hydroxy-*N*,*N*-dipropyl-3-quinolinamine (**42b**) as an oil: NMR (CD_3OD) δ 0.90 (t, 6 H), 1.47 (m, 4 H), 2.54 (m, 4 H), 2.79 (m, 2 H), 3.07 (m, 1 H), 3.42 (m, 1 H), and 6.47 (m, 3 H). The bulk of the product (0.59 g, 2.4 mmol) was dissolved in THF (10 mL) and 1,1'-carbonyldiimidazole (0.46 g, 2.8 mmol) was added. After 30 min, the solvent was removed and the residue was dissolved in ethyl acetate and chromatographed on silica gel using 5% ethyl acetate in hexane as the initial eluant to give 0.57 g (66%) of **11** as an oil. The bulk of the product was converted to the *p*-toluenesulfonate salt, mp 192–4 °C from methanol/ether. Anal. ($C_{16}H_{22}N_2O_2\cdot C_7H_8O_3S$) C, H, N, S.

6-(Dipropylamino)-6,7-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3(2*H*)-one (20). Sodium methoxide in methanol (1.05 mL of 4.2 M, 4.4 mmol) was added to a stirred solution of 1,2,3,4-tetrahydro-8-hydroxy-*N*,*N*-dipropyl-3-quinolinamine (1.0 g, 4.0 mmol) in THF (40 mL). Methyl bromoacetate (0.81 g, 5.2 mmol) was added, and after 1 h, the solution was refluxed for 1 h. The solvent was evaporated, the product was partitioned between ethyl acetate and water, and the ethyl acetate was evaporated. The crude product was chromatographed to give 230 mg (20%) of **20**. The product was converted to the maleate salt, mp 124–6 °C from methanol/ether. Anal. ($C_{17}H_{24}N_2O_2\cdot C_4H_4O_4$) C, H, N.

Diethyl (Dipropylamino)[(2-nitrophenyl)methyl]-propanedioate (43). Diethyl (dipropylamino)malonate (25.9 g, 0.10 mol) was added to a stirred solution of sodium ethoxide in ethanol (prepared from 2.3 g of sodium and 250 mL of ethanol, 0.10 mol). After 5 min, 2-nitrobenzyl chloride (17.2 g, 0.10 mol) was added and the solution was stirred under reflux for 2 h. The solvent was removed under reduced pressure, and the product

was partitioned between ethyl acetate and water. The ethyl acetate was removed, and the residual oil was chromatographed on silica gel using ethyl acetate/hexane (1:20) as the eluant to give 18.9 g (48%) of **43** as an oil.

Ethyl 3-(Dipropylamino)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carboxylate (44). A mixture of diethyl (dipropylamino)[(2-nitrophenyl)methyl]propanedioate (**43**, 16 g, 40 mmol) and 10% Pd/C (1.0 g) in ethanol (150 mL) was hydrogenated until uptake of hydrogen ceased (15 min). The catalyst was filtered off and the reaction solution was refluxed for 2 h to effect cyclization of the initially formed diethyl (dipropylamino)[(2-aminophenyl)methyl]propanedioate. The ethanol was removed, and the residual oil was purified by chromatography on silica gel using ethyl acetate/hexane (1:10) as the eluant. Fractions containing **44** were pooled and crystallized from hexane to give 8.9 g (69%) of product, mp 103–5 °C. Anal. ($C_{18}H_{26}N_2O_3$) C, H, N.

3-(Dipropylamino)-3,4-dihydro-2(1*H*)-quinolinone (45). Sodium hydroxide solution (120 mL of 4.0 N, 0.48 mol) was added to a stirred solution of ethyl 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-3-quinolinecarboxylate (**44**, 47.8 g, 0.15 mol) in methanol (350 mL), and the solution was heated under reflux for 18 h. The solution was cooled, neutralized with hydrochloric acid, evaporated, and partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave a solid (37 g) which was crystallized from hexane to give 34.8 g (94%) of **45**, mp 94–6 °C. Anal. ($C_{15}H_{22}N_2O$) C, H, N.

***tert*-Butyl 3-(Dipropylamino)-3,4-dihydro-1(2*H*)-quinolinecarboxylate (46).** Lithium aluminum hydride (11.4 g, 0.30 mol) was added to a stirred solution of 3-(dipropylamino)-3,4-dihydro-2(1*H*)-quinolinone (**45**, 37.0 g, 0.15 mol) in ether (800 mL). The solution was heated under reflux for 1.5 h and cooled, and methanol was added to destroy excess hydride. After evaporation of the ether, the residue was partitioned between ethyl acetate and water; evaporation of the ethyl acetate gave 34.3 g of 1,2,3,4-tetrahydro-*N*,*N*-dipropyl-3-quinolinamine which was used without further purification. The bulk of this material (31.4 g, 0.135 mol) and di-*tert*-butyl dicarbonate (32.5 g, 0.149 mol) were heated at 100 °C for 1 h. The product was chromatographed on silica gel using ethyl acetate/hexane as the eluant to give 42.6 g of **46**: (94%) mp 40–2 °C; NMR δ 0.89 (t, 6 H), 1.47 (m, 4 H), 1.52 (s, 9 H), 2.51 (m, 4 H), 2.71 (m, 1 H), 2.92 (m, 1 H), 3.05 (m, 1 H), 3.15 (m, 1 H), 4.10 (m, 1 H), 7.00 (m, 1 H), 7.11 (m, 2 H), and 7.58 (m, 1 H). A portion of the product (1.0 g) was converted to the hydrochloride salt (1.07 g), mp 168 °C dec from THF/ether. Anal. ($C_{20}H_{32}N_2O_2$·HCl) C, H, Cl, N.

***tert*-Butyl 5-(Dipropylamino)-3,4-dihydro-8-methyl-1-(2*H*)-quinolinecarboxylate (47a).** *sec*-Butyllithium (35.0 mL of 1.3 M in hexane, 0.045 mol) was added at −78 °C to a stirred solution of **46** (10 g, 0.030 mol) in THF (200 mL). After 15 min, methyl iodide (17.1 g, 0.13 mol) was added, and the solution was allowed to warm to room temperature. The THF was removed under reduced pressure, and the residual oil was partitioned between ethyl acetate and water. The ethyl acetate was evaporated and the residual oil was chromatographed on silica gel to afford 9.85 g (95%) of **47a** as an oil.[48]

5-(Dipropylamino)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-2(1*H*)-one (12). *sec*-Butyllithium (13.3 mL of 1.3 M in hexane, 17.3 mmol) was added at −78 °C to a stirred solution of **47a** (3.0 g, 8.6 mmol) in THF (60 mL). After 5 min carbon dioxide was bubbled in, and the solution was allowed to warm to room temperature while continuing addition of CO_2. The solvent was evaporated, and the residue was partitioned between ether and sodium hydroxide solution (20 mL of 1.0 N); evaporation of the ether gave 1.1 g of recovered **47a**. The aqueous phase containing the sodium salt of **47b** was neutralized, evaporated, and reconstituted in TFA (30 mL). After 1 h, the bulk of the TFA was evaporated, ethanol was added, the solution was refluxed for 2 h, and the ethanol was evaporated. The product was partitioned between ethyl acetate and NaOH solution, the ethyl acetate was washed with water and evaporated. The residue was chromatographed using ethyl acetate/hexane (1:20) as the initial eluant and the purified product was crystallized from ethyl acetate/hexane to give 1.02 g of **12** (44% from **47a**) mp 86–8 °C. Anal. ($C_{17}H_{24}N_2O$) C, H, N.

Lithium Aluminum Hydride Reduction of 5-(Dipropylamino)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2(1*H*)-one (12). A mixture of **12** (0.75 g, 2.75 mmol) and lithium aluminum hydride (0.21 g, 5.53 mmol) was stirred in ether (20 mL) for 45 min. The reaction was quenched with methanol, evaporated, and partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave an oil which was chromatographed on silica gel using ethyl acetate/hexane (1:20) as eluant to give, as the first compound eluted from the column 0.27 g (38%) of 5,6-dihydro-*N*,*N*-dipropyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-5-amine (**13**); the compound was converted to the maleate salt, mp 139–40 °C from THF/ether. Anal. ($C_{17}H_{24}N_2$·$C_4H_4O_4$) C, H, N. Continued elution of the column gave 0.34 g (48%) of 1,2,5,6-tetrahydro-*N*,*N*-dipropyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-5-amine (**14**); the compound was converted to the maleate salt, mp 114–5 °C from THF/ether. Anal. ($C_{17}H_{26}N_2$·$C_4H_4O_4$) C, H, N.

5-(Dipropylamino)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinolin-2,3-dione (15). *sec*-Butyllithium (19.6 mL of 1.3 M in hexane, 25.5 mmol) was added at −78 °C to a stirred solution of **46** (5.6 g, 17 mmol) in THF (100 mL). After 15 min, diethyl oxalate (7.5 g, 51 mmol) was added and the solution was allowed to warm to room temperature. The product was partitioned between ethyl acetate and NaOH solution, and the ethyl acetate was washed with water and evaporated. The residual oil was chromatographed using ethyl acetate/hexane (1:20) as the initial eluant to give 4.9 g (67%) of **47c**[48] which was dissolved in trifluoroacetic acid (200 mL). After 1 h, the solvent was removed and the residual oil was partitioned between ethyl acetate and excess saturated sodium bicarbonate solution. The ethyl acetate was washed with water and evaporated, and the residue was chromatographed using 1% methanol in chloroform as the initial eluant to give 2.88 g of product (53% from **46**). This was crystallized from ethyl acetate/hexane to give 2.54 g of **15**, mp 110–2 °C. Anal. ($C_{17}H_{22}N_2O_2$), C, H, N.

Methyl 5-(Dipropylamino)-1,2,3,4-tetrahydro-α-oxo-8-quinolinebutenoate (48a). *sec*-Butyllithium (19.3 mL of 1.3 M in hexane, 25.1 mmol) was added at −78 °C to a stirred solution of **46** (6.6 g, 20 mmol) in THF (100 mL). After 15 min, ethyl formate (4.44 g, 60 mmol) was added, and the solution was allowed to warm to room temperature. The product was partitioned between ethyl acetate and NaOH solution, and the ethyl acetate was washed with water and evaporated. The residue was chromatographed using ethyl acetate/hexane (1:10) as the initial eluant to give 5.9 g (82%) of **47d**.[48] A part of this (3.6 g, 10 mmol) was added to a stirred solution of trimethyl phosphonoacetate (3.64 g, 20 mmol) and sodium hydride (0.96 g of 40% in oil, 20 mmol) in acetonitrile (75 mL). The reaction was complete within 5 min, and the solution was evaporated, partitioned between ethyl acetate and water, and chromatographed to afford 3.69 g (88%) of methyl 5-(dipropylamino)-1,2,3,4-tetrahydro-1-(*tert*-butoxycarbonyl)-α-oxo-8-quinolinebutenoate (**47e**) as an oil.[48] This was dissolved in TFA (100 mL); after 15 min, the TFA was evaporated, the residue was partitioned between ethyl acetate and 4 N sodium hydroxide solution, and the ethyl acetate was washed with water and evaporated. The residue was chromatographed using ethyl acetate/hexane (1:20) as the initial eluant to give 2.18 g of **48a**. A portion of the product (0.4 g) was converted to the dihydrochloride salt (0.44 g), mp 133–7 °C from methanol/ether. Anal. ($C_{19}H_{28}N_2O_2$·2HCl) C, H, N.

6-(Dipropylamino)-6,7-dihydro-3*H*,5*H*-benzo[*ij*]-quinolizin-3-one (21). A solution of methyl 5-(dipropylamino)-1,2,3,4-tetrahydro-α-oxo-8-quinolinebutenoate (**48a**, 1.0 g, 3.2 mmol) and *p*-toluenesulfonic acid (1.2 g, 6.2 mmol) in methanol (10 mL) was heated under reflux for 18 h. The product was partitioned between ethyl acetate and NaOH solution, and the ethyl acetate was washed with water and evaporated. The residue was chromatographed using ethyl acetate/hexane (1:20) as the initial eluant to give 0.77 g (78%) of **21** which was crystallized from hexane, mp 82–4 °C. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

6-(Dipropylamino)-1,2,6,7-tetrahydro-3*H*,5*H*-benzo[*ij*]-quinolizin-3-one (22). Methyl 5-(dipropylamino)-1,2,3,4-tetrahydro-α-oxo-8-quinolinebutenoate (**48a**, 0.7 g, 2.2 mmol) was

(48) NMR signals for compounds **47a–g** were extremely broad; removal of the *tert*-butoxycarbonyl group improved spectrum sharpness.

dissolved in ethanol (150 mL) and hydrogenated in the presence of 10% Pd/C (0.7 g) for 2 h. The catalyst was filtered off, and the solution of methyl 5-(dipropylamino)-1,2,3,4-tetrahydro-α-oxo-8-quinolinebutanoate (**48b**) thus obtained was refluxed for 18 h to effect cyclization to **22**. The ethanol was evaporated and the residue was crystallized from pentane to give 224 mg of **22**, mp 44–6 °C. Anal. ($C_{18}H_{26}N_2O$) C, H, N.

Methyl 3-(Dipropylamino)-1,2,3,4-tetrahydro-8-quinolinecarboxylate (48c). *sec*-Butyllithium (15.3 mL of 1.3 M in hexane, 20 mmol) was added at −78 °C to a stirred solution of **46** (4.4 g, 13.2 mmol) in THF (60 mL). After 15 min, methyl chloroformate (4.69 g, 50 mmol) was added, the solution was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The product was partitioned between ethyl acetate and water, and the ethyl acetate was evaporated. The residue was chromatographed using ethyl acetate/hexane (1:10) as the initial eluant to give 3.21 g (83%) of **47f**.[48] This was stirred in methanolic hydrogen chloride (50 mL of 5.2 N) for 1 h, evaporated, and partitioned between ethyl acetate and sodium hydroxide solution. Evaporation of the ethyl acetate gave 2.2 g of **48c**: NMR δ 0.88 (t, 6 H), 1.43 (m, 4 H), 2.51 (m, 4 H), 2.78 (d of d, J = 10.0 and 16.0 Hz, 1 H, C(4)H_{ax}), 2.84 (d of d, J = 5.5 and 16.0 Hz, 1 H, C(4)H_{eq}) 3.08 (m, 1 H, C(3)H_{ax}), 3.19 (d of d, J = 11.1 and 11.7 Hz, 1 H, C(2)H_{ax}), 3.50 (m, 1 H, C(2)H_{eq}), 3.88 (s, 3 H), 6.46 (t, 1 H), 7.07 (d, 1 H), 7.70 (d, 1 H), and 7.73 (s, 1 H).

3-(Dipropylamino)-1,2,3,4-tetrahydro-8-quinolinemethanol (48d). Sodium bis(2-methoxyethoxy)aluminum hydride (4.83 mL of 3.4 M in toluene, 16.4 mmol) was added to a stirred solution of methyl 3-(dipropylamino)-1,2,3,4-tetrahydro-8-quinolinecarboxylate (**48c**, 1.0 g, 3.3 mmol) in THF (20 mL). After 1 h ethyl acetate was added and the solvents were removed. The product was partitioned between ethyl acetate and water and chromatographed on silica gel to give 0.69 g (80%) of **48d**. Crystallization from ethyl acetate/hexane gave 0.58 g of product, mp 66–9 °C. Anal. ($C_{16}H_{28}N_2O$) C, H, N.

6-(Dipropylamino)-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[1,2,3-*ij*]-3,1-benzoxazin-3-one (23). Phosgene (1.4 mL of 1.93 M in toluene, 2.7 mmol) was added to a stirred solution of **48d** (0.69 g, 2.6 mmol) in THF (10 mL). Triethylamine was added after 45 min, and after a further 30 min, the solvent was evaporated and the residual oil was partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate was evaporated, and the residue was chromatographed on silica gel using ethyl acetate/hexane (1:10) as the initial eluant to give 0.45 g (53%) of **23**. The product was dissolved in methanol/ether and acidified with ethereal hydrogen chloride to give 0.37 g of the hydrochloride salt of **23**, mp 192–5 °C dec. Anal. ($C_{17}H_{24}N_2O_2$·HCl) C, H, Cl, N.

3-(Dipropylamino)-1,2,3,4-tetrahydro-8-quinolinecarboxamide (48e). Phosgene (1.5 mL of 1.93 M in toluene, 2.9 mmol) was added to a stirred solution of **48c** (0.41 g, 2.6 mmol) in THF (20 mL). Ammonia gas was passed through the solution for 15 min, and the solvents were evaporated. The product was partitioned between ethyl acetate and water and chromatographed on silica gel using ethyl acetate/hexane as the eluant to give 0.31 g of **48e**. Crystallization from ethyl acetate/hexane gave 0.22 g of product, mp 102–4 °C. Anal. ($C_{18}H_{27}N_3O_2$) C, H, N.

6-(Dipropylamino)-1,2,6,7-tetrahydro-3*H*,5*H*-pyrido-[3,2,1-*ij*]quinazolin-3-one (24). Sodium bis(2-methoxyethoxy)aluminum hydride (4.83 mL of 3.4 M in toluene) was added to a stirred solution of 3-(dipropylamino)-1,2,3,4-tetrahydro-8-quinolinecarboxamide (0.55 g) in THF (20 mL). After 1 h ethyl acetate was added and the solvents were removed. The product was partitioned between ethyl acetate and water and chromatographed on silica gel to give 0.40 g of **48f**: NMR δ 0.89 (t, 6 H), 1.51 (m, 4 H), 2.54 (m, 4 H), 2.87 (m, 2 H), 3.15 (m, 2 H), 3.50 (m, 1 H), 3.84 (s, 2 H), 6.57 (t, 1 H), 6.88 (d, 1 H), and 7.95 (d, 1 H).

This was dissolved in THF (10 mL) and 1,1′-carbonyldiimidazole (300 mg) was added. After 30 min, the solvent was removed and the residual oil was chromatographed on silica gel using chloroform as the eluant to obtain the pure product. Crystallization from ethyl acetate/hexane gave 315 mg of **24**: mp 116–9 °C; NMR δ 0.88 (t, 6 H), 1.46 (m, 4 H), 2.53 (m, 4 H), 2.81 (d, J = 7.9 Hz, 2 H, C(7)H_2), 3.05 (m, 1 H, C(6)H_{ax}), 3.17 (d of d, J = 11.1 and 11.9 Hz, 1 H, C(5)H_{ax}), 4.37 (d of d, J = 3.0 and 11.9 Hz, 1 H, C(5)H_{eq}), 4.40 (d of d, J = 3.0 and 13.5 Hz, 1 H, C(1)H), 4.45 (d of d, J = 2.0 and 13.5 Hz, 1 H, C(1)H), 5.07 (s, 1 H, NH), 6.90 (m, 2 H), and 7.02 (m, 1 H). Anal. ($C_{17}H_{25}N_3O$) C, H, N.

Diethyl (1-Oxopropyl)malonate. Triethylamine (20 g, 0.20 mol) and propionic anhydride (12.54 g, 0.096 mol) were added to diethyl aminomalonate hydrochloride (20.40 g, 0.096 mol) in THF (300 mL), and the reaction was stirred at room temperature for 45 min. The solvent was removed under reduced pressure and the crude product was partitioned between ethyl acetate and water. The ethyl acetate phase was separated and evaporated to give 34.64 g of white solid. This was dissolved in hot ethyl acetate (60 mL), hexane (60 mL) was added, and the solution was filtered to remove insoluble material. The solution was cooled to −10 °C and filtered to give 17.63 g (72%) of diethyl (1-oxopropyl)malonate, mp 89–93 °C. Anal. ($C_{10}H_{17}NO_5$) C, H, N.

Diethyl [(1-Oxopropyl)amino](8-quinolinylmethyl)-propanedioate (50). Diethyl (1-oxopropyl)malonate (15.14 g, 0.065 mol) was added to a stirred solution of sodium ethoxide in ethanol (165 mL of 0.4 M, 0.066 mol). After 5 min, 8-(bromomethyl)quinoline[26] (13.15 g, 0.059 mol) was added and the solution was stirred for an additional 15 min. The solvent was removed under reduced pressure and the product was dissolved in ethyl acetate (300 mL) which was washed with water (3 × 10 mL). The ethyl acetate was removed and the residual solid (27.3 g) was crystallized from ethyl acetate/hexane to give 21.6 g (98%) of **50**, mp 80–100 °C. Recrystallization of an aliquot (4 g) from ethyl acetate/hexane gave 2.87 g of product, mp 104–6 °C. Anal. ($C_{20}H_{24}N_2O_5$) C, H, N.

Ethyl 2,3,6,7-Tetrahydro-3-oxo-2-[(1-oxopropyl)amino]-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylate (51). A mixture of diethyl [(1-oxopropyl)amino](8-quinolinylmethyl)propanedioate (**50**, 17.47 g, 0.047 mol) and platinum oxide (0.72 g) in glacial acetic acid (150 mL) was hydrogenated (50 lb initial pressure) until hydrogen uptake ceased (1.8 equiv). The mixture was filtered through Celite and the solvent removed under reduced pressure. The product was crystallized from ethyl acetate to give 12.08 g (78%) of **51**, mp 136–40 °C. A sample was recrystallized from ethyl acetate for analysis, mp 137–41 °C. Anal. ($C_{18}H_{22}N_2O_4$) C, H, N.

***N*-(2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo[*ij*]quinolizin-2-yl)propanamide (52).** Sodium hydroxide solution (10 mL of 4.0 N, 0.04 mol) was slowly added to ethyl 2,3,6,7-tetrahydro-3-oxo-2-[(1-oxopropyl)amino]-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylate (**51**, 3.30 g, 10 mmol) in methanol (50 mL). After stirring at room temperature for 30 min, the solvent was removed under reduced pressure. The resulting solid was dissolved in water (20 mL) and methanol (trace), neutralized with 4 N HCl (10 mL, 0.04 mol), and cooled to −10 °C, and the precipitate was filtered off and air dried to give 2.86 g of 2,3,6,7-tetrahydro-3-oxo-2-[(1-oxopropyl)amino]-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid. This was refluxed in ethanol for 20 min to effect decarboxylation. The ethanol was removed under reduced pressure and the solid was crystallized from ethyl acetate/hexane to give 1.85 g (69%) of **52**, mp 151–4 °C. Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

2,3,6,7-Tetrahydro-*N*-propyl-1*H*,5*H*-benzo[*ij*]quinolizin-2-amine (53). *N*-(2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo[*ij*]-quinolizin-2-yl)propanamide (2.5 g, 0.01 mol) was dissolved in anhydrous ether (500 mL). The solution was cooled to 0 °C, lithium aluminum hydride (1.46 g, 0.038 mol) was added, and the reaction was refluxed for 4 h. The reaction was quenched with ethyl acetate and methanol, the solvents were removed under reduced pressure, and the material was partitioned between ethyl acetate (400 mL) and water (50 mL). Evaporation of the ethyl acetate phase gave 2.35 g of yellow oil. The product was purified by chromatography on silica gel. Elution of the column with 1% and 2.5% methanol/chloroform gave 2.07 g (93%) of **53**. The bulk of the product was converted to the hemifumarate salt which was recrystallized from methanol/ether; mp 190–4 °C. Anal. ($C_{15}H_{22}N_2$·0.5$C_4H_4O_4$) C, H, N.

2,3,6,7-Tetrahydro-*N*,*N*-dipropyl-1*H*,5*H*-benzo[*ij*]-quinolizin-2-amine (25). A mixture of 2,3,6,7-tetrahydro-*N*-propyl-1*H*,5*H*-benzo[*ij*]quinolizin-2-amine (**53**, 2.33 g, 0.01 mol), propyl iodide (5.16 g, 0.03 mol) and anhydrous potassium carbonate (3 g, 0.02 mol) in dimethylformamide (75 mL) was stirred

for 5 h at 90 °C. At this time additional propyl iodide (1.72 g, 0.01 mol) and potassium carbonate (0.5 g, 0.0036 mol) were added and the reaction was continued for an additional 2 h. The reaction was cooled and filtered to remove inorganic material, and the solvent was removed under reduced pressure. The product was partitioned between ethyl acetate (800 mL) and 4 N sodium hydroxide (20 mL, 0.08 mol), the organic layer concentrated, filtered, and chromatographed on silica gel in 5–30% ethyl acetate/hexane to give 2.19 g (79%) of **25**. A portion of the product was converted to the fumarate salt, mp 112.5–6 °C. Recrystallization from methanol/ether gave light brown crystals, mp 112–6 °C. Anal. ($C_{18}H_{28}N_2 \cdot C_4H_4O_4$) C, H, N.

***tert*-Butyl (6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)carbamate (54).** A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (**30**, 3.45 g, 0.01 mol), di-*tert*-butyl dicarbonate (3.0 g, 0.014 mol) and triethylamine (2.0 g, 0.02 mol) in DMF (50 mL) was stirred at room temperature for 1 h. Water (7 mL) was slowly added to the stirred solution. The precipitate was filtered off, washed with water, and air dried to give 3.7 g of **54**, mp 193–5 °C. Anal. ($C_{14}H_{18}BrN_3O_4$) C, H, N, Br.

***tert*-Butyl (1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)carbamate (55).** A mixture of *tert*-butyl (6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)carbamate (**54**, 3.72 g, 0.01 mol), absolute ethanol (150 mL), and 10% palladium on carbon (0.60 g) was hydrogenated (50 lb hydrogen pressure) for 18 h. The mixture was filtered through Celite and the solvent removed. The residual foam was partitioned between ethyl acetate and 1 N sodium hydroxide, and the ethyl acetate phase was evaporated under reduced pressure to give 2.72 g of *tert*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolinyl)carbamate as an oil. This was dissolved in THF (100 mL) and stirred while a solution of phosgene in THF (20.7 mL of 0.40 M, 0.093 mol) was added. After 5 min, triethylamine (2.08 g, 0.020 mol) was added and the solution stirred for an additional 10 min. The THF was removed under reduced pressure, and the material was partitioned between chloroform (250 mL) and water (20 mL). The chloroform was washed with 4 N sodium hydroxide (5 mL) and evaporated. The crude material was purified by chromatography on silica gel in 1% methanol/chloroform to give 1.90 g of product. Crystallization from methanol/ether (1:1) gave 1.33 g (54%) of **55**, mp 235–6 °C. Anal. ($C_{15}H_{19}N_3O_3$) C, H, N.

5-Amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (56). Compound **55** (2.43 g, 8.4 mmol) was stirred in methanolic hydrogen chloride (220 mL of 4 N) until deprotection was complete (5 h). The solvent was evaporated, and the residue was crystallized from methanol/ether to give 1.92 g of **56**, mp >300 °C. Anal. ($C_{10}H_{11}N_3O \cdot HCl \cdot 0.5H_2O$) C, H, Cl, N.

Preparation of Amines 57–66. The propylamine analogue **57** was prepared by reductive amination of **56** with propionaldehyde and sodium cyanoborohydride (see below). The synthesis of dimethylamine **61** is also described below. By reaction of **56** with the appropriate alkyl halide using the general conditions used to prepare **32** described above, a mixture of secondary and tertiary amines was obtained which were separated by chromatography. By using allyl bromide as the halide, compounds **58** and **62** were obtained; cyclopropylmethyl bromide afforded **59** and **65**; butyl bromide gave **60** and **66**.

5-(Propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-quinolin-2(1*H*)-one Hydrochloride (57). A mixture of 5-amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (**56**, 1.90 g, 8.4 mmol), methanol (175 mL), sodium methoxide (0.85 mL of 25% in methanol), propionaldehyde (1.5 g), and sodium cyanoborohydride (0.16 g) was stirred at room temperature for 5 h. Methanolic ammonia solution was added, and, after 30 min, the solvent was evaporated. The residual oil was partitioned between ethyl acetate and water, the ethyl acetate was evaporated, and the residual oil was dissolved in chloroform and chromatographed on silica gel using 2.5% methanol/chloroform as the eluant to give 1.24 g (64%) of product. This was dissolved in methanol (6 mL) and acidified with 4 N methanolic HCl and filtered to give 1.13 g (50%) of **57** as the hydrochloride salt, mp >300 °C. Anal. ($C_{13}H_{17}N_3O \cdot HCl$) C, H, Cl, N.

5-(Dimethylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-quinolin-2(1*H*)-one Hydrochloride (61). 5-Amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one hydrochloride (**56**, 0.73 g, 3.2 mmol) was dissolved in 1 N sodium hydroxide solution (3.2 mL). Ethanol (100 mL), 37% formaldehyde solution (1.3 mL), and 10% palladium on carbon (0.65 g) were added, and the mixture was hydrogenated (50 lb initial hydrogen pressure) until hydrogen uptake ceased (reaction time 5 h). The mixture was filtered and evaporated, and the crude material was combined with that of a previous reaction (2.5 mmol), dissolved in chloroform, and gravity filtered to remove paraformaldehyde. The compound was purified by chromatographing on silica gel in 10% methanol/chloroform to give 0.88 g (71%) of **61**. The product was treated with methanolic HCl, and the hydrochloride salt was crystallized from methanol/ether to give 0.95 g (65% yield) of white powder, mp 220–3 °C. Anal. ($C_{12}H_{15}N_3O \cdot HCl \cdot 0.5H_2O$) C, H, Cl, N.

Determination of Crystal Structure and Absolute Configuration of (*R*)-5. Intensity data from a clear needle 0.12 × 0.13 × 0.33 mm, was collected on a Siemens $P2_1$ diffractometer with graphite monochromator, controlled by a Harris computer, using Cu Kα radiation, λ(Cu Kα) = 1.5418 Å; the maximum 2θ was 135°. A total of 2735 unique reflections were measured, using 4°/min $\theta/2\theta$ step scans, and scan widths > 3.4°. A total of 2694 reflections had intensities > 2σ. Ten reflections periodically monitored showed no trend towards deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $0.01I^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least-squares fit of Kα_1 2θ values (λKα_1 = 1.5402) for 25 high 2θ reflections.[49] Lorenz and polarization correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[50] A partial trial solution (10 atoms), obtained by direct methods, using DIREC,[51] was extended using successive Fourier syntheses; hydrogens were found in difference maps very close to positions generated using planar or tetrahedral geometry. Least-squares refinement included coordinates of all atoms (except coordinates of one bromine atom were fixed to satisfy the space group constraint) and anisotropic thermal parameters for non-hydrogen atoms. Isotropic thermal parameters of hydrogen atoms were set 0.5 unit higher than those for attached carbons. The function minimized in the refinement was $\sum w(F_o^2 - F_c^{2*})^2$ where weights w were $1/\sigma^2(F_o^2)$, and F_c^* was as defined by Larson.[52] Atomic form factors were from Doyle and Turner,[53] and, for hydrogen, from Stewart et al.[54] The absolute configuration was determined by the method of Bijvoet,[55] comparing accurate measurements of six Friedel pairs of reflections which were very strongly influenced by anomalous dispersion. All six comparisons indicated unequivocally that the enantiomer shown is the correct one.

The final agreement index R was 0.051 when all except eight very intense reflections were included in the refinement, but for this refinement the B_{11} thermal parameters for several atoms in proximity to the bromine atoms refined to negative values, a physical impossibility. To avoid this, a final refinement was carried out using only 1892 reflections with 2θ < 110°, and with the same eight intense reflections given zero weight. In the final refinement cycle, all shifts were <0.6σ, and the principal axes of the thermal ellipsoids were all positive. Final R was 0.031, wR

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was 0.079, and the standard deviation of fit was 8.9. The coordinates reported in the supplementary material are for this refinement. The CRYM system of computer programs was used.[51]

Data for (*R*)-5: $C_{16}H_{23}N_3O \cdot HBr \cdot H_2O$ M_r = 291.391 × 80.92 × 18.01; triclinic; space group $P1$; unit cell a = 7.284 (4) Å, b = 8.417 (2) Å, c = 14.519 (4) Å; α = 81.12 (3)°, β = 102.68 (4)°, γ = 102.53 (3)°; V = 842.39 Å^3; Z = 2; D_c = 1.46 g cm^{-3}; λ(Cu Kα) = 1.5418 Å; μ = 3.2 mm^{-1}; T = 123(2) K.

Dopamine and Serotonin Binding Assays. Receptor binding studies for the D2 dopamine receptor were carried out using [^{3}H]raclopride (specific activity 80 Ci/mmol, NEN) using homogenates of rat striata prepared with a Polytron and diluted 1:300.[29] Incubation was for 1 h at room temperature, at which time samples were filtered over SS #24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Filters were counted using standard liquid scintillation techniques. Nonspecific binding was determined using haloperidol (1 μM). IC_{50} values were obtained using at least four concentrations of the drug, in triplicate, and calculated using log-probit analysis. K_i values were calculated from IC_{50} values using standard methods; standard error was <5%.

Receptor binding studies for the $5HT_{1A}$ receptor were carried out using [^{3}H]DPAT (specific activity 85 Ci/mmol, NEN) using homogenates of bovine hippocampus prepared with a Polytron and diluted 1:400.[30] Incubation was for 1 h at room temperature, at which time samples were filtered over SS #24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Nonspecific binding was determined using serotonin (1 μM).

Amine Synthesis. Brain levels of DOPA and 5-HTP in the rat were determined as described previously.[10] Briefly, Upjohn CF-1 rats were injected sc with test drug or vehicle at time zero. Fifteen minutes later the rats received an aromatic decarboxylase inhibitor (*m*-hydroxybenzylhydrazine at 100 mg/kg ip). The rats were sacrificed 30 min later, and the tissues in the ventral limbic brain area were removed and frozen for later analysis. Tissues were weighed and extracted in 0.1 N perchloric acid containing an internal standard of dihydroxybenzylamine (2 μg/mL). The extract was then analyzed by HPLC using a Bioanalytical Systems ODS column. DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima software. Biochemical differences were compared between a control (n = 6) and a test group (n = 6) by unpaired t test.

Recordings from Dopaminergic and Serotonergic Neurons. Charles River male Sprague-Dawley rats (280–330 g) were anesthetized with chloral hydrate (400 mg/kg ip). Supplemental doses were administered as needed to maintain anesthesia. The femoral artery and vein were cannulated for blood pressure and drug administration. The animal's head was held in a stereotaxic device and a small burr hole drilled at the appropriate location. Extracellular action potentials were recorded with a glass microelectrode (tip size < 1 μm) filled with pontamine sky blue dye in 2 M sodium chloride. Dopaminergic neurones were identified by their long duration action potential (>2.5 ms), shape, and firing pattern (>12 spikes/s) as previously described.[56] The recording electrode was hydraulically lowered into the substantia nigra pars compacta area (P 5.0–6.0 mm, L 2.0–2.2 mm, V 7.0–8.0 mm) according to the coordinates of Paxinos and Watson.[57] Serotonergic neurones were identified by their large, biphasic positive–negative action potentials with slow and regular firing rates (approximately 0.8–2.5 spikes/s) as previously described.[58] The recording electrode was hydraulically advanced to reach the dorsal raphe nucleus (A 0.5–1.7 mm, L 0 mm, V 3.5–4.2 mm) according to the coordinates of Paxinos and Watson.[57] At the termination of each recording session, the location of the cell was identified by passing a 10-μA cathodic current for 10–20 mins. The brain was then removed, sectioned, and stained, and the pontamine sky blue deposit verified in each animal. Only those cells found to be in the appropriate area were included in the study. All drug solutions were made in distilled water. Each drug injection contained no more than 0.15 mL of a given concentration, followed by 0.2–0.4 mL of physiological saline to clean the catheter of any residual drug. Drug effects were measured as changes in firing rates as indicated by an integrated ratemeter output throughout the experiment. The dose required to depress neuronal firing by 50% was taken as the ED_{50}, measured by interpolation of the dose–response curve for each individual cell.

Supplementary Material Available: Tables of atomic coordinates, isotropic thermal parameters, bond lengths and angles, torsion angles, anisotropic thermal parameters, hydrogen bonds, and close intermolecular contacts (6 pages). Ordering information is given on any current masthead page. The atomic coordinates are deposited at the Cambridge Crystallographic Data Centre.

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Noncataleptogenic, Centrally Acting Dopamine D-2 and Serotonin 5-HT$_2$ Antagonists within a Series of 3-Substituted 1-(4-Fluorophenyl)-1*H*-indoles

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A series of 1-(4-fluorophenyl)-1*H*-indoles substituted at the 3-position with 1-piperazinyl, 1,2,3,6-tetrahydro-4-pyridinyl, and 4-piperidinyl was synthesized. Within all three subseries potent dopamine D-2 and serotonin 5-HT$_2$ receptor affinity was found in ligand binding studies. Quipazine-induced head twitches in rats were inhibited by most derivatives as a measure of central 5-HT$_2$ receptor antagonism. Piperazinyl and tetrahydropyridyl indoles were cataleptogenic, while piperidyl substituted indoles surprisingly were found to be noncataleptogenic or only weakly cataleptogenic. Noncataleptogenic piperidyl derivatives also failed to block dopaminergic-mediated stereotypies, that is methyl phenidate-induced gnawing behavior in mice. These profiles resemble that of the atypical neuroleptic clozapine. 1-Ethyl-2-imidazolidinone was found to be the optimal substituent of the basic nitrogen atom in order to avoid catalepsy. The atypical neuroleptic 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (sertindole, compound 14c) was selected for further development as a result of these structure/activity studies.

Introduction

Treatment of psychoses such as schizophrenia, mania, paranoia, and the like with neuroleptic drugs has been well established since the introduction of chlorpromazine about 40 years ago. For most schizophrenic patients, positive symptoms like hallucinations and delusions are alleviated by this medication while negative symptoms like blunted affect, emotional withdrawal, apathy, and motor retardation are poorly treated. Severe side effects are frequently experienced during antipsychotic drug treatment. In-

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