Amino acid and peptide derivatives have a variety of medicinally and agriculturally important activities. QSAR approaches to these classes of compounds have been scarce, probably because of insufficient hydrophobicity data and the lack of a way to express their steric features. The work of Fauchere and Pliska[5] provided us with the basis for the present study with respect to hydrophobicity. They analyzed some medicinal peptides by using steric bulk parameters,[14] but their results can perhaps be further elaborated. Directional steric parameters based on the CPK model are useful in the study of structure-activity relationships of dipeptide sweeteners.[15] The dimensional parameter *D* has been developed for analysis of long-chain terpenoid molecules with insect juvenile hormone activity.[13] The results led to the development of new classes of active compounds.[16] The present study and the related ones cited above may serve as prototypes of how to unravel structure-activity puzzles of such complex molecules as amino acids, peptides, and their derivatives.

Experimental Section

Test Compounds. Compounds **1-8**, **10**, and **75** were kindly provided by the Tanabe Seiyaku Co., Ltd., and others were purchased from the Sigma Chemical Co., Wako Pure Chemical Industries, Ltd., and Tokyo Kasei Kogyo Co. Ltd.

Bitter Thresholds. The preparation of the test solution and the methods of evaluation were essentially the same as those reported by Wieser and Belitz.[1,2] Briefly, a series of solutions of increasing concentration in which one solution was twice as strong as the preceding one was prepared, and a 2-3-mL portion of each was tested by each person. The panel consisted of six persons. When the compound was a hydrochloride or an *N*-acyl derivative, the solution was neutralized with 0.1 N NaOH. The standard error of the determination was within ±15%.

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Registry No. **1**, 72-18-4; **2**, 61-90-5; **3**, 73-32-5; **4**, 147-85-3; **5**, 63-91-2; **6**, 60-18-4; **7**, 73-22-3; **8**, 56-87-1; **9**, 74-79-3; **10**, 71-00-1; **11**, 1963-21-9; **12**, 869-19-2; **13**, 688-13-1; **14**, 19461-38-2; **15**, 704-15-4; **16**, 3321-03-7; **17**, 34258-14-5; **18**, 2390-74-1; **19**, 658-79-7; **20**, 3303-45-5; **21**, 3303-34-2; **22**, 3061-90-3; **23**, 686-43-1; **24**, 27493-61-4; **25**, 3918-94-3; **26**, 3989-97-7; **27**, 686-50-0; **28**, 7298-84-2; **29**, 3303-31-9; **30**, 17665-02-0; **31**, 38689-30-4; **32**, 3063-05-6; **33**, 5156-22-9; **34**, 968-21-8; **35**, 868-28-0; **36**, 24787-73-3; **37**, 41017-96-3; **35**, 26462-22-6; **39**, 42537-99-5; **40**, 37462-92-3; **41**, 13589-06-5; **42**, 59652-59-4; **43**, 54532-76-2; **44**, 59652-60-7; **45**, 42516-53-0; **46**, 22677-60-7; **47**, 6403-14-1; **48**, 59652-61-8; **49**, 6422-36-2; **50**, 52899-07-7; **51**, 51926-51-3; **52**, 19786-36-8; **53**, 13589-02-1; **54**, 721-90-4; **55**, 3303-55-7; **56**, 7669-65-0; **57**, 2577-40-4; **58**, 17355-18-9; **59**, 36099-95-3; **60**, 20696-60-0; **61**, 17355-10-1; **62**, 6665-16-3; **63**, 14857-82-0; **64**, 59685-29-9; **65**, 4306-24-5; **66**, 1187-50-4; **67**, 19408-48-1; **68**, 58337-01-2; **69**, 10329-75-6; **70**, 56243-96-0; **71**, 58337-00-1; **72**, 2743-60-4; **73**, 2577-90-4; **74**, 21685-51-8; **75**, 1080-06-4; **76**, 949-67-7; **77**, 4299-70-1; **78**, 7479-05-2; **79**, 1499-46-3; **80**, 1188-21-2; **81**, 2018-61-3; **82**, 1218-34-4; **83**, 495-69-2; **84**, 2198-64-3; **85**, 17966-60-8; **86**, 1492-11-1; **87**, 2361-96-8; **88**, 21156-62-7; **89**, 2382-80-1; **90**, 840-97-1; **91**, 54793-73-6; **92**, 27560-15-2; **93**, 38155-19-0; **94**, 29852-55-9; **95**, 4033-42-5; **96**, 38155-16-7; **97**, 59652-62-9; **98**, 17554-10-8; **99**, 38155-11-2; **100**, 56-40-6; **101**, 56-41-7; **102**, 70-47-3; **103**, 56-84-8; **104**, 56-85-9; **105**, 56-86-0; **106**, 56-45-1; **107**, 72-19-5; **108**, 52-90-4; **109**, 63-68-3; **110**, 556-50-3; **111**, 926-77-2; **112**, 1188-01-8; **113**, 2867-20-1; **114**, 2578-57-6; **115**, 52899-09-9; **116**, 556-33-2; **117**, 997-05-7; **118**, 58336-99-5; **119**, 54865-20-2; **120**, 22849-49-6; **121**, 40204-87-3; **122**, 59005-83-3; **123**, 109552-74-1; **124**, 58337-03-4; **125**, 10576-91-7; **126**, 327-57-1; **127**, 6600-40-4; **128**, 70-26-8; **129**, 80-60-4.

Synthesis of Some [*N*-(2-Haloalkyl)amino]tetralin Derivatives as Potential Irreversible Labels for Bovine Anterior Pituitary D_2 Dopamine Receptors

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A series of hydroxylated 2-aminotetralins were prepared in the search for irreversible labels for D_2 dopamine receptors. *N*-2-Haloacetyl and *N*-2-haloalkyl substituents were chosen as potential receptor alkylating groups. Titrimetric studies were carried out on [*N*-(chloroethyl)-*N*-methylamino]tetralins **10**, **10a**, **24**, and **26** to demonstrate that aziridinium ions were formed as reactive intermediates from these compounds. This observation was confirmed by ^{1}H NMR studies on compound **10**. The majority of the aminotetralins prepared showed reasonably high affinity binding to anterior pituitary D_2 dopamine receptors and exhibited agonist properties. Structure-activity results are presented together with preliminary studies designed to identify irreversible receptor binding agents. [*N*-(2-Chloroethyl)-*N*-propylamino]-6,7-dihydroxytetralin hydrobromide (**18**) proved most promising in these studies.

Many of the important physiological actions of dopamine are mediated via its binding to D_2 dopamine receptors, and these receptors are also key sites of action of antipsychotic and anti-Parkinsonian drugs. The receptors have been extensively characterized recently by using the ligand binding technique,[1] the mechanism of action of the receptor has been probed,[2,3] and progress has been made toward isolation of the receptor protein.[4]

A selective irreversible label for the receptor would be an extremely useful tool for studying the receptor, and recently several photolabile-modified dopamine antagonists have been prepared, e.g., azidoclebopride,[5,6] azidosulpiride,[7] and *N*-(*p*-azido-*m*-iodophenethyl)spiperone.[8] An agonist-derived irreversible label would also be useful for studying the receptor, and *N*-(chloroethyl)norapomorphine was prepared[9] in this regard. Although early studies in-

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[‡] Queen's Medical Centre.

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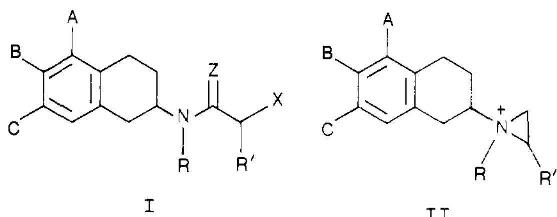
dicated that this compound might be useful,[9,10] subsequent work has cast doubts on its specificity.[11,12] Aminotetralins are fairly selective D_2 receptor agonists[1] so that irreversible labels based on this structure might be of use. In this paper we report the synthesis of a number of aminotetralins (I) with *N*-2-haloacetyl or *N*-2-haloalkyl substituents as potential irreversible agents. These substituents should provide alkylating groups, the latter after conversion to aziridinium ions (II). Preliminary biological studies on the interaction of these compounds with D_2 dopamine receptors from anterior pituitary are also reported.



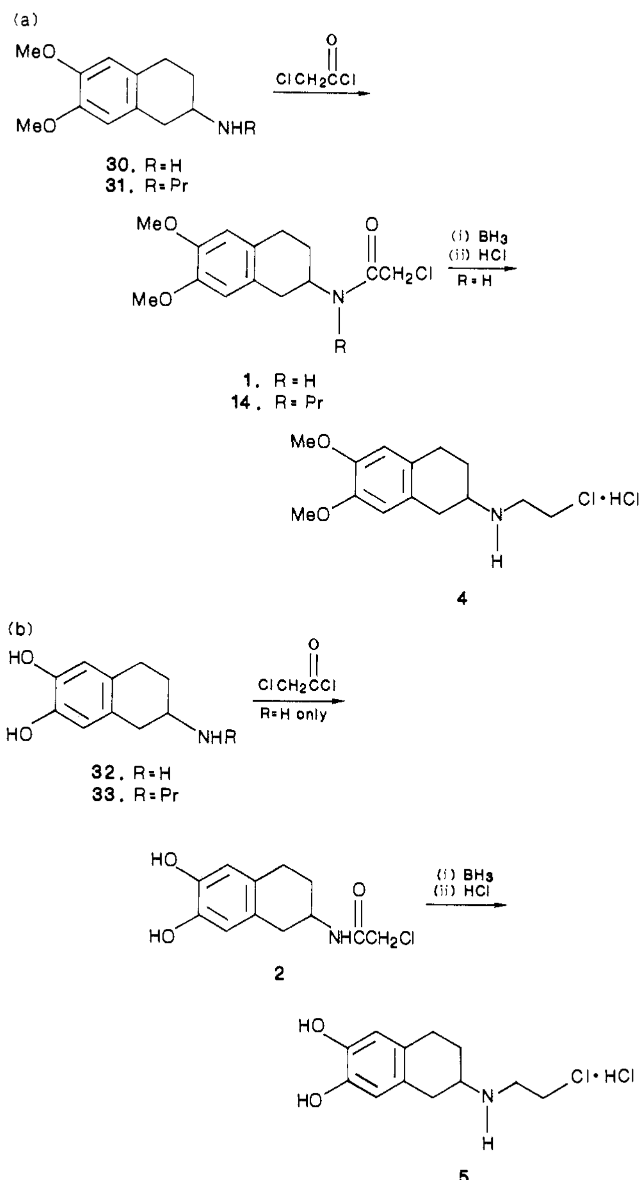
A,B,C = OMe, OH, or H; X = halogen; R, R′ = H or alkyl; Z = O or H, H

Synthesis of [*N*-(Haloalkyl)amino]tetralins. Three series of compounds were prepared (Table I). Most attention was focused on the 6,7-dioxygenated aminotetralins although a limited number of 5,6-dioxygenated and 6-oxygenated compounds were also prepared. Two synthetic routes were explored, and these are illustrated in Schemes I and II with representative examples from the 6,7-dioxygenated series.

The Acylation–Reduction Approach (A, Scheme I). This approach provides a means of obtaining both *N*-haloacetyl and, by subsequent amide reduction, the required *N*-haloalkyl derivatives. Since both types of compound were of interest as potential irreversible binding agents, this approach was investigated first. The amines **30** and **31** were prepared from the corresponding tetralone[13a] by using literature procedures[13b] and were acylated with chloroacetyl chloride to give the chloro amides **1** and **14**. All attempts to demethylate these compounds to produce the corresponding 6,7-dihydroxy derivatives were unsuccessful. Fortunately, the 6,7-dihydroxy chloro amide **2** could be prepared directly by treatment of the dihydroxy amine **32**[13] with chloroacetyl chloride in methanol although attempts to use this procedure for the acylation of the corresponding *N*-propyl analogue **33**[13] were not successful. Reduction of amides **1** and **2** with diborane in THF[14] gave the corresponding *N*-chloroethyl compounds **4** and **5** in good yield. This approach was not used for the synthesis of any other *N*-haloalkyl compounds because of the greater efficiency and flexibility of the reductive amination route.

The Reductive Amination Route (B, Scheme II). It was found that 6,7-dimethoxytetralone **34**[15] undergoes

Scheme I



efficient reductive amination on treatment with ethanolamine (or 2-hydroxypropylamine) and sodium cyanoborohydride.[13,16] Attempts to use *N*-(2-hydroxyethyl)propylamine in this reaction and so prepare tertiary amines directly were unsuccessful.

Treatment of the resulting amino alcohol **3** with refluxing hydrobromic acid leads to O-demethylation and bromide formation giving the *N*-bromoethylamine **6**. Alternatively, the amino alcohol **3** could be subjected to a second reductive amination, formaldehyde, glycoaldehyde, and propionaldehyde being used in the present work. Demethylation of the resulting tertiary amino alcohol **15** with hydrobromic acid gave the *N*-bromoethyl derivative **19** and the corresponding *N*-hydroxyethyl compound **16** when boron tribromide[17] in dichloromethane was employed. The corresponding *N*-chloroethyl compound **18** could be obtained by treating the amino alcohol **15** with thionyl chloride and then carrying out the demethylation of chloride **17** with boron tribromide[17] or boron tri-

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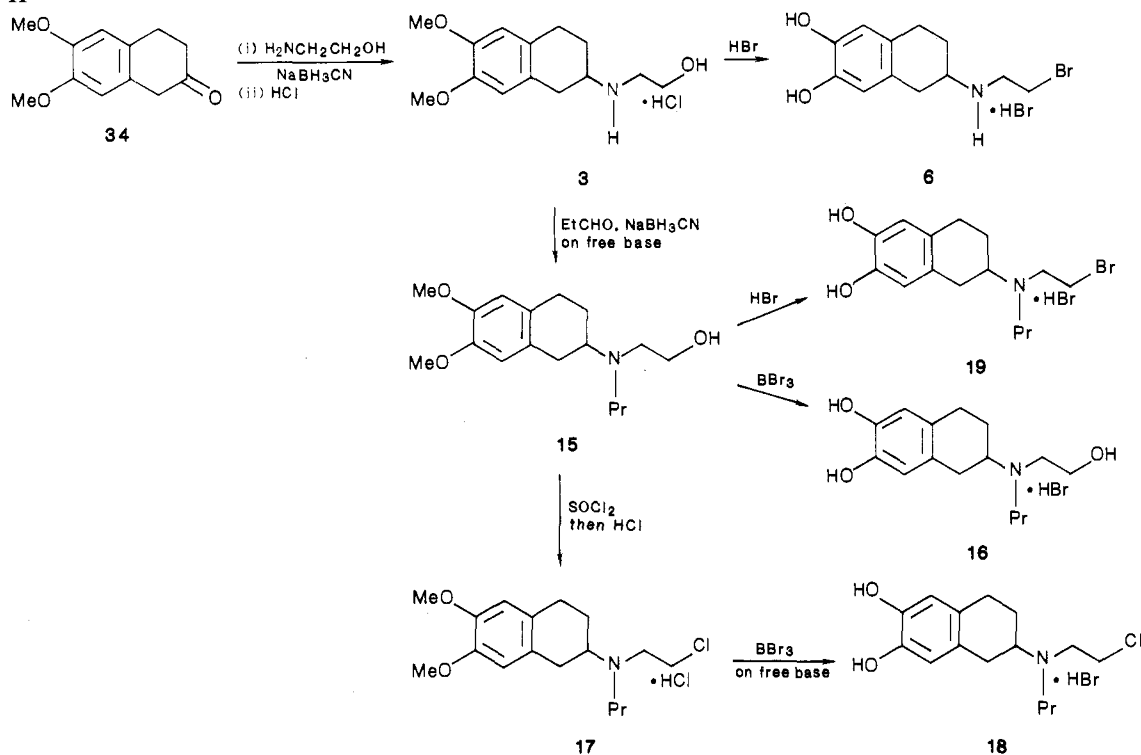
Scheme II



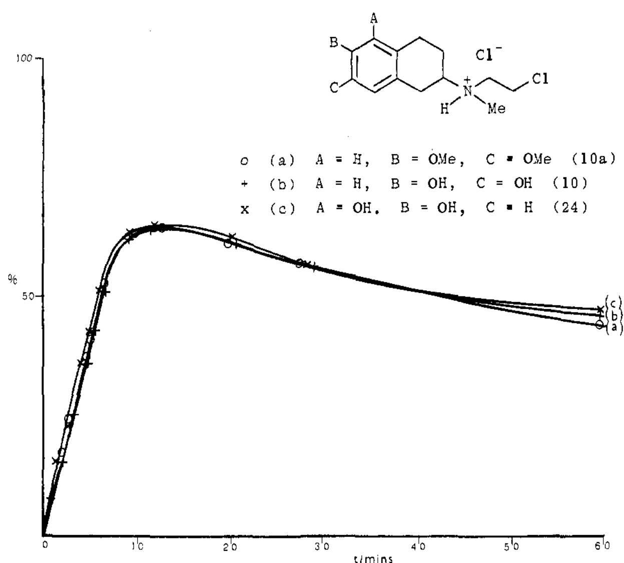


Figure 1. Formation and decay of aziridinium ions from [*N*-(2-chloroethyl)-*N*-methylamino]-6,7-dimethoxy- and 6,7- and -5,6-dihydroxytetralins **10a**, **10**, and **24** in phosphate buffer at pH 7.4, 25 °C.

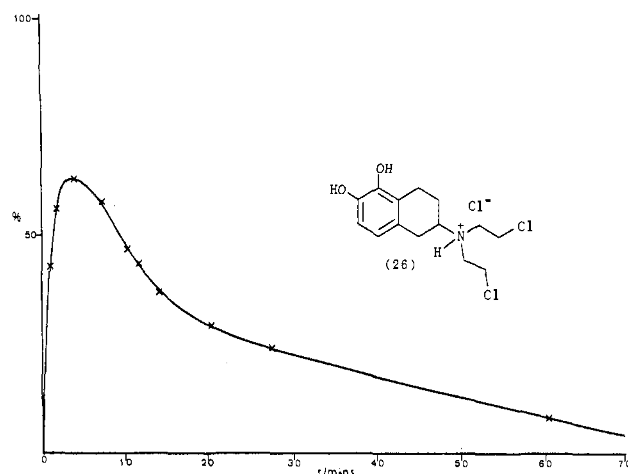


Figure 2. Formation and decay of aziridinium ion from the [*N*,*N*-bis(2-chloroethyl)amino]tetralin **26** in phosphate buffer at pH 7.4, 25 °C.

chloride.[17] The latter reagent was preferred since halide exchange was sometimes observed when *N*-chloroethyl compounds were treated with boron tribromide, up to 10% of the corresponding *N*-bromoethyl compound being obtained. Similar transformations to those shown in Scheme II were employed to prepare the remaining compounds in the table. 5,6-Dimethoxytetralone **35**[15] and 6-methoxytetralone **36**[18] were used as starting materials for **22–26** and **27–29**, respectively.

Kinetic Studies. The cyclization of *N*-(2-haloalkyl)-alkylamines to give the potentially pharmacologically active aziridinium ions (i.e., I → II) can be monitored in a number of ways.[19-21] Titrimetric[20] and spectroscopic[21] studies of selected [*N*-(haloalkyl)amino]tetralins were carried out in order to confirm that aziridinium ion intermediates are produced and to establish the rate of the cyclization reaction and the rate of aziridinium ion hydrolysis. This information was valuable when the bioassay protocols were being designed.

a. Iodine–Thiosulfate Titration Procedure.[20] The formation and decay of aziridinium ions was first estimated by their quantitative reaction with thiosulfate[20a] by using the iodine back-titration procedure described by Gill and Rang[20b] and Young et al.[20c] (see Experimental Section for

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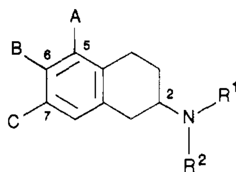
Table I[a]



no.	A	B	C	R^1	R^2	salt	synth route[b]	control: corrected IC_{50}, μM	control: n	control: no. of expts	+ 100 μM GTP: corrected IC_{50}, μM	+ 100 μM GTP: n	+ 100 μM GTP: no. of expts
1	H	MeO	MeO	H	$COCH_2Cl$		A	NA					
2	H	HO	HO	H	$COCH_2Cl$		A	NA					
3	H	MeO	MeO	H	CH_2CH_2OH	HCl	B	NA					
4	H	MeO	MeO	H	CH_2CH_2Cl	HCl	A	NA					
5	H	HO	HO	H	CH_2CH_2Cl	HCl	A	0.30 ± 0.06	0.56 ± 0.03	4	>100		2
6	H	HO	HO	H	CH_2CH_2Br	HBr	B	0.17 ± 0.03	0.67 ± 0.06	4	0.42 ± 0.02	0.82 ± 0.03	2
7	H	MeO	MeO	H	$CH_2CH(CH_3)OH$	HCl	B						
8	H	HO	HO	H	$CH_2CH(CH_3)Br$	HBr	B	0.30 ± 0.08	0.57 ± 0.03	4	1.01 ± 0.60	0.60 ± 0.14	2
9	H	MeO	MeO	Me	CH_2CH_2OH	HCl	B						
10	H	HO	HO	Me	CH_2CH_2Cl	HCl	B	1.82	0.52	1	3.72	0.63	1
11	H	MeO	MeO	CH_2CH_2OH	CH_2CH_2OH		B						
12	H	HO	HO	CH_2CH_2Cl	CH_2CH_2Cl	HCl	B	NA					
13	H	HO	HO	CH_2CH_2Br	CH_2CH_2Br	HBr	B	22.0 ± 6.5	0.66 ± 0.02	3	40.7 ± 2.0	0.55 ± 0.04	2
14	H	MeO	MeO	Pr	$COCH_2Cl$		A	NA					
15	H	MeO	MeO	Pr	CH_2CH_2OH		B	NA					
16	H	HO	HO	Pr	CH_2CH_2OH	HBr	B	0.42 ± 0.03	0.55 ± 0.03	3	2.42 ± 0.38	0.70 ± 0.03	2
17	H	MeO	MeO	Pr	CH_2CH_2Cl	HCl	B	NA					
18	H	HO	HO	Pr	CH_2CH_2Cl	HBr	B	0.076 ± 0.017	0.78 ± 0.03	3	0.26 ± 0.06	0.73 ± 0.08	2
19	H	HO	HO	Pr	CH_2CH_2Br	HBr	B	1.97 ± 0.84	0.59 ± 0.07	2	>100		1
20	H	MeO	MeO	Pr	$CH_2CH(CH_3)OH$		B						
21	H	HO	HO	Pr	$CH_2CH(CH_3)Br$	HBr	B	NA					
22	MeO	MeO	H	H	CH_2CH_2OH	HCl	B						
23	MeO	MeO	H	Me	CH_2CH_2OH	HCl	B						
24	HO	HO	H	Me	CH_2CH_2Cl	HCl	B	32.2 ± 0.1	0.57 ± 0.02	2	>100		1
25	MeO	MeO	H	CH_2CH_2OH	CH_2CH_2OH		B						
26	HO	HO	H	CH_2CH_2Cl	CH_2CH_2Cl	HCl	B	NA					
27	H	MeO	H	H	CH_2CH_2OH	HCl	B						
28	H	MeO	H	Me	CH_2CH_2OH		B						
29	H	HO	H	Me	CH_2CH_2Cl	HCl	B	2.97	1.01	1			

[a] The ability of compounds to displace [^{3}H]spiperone binding from anterior pituitary D_2 dopamine receptors was determined as described in ref 23 and data analyzed to give IC_{50} values (concentration of substance that inhibits half the total specific [^{3}H]spiperone binding; corrected for [^{3}H]spiperone concentration as in ref 23) and pseudo Hill coefficients (n). NA = inactive; where no values are given the compound was not tested. Data are given as mean ± SEM ($n \geq 3$) or mean ± range ($n = 2$). [b] A = acylation–amide reduction approach (see Scheme I). B = reductive amination approach (see Scheme II).

details). Initial studies were carried out at pH 7.4 and 25 °C on the [*N*-(chloroethyl)-*N*-methylamino]tetralins **10a**, **10**, and **24**. The results, which confirmed the formation of aziridinium ion intermediates, are displayed in Figure 1.

The rate of aziridinium ion formation and decay does not appear to be influenced by the oxygenation pattern (5,6 or 6,7) or by the nature of the oxygen-containing groups (HO or MeO). With all three compounds, the highest aziridinium ion concentration (ca. 65% theoretical) occurred after 10–15 min and the decay was relatively slow. These results were consistent with those in the literature.[19,20b,c] The *N*,*N*-bis(2-chloroethyl)amine **26** was studied under the same conditions (Figure 2) and underwent aziridinium ion formation and decay at even faster rates than the corresponding *N*-methyl compounds. Again, this observation finds precedent in the literature.[21] The pH dependence of aziridinium ion decay was established by using the *N*-propyl-*N*-chloroethyl compound **17** as shown in Figure 3. As expected, aziridinium ion decay is fastest at highest hydroxide concentrations.

b. ^{1}H NMR Studies. The cyclization of the [*N*-(chloroethyl)-*N*-methylamino]tetralin **10** was also studied by using ^{1}H NMR, following the general procedure of Levins and Papanastassiou[21] (see Experimental Section for details). Spectra taken 30 and 120 s after liberation of the free base from the hydrochloride salt are shown in

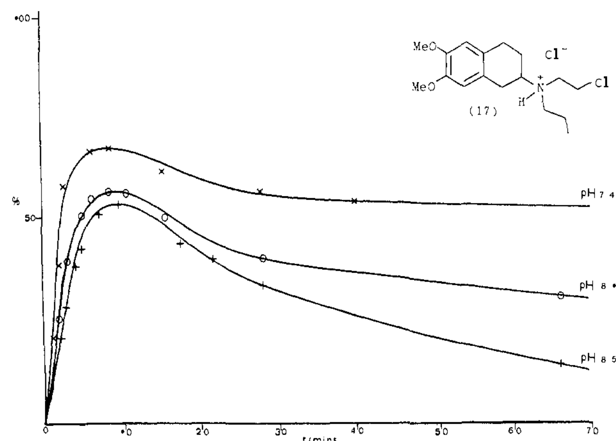


Figure 3. Formation and decay of aziridinium ion from the [*N*-(2-chloroethyl)-*N*-propylamino]tetralin **17** in phosphate buffer at pH 7.4, 8.1, and 8.5, 25 °C.

Figure 4. The progress of the reaction can best be appreciated by observing the *N*-methyl signal as it moves from δ 2.34 (A) in the starting material **10** to δ 2.98 (E) in the aziridinium ion **37**. The methylene signals from the aziridinium ion (δ 3.10 and 3.16) (D) can also be seen increasing in size during these first stages of the reaction as the methylene signals from the starting material de-

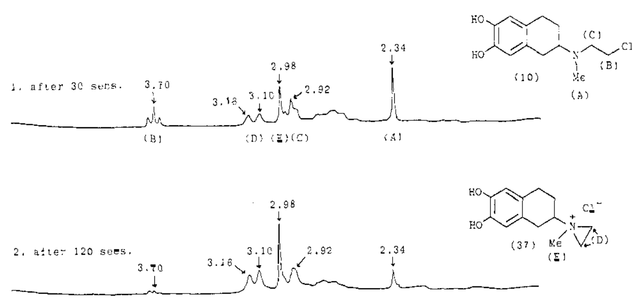


Figure 4. ^{1}H NMR study of the solvolysis of the [*N*-(2-chloroethyl)-*N*-methylamino]tetralin **10** in basic D_2O at 25 °C. Chemical shift values in ppm.

crease (B and C). These assignments are in good agreement with published ^{1}H NMR data for aziridinium ions.[22]

In order to illustrate the formation and decay of the aziridinium ion intermediate, spectra were accumulated at 10-s intervals and displayed in a two-dimensional stacked format (Figure 5). The decay of the starting material **10** and concomitant rise in the concentration of aziridinium intermediate **37** can be seen clearly from the *N*-methyl signals at δ 2.34 (A) and δ 2.98 (E). As the reaction proceeds, the aziridinium ion concentration decreases and a new product [presumably the *N*-(2-hydroxyethyl)amine **38**] is formed, with an *N*-methyl signal at δ 2.30 (G).

Biological Results

Binding of Aminotetralins to Anterior Pituitary D_2 Dopamine Receptors. Binding of compounds indicated in the table to D_2 receptors was tested by displacement of [^{3}H]spiperone binding from anterior pituitary D_2 receptors which have been well characterized.[23] Binding data were obtained in the absence and presence of GTP (100 μM) and analyzed to give IC_{50} values and pseudo Hill coefficients (see Figure 6 for representative data).

Compound **18** has been evaluated for its ability to inactivate D_2 receptors irreversibly, owing to its high affinity for the receptor. Preincubation of **18** in buffer of pH 7.4 for 30 min allowed formation of the aziridinium ion by analogy with the results described above. This solution was then used to treat anterior pituitary membranes for 30 min, after which the membranes were diluted and saturation analysis of [^{3}H]spiperone binding was determined. In a similar experiment with phenoxybenzamine (Figure 7), which is known to act as an irreversible inhibitor of D_2 dopamine receptors,[23] a 42% decrease in the B_{max} for [^{3}H]spiperone binding and an increase in the K_d were observed (control, B_{max} = 56 fmol/mg protein, K_d = 58 pM; + 10 μM phenoxybenzamine, B_{max} = 32 fmol/mg protein, K_d = 271 pM). In the experiments with **18** (Figure 8), a 71% reduction in B_{max} and an increase in K_d were observed (control, B_{max} = 114 fmol/mg protein, K_d = 111 pM; + **18**, B_{max} = 33 fmol/mg protein, K_d = 310 pM). The dimethoxy compound **17**, which is inactive for receptor binding but otherwise structurally similar to **18**, was without effect (B_{max} = 107 fmol/mg protein, K_d = 120 pM, control values as for the experiment with **18**), showing that the effects of **18** were not nonspecific.

Discussion

The majority of the compounds synthesized showed reasonably high affinity binding to anterior pituitary D_2 dopamine receptors, although, except in the case of **18**, the affinities were reduced compared to the parent 6,7-dihydroxy-2-aminotetralin and 6,7-dihydroxy-2-(*N*-propylamino)tetralin (corrected IC_{50} = 74 nM and 75 nM, respectively[23]). In addition, for all the compounds tested (except **29**), displacement of [^{3}H]spiperone was characterized by a pseudo Hill coefficient less than one and displacement occurred with a reduced affinity in the presence of GTP. As we have argued elsewhere,[23] these properties are characteristic of agonists, and it thus may be tentatively concluded that the compounds synthesized are agonists.

With regard to the effects of structure on activity, the following observations may be made.

(i) The presence of methoxyl groups on the aminotetralin ring eliminates receptor binding (compare **17** and **18**). This is in agreement with the proposed requirement of hydroxyl groups for hydrogen bonding to the receptor (see for example ref 1).

(ii) The presence of a haloacetyl group on the 2-amino function eliminates receptor binding (compare **2** and **5**).

(iii) A single *N*-alkyl substituent causes a reduction in binding affinity relative to the parent 6,7-dihydroxyaminotetralin (corrected IC_{50} = 74 nM) except for the case of propyl substitution (corrected IC_{50} = 75 nM).[23]

Substitution of two groups on the 2-amino function causes further reduction in affinity relative to the monosubstituted compounds (e.g., the 6,7-dihydroxy compounds **10** and **13**). The 6,7-dihydroxy-*N*-propyl-*N*-chloroethyl compound **18** (corrected IC_{50} = 76 nM) is an exception to this trend. These results are consistent with a steric inhibition of binding with increasing N-substitution, with the exception that an *N*-propyl group enhances binding by interaction with an additional binding site postulated to exist at the receptor.[24]

Compound **18** was chosen for testing for irreversible interaction with D_2 receptors, owing to its high affinity for the receptor. It was tested by inclusion of the cyclized material in saturation binding assays with [^{3}H]spiperone. A similar experimental strategy showed that phenoxybenzamine, which is known to interact irreversibly with D_2 receptors,[23] lowered the B_{max} for [^{3}H]spiperone binding consistent with its irreversible interaction. A similar result was obtained with **18**, indicating an irreversible interaction. The other potential irreversible agonist affinity label for D_2 dopamine receptors, *N*-(chloroethyl)norapomorphine, has also been shown to interact with D_2 dopamine receptors in an irreversible manner[9,10] when used in a nonradioactive form.

In addition, [^{3}H]-*N*-(chloroethyl)norapomorphine irreversibly labels brain membranes, but the binding did not show the specificity of interaction of a D_2 dopamine receptor.[12] The high selectivity of aminotetralins for dopamine receptors may mean that **18**, in a tritiated form, can be used to provide a more selective probe for irreversible labeling of D_2 dopamine receptors.

Experimental Section

Ligand Binding Assays. Bovine anterior pituitary membranes were prepared and ligand binding assays performed by using [^{3}H]spiperone binding and 3.3 μM (+)-butaclamol to define specific [^{3}H]spiperone binding as described in ref 23 except that ascorbic acid (0.1%) replaced dithiothreitol in the buffer. Displacement data were analyzed by nonlinear least squares computer curve fitting to give IC_{50} values (concentration of displacing ligand that inhibits half the specific [^{3}H]spiperone binding) and pseudo Hill coefficients (*n*) as in ref 23 and 25.

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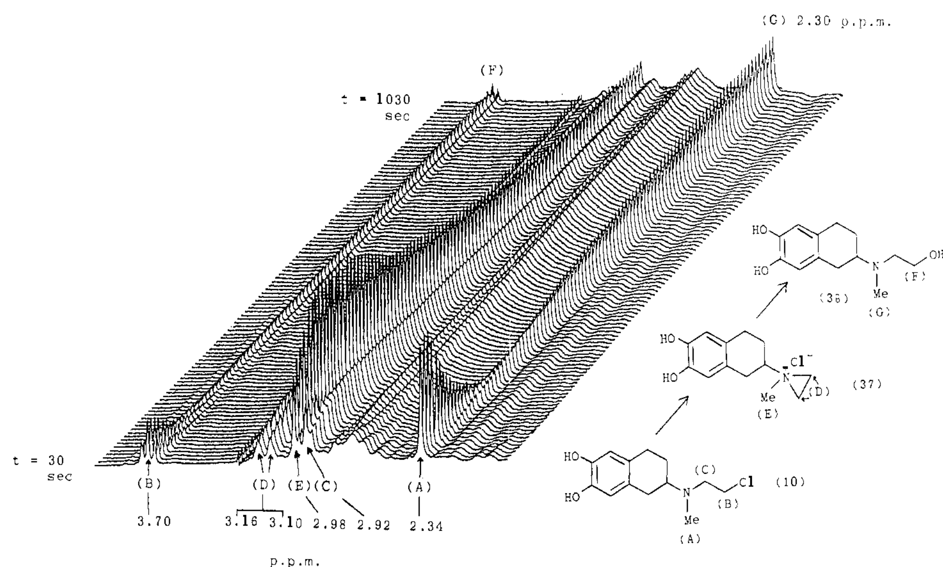

Figure 5. Superimposed ^{1}H NMR spectra to show the solvolysis of the [*N*-(2-chloroethyl)-*N*-methylamino]tetralin **10** in basic D_2O at 25 °C. Chemical shift values in ppm.

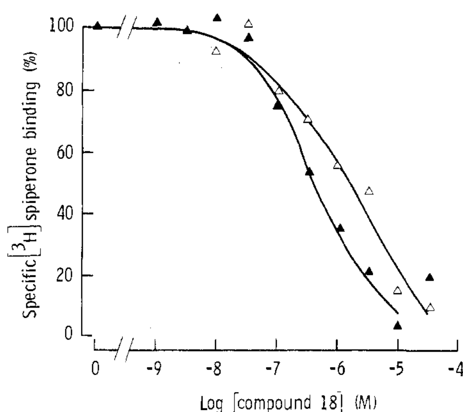

Figure 6. Inhibition of specific [^{3}H]spiperone binding to anterior pituitary D_2 dopamine receptors by compound **18**. [^{3}H]Spiperone (ca. 500 pM) binding to bovine anterior pituitary membranes was determined as described in the presence of different concentrations of compound **18** in the absence (▲) and presence (△) of 100 μM GTP. Data are from one representative experiment replicated as in Table I. Data points are the means of triplicate determinations.

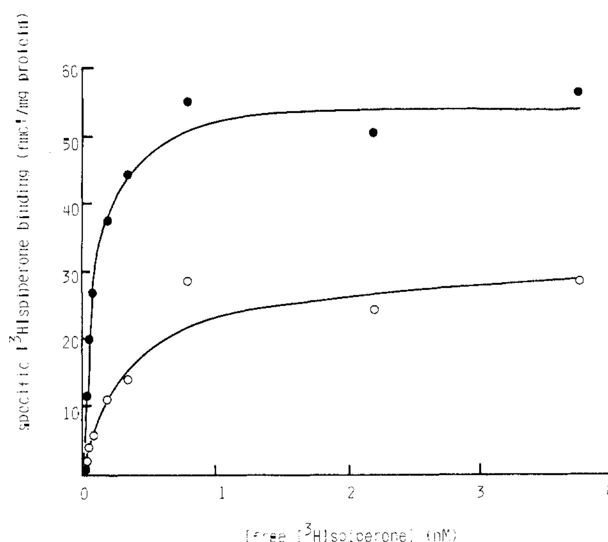

Figure 7. Saturation analysis of [^{3}H]spiperone binding to anterior pituitary membranes in the absence (●) and presence (○) of phenoxybenzamine (10 μM). Specific [^{3}H]spiperone binding to bovine anterior pituitary membranes was determined for a range of [^{3}H]spiperone concentrations as described; 10 μM phenoxybenzamine was included in one set of assays. The data are from a representative experiment, with data points being the means of triplicate determinations.

Experiments to investigate irreversible interaction of a compound with the receptor were performed as follows. The compound to be tested was incubated in 10 mM phosphate buffer, pH 7.4, containing 0.1% ascorbic acid and 20% (v/v) ethanol at a concentration of 0.8 mM at 25 °C for 30 min. Bovine anterior pituitary membranes (3.5 mg of protein/mL) were then incubated at 25 °C for 30 min in 10 mM phosphate buffer, pH 7.4, containing 0.1% ascorbic acid with the preincubated compound at a concentration of 10 μM. Treated membranes or control membranes (treated as above but with no compound) were then assayed for specific [^{3}H]spiperone binding (20–5000 pM concentration added); 0.35 mg of protein was used per assay, with a final volume of 1 mL of HEPES–phosphate saline buffer,[26] thus diluting the membranes and added compounds 10-fold. The ligand binding assay was performed otherwise as in ref 23.

Synthetic Chemistry. Commercial (Aldrich) solutions of boron tribromide and boron trichloride in dichloromethane and diborane in THF were employed. Amines were normally liberated from the corresponding ammonium salts by treating an aqueous solution of the salt with 1 M NaOH solution to attain pH 9–10 and then extracting the free base into dichloromethane. Ether refers to diethyl ether. Column chromatography was performed with silica gel (Merck 7734). Melting points are uncorrected. All compounds gave consistent IR, ^{1}H NMR, and ^{13}C NMR spectra. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin-Elmer R12, JEOL PMX 60, or JEOL FX 100 spectrometer; ^{13}C NMR spectra were obtained on the last-mentioned instrument. The NMR kinetic studies were carried out on a Bruker CXP 200 spectrometer. Mass spectra were obtained on a Kratos MS25 (low resolution) or VG analytical ZAB-IF or Kratos MS902/DMS 50 SM (high resolution) instrument. Elemental analyses, except where indicated, were within 0.4% of the calculated ratios for the elements specified. The *N*-2-haloalkyl derivatives were extremely hygroscopic and reactive. In most cases it was not possible to obtain an accurate elemental analysis. Characterization was achieved by using high-resolution mass spectrometry and ^{13}C NMR spectroscopy, the results being consistent with the assigned

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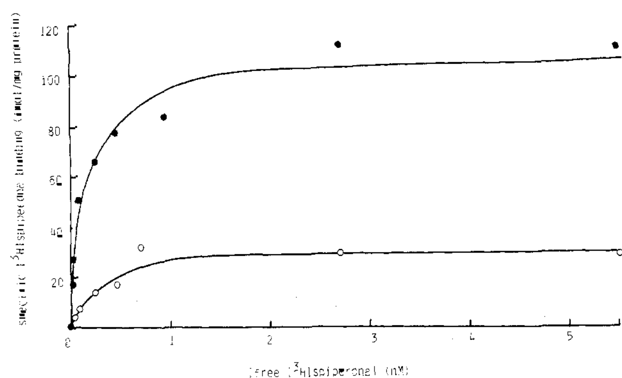

Figure 8. Saturation analysis of [^{3}H]spiperone binding to anterior pituitary membranes in the absence (●) and presence (○) of 1 μM 18. Bovine anterior pituitary membranes were incubated with precyclized 18 or buffer for 30 min, 25 °C, prior to determination of specific [^{3}H]spiperone binding for a range of [^{3}H]spiperone concentrations. Data are from a representative experiment, and data points are the means of triplicate determinations.

structures. The purity of these samples was evident from the ^{13}C NMR spectra and was confirmed by TLC with CH_2Cl_2–MeOH mixtures as solvent.

***N*-(2-Chloroacetyl)-*N*-propyl- and *N*-(2-Chloroacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (14 and 1).** **a.** 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (**30**)[13] (0.20 g, 0.82 mmol) was stirred in toluene (20 mL) and triethylamine (0.18 g, 1.80 mmol) added. The mixture was cooled to 0 °C and chloroacetyl chloride (0.11 g, 0.97 mmol) added dropwise. When addition was complete, the mixture was stirred at room temperature for 45 min, then washed with water (3 × 50 mL) and sodium carbonate solution, and dried ($MgSO_4$). Volatiles were removed under reduced pressure, and column chromatography (CH_2Cl_2–CH_3OH, 1:50) gave the *N*-2-chloroacetyl derivative **1** (0.117 g, 50%) as a yellow solid: mp 132–133 °C; MS, *m/z* 283, 285 (M^+). Anal. ($C_{14}H_{18}ClNO_3$) C, H, Cl, N.

b. *N*-Propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (**31**)[13] was treated with chloroacetyl chloride in the same manner to give the *N*-2-chloroacetyl-*N*-propyl derivative **14** (25%) as a yellow oil. Anal. ($C_{17}H_{24}ClNO_3$) C, H, N.

***N*-(2-Chloroacetyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine (2).** 1,2,3,4-Tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (**32**)[13] (0.24 g, 0.92 mmol) was dissolved in methanol (5 mL), triethylamine (0.141 g, 1.4 mmol) was added, and the mixture was stirred for 15 min, during which time the resultant solution turned dark green. Volatiles were removed under reduced pressure to leave a dark green oil, which was dried under vacuum to remove all traces of triethylamine. The oil was dissolved in methanol (5 mL) and the flask cooled to 0 °C. Chloroacetyl chloride (0.208 g, 1.85 mmol) was added, slowly with stirring, and when addition was complete, stirring of the mixture was continued at room temperature. When no further reaction was seen to occur by TLC (45 min), volatiles were removed under reduced pressure and the residue was redissolved in methanol (5 mL). The whole cycle involving treatment with triethylamine and chloroacetyl chloride was then repeated exactly as before. Volatiles were then removed to leave a yellow oil, which was dissolved in methanol (3 mL). Diethyl ether (30 mL) was added and the mixture filtered to remove the resulting precipitate. The precipitate was washed with acetone, and the combined filtrates were evaporated under reduced pressure to leave a yellow oil. Column chromatography (methanol–dichloromethane, 1:50) gave the title amide **2** (0.16 g, 67%) as a yellow oil: MS, *m/z* 255, 257 (M^+). Anal. ($C_{12}H_{14}ClNO_3$) C, H, Cl; N: calcd, 5.48; found, 4.94.

***N*-(2-Chloroethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy- and -6,7-dihydroxy-2-naphthylamine Hydrochloride (4 and 5).** **a.** Dimethoxy chloro amide **1** (0.32 g, 1.13 mmol) was dissolved in THF (10 mL) under N_2. Diborane in THF (1 M, 2 mL) was added and the mixture stirred for 2 h. Water (1 mL) and concentrated HCl (1 mL) were then added to quench the reaction, and volatiles were removed under reduced pressure. The resulting solid was warmed with methanol (20 mL) and filtered. The filtrate was evaporated to leave a white solid, which was recrystallized from ether–methanol (10:1), giving the dimethoxy chloroethyl derivative **4** (0.263 g, 76%) as a white powder: mp 202–205 °C; MS, *m/z* 269, 271 (M^+). Anal. ($C_{14}H_{21}Cl_2NO_2$) C, H, Cl, N.

b. Dihydroxy chloro amide **2** was treated with diborane in the same manner to give the dihydroxy chloroethyl derivative **5** (72%): mp 206–208 °C; MS, *m/z* 241, 243 (M^+); found M^+ 241.0849, $C_{12}H_{16}{}^{35}ClNO_2$ requires M^+ 241.0855.

Reductive Aminations of Tetralones 34–36. Preparation of Amine Hydrochlorides 3, 7, 22, and 27. The hydroxy amine (ethanolamine or 1-amino-2-propanol; 6 molar equiv) was treated with excess methanolic hydrochloric acid (concentrated HCl–MeOH, 1:2.4) to obtain a pH of 6–7. The tetralone (1 molar equiv) was added followed by sodium cyanoborohydride (1.2 molar equiv). The resulting mixture was stirred at room temperature for 25 h. Excess concentrated hydrochloric acid (ca. 3 mL/mmol of tetralone) was added to the mixture. After the effervescence had subsided, volatiles were removed under reduced pressure to leave a red solid, which was redissolved in water. The aqueous solution was washed twice with ether and then potassium hydroxide solution added to obtain a pH of 10–11. The solution was extracted three times with dichloromethane, and the combined extracts were washed twice with water. After drying ($MgSO_4$), the solvent was removed under reduced pressure. The resulting oil was dissolved in dry ether and HCl gas passed through to precipitate a solid, which, if colored, was treated with decolorizing charcoal in refluxing methanol and then recrystallized from ether–methanol (10:1).

a. *N*-(2-Hydroxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (3): prepared on a 1-mmol scale (65%) as a white powder; mp 215–217 °C; MS, *m/z* 251 (M^+). Anal. ($C_{14}H_{22}ClNO_3$) C, H, N.

b. *N*-(2-Hydroxypropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (7): prepared on a 1-mmol scale (70%) as a white powder; mp 210–213 °C; MS, *m/z* 265 (M^+); found M^+ 265.1674, $C_{15}H_{23}NO_3$ requires M^+ 265.1679. Anal. ($C_{15}H_{24}O_3NCl$) H, N, Cl; C: calcd, 59.69; found, 58.94.

c. *N*-(2-Hydroxyethyl)-1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthylamine hydrochloride (22): prepared on a 4-mmol scale (51%) as a white powder; mp 197–199 °C; MS, *m/z* 251 (M^+). Anal. ($C_{14}H_{22}O_3NCl$) C, H, N.

d. *N*-(2-Hydroxyethyl)-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine hydrochloride (27): prepared on a 4-mmol scale (59%); mp 159–160 °C; MS, *m/z* 221 (M^+). Anal. ($C_{13}H_{20}ClNO_2$) C, H, N, Cl.

***N*-Alkylation via Reductive Amination. Preparation of Amines 9, 11, 15, 20, 23, 25, and 28.** The precursor amines (1 molar equiv) as free bases were dissolved in methanol (ca. 5 mL/mmol) under nitrogen, and aqueous formaldehyde (40% w/v), glycolaldehyde, or propionaldehyde (3 molar equiv) was added followed by 4A molecular sieves (ca. 0.5 g/mmol) and sodium cyanoborohydride (1.5 molar equiv). The reaction mixture was stirred for 15–18 h and then filtered, the solid being washed well with methanol. Methanolic hydrochloric acid (concentrated HCl–MeOH, 1:2.4) was added to the combined filtrates, and after effervescence had ceased, volatiles were removed under reduced pressure to leave an oily solid. This solid was dissolved in water and the aqueous solution washed twice with ether. Sodium hydroxide solution was added to the aqueous layer to obtain a pH of 10–11, and two extractions with dichloromethane were carried out. The combined dichloromethane extracts were washed with 2% aqueous ammonia and dried ($MgSO_4$). The solvent was removed under reduced pressure, and either the resulting oils were purified by column chromatography (dichloromethane–methanol, 10:1) to give the free amines or they were dissolved in ether and the amine hydrochlorides precipitated by the addition of HCl gas. The hydrochlorides were then recrystallized from ether–methanol (10:1).

***N*-(2-Hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (9):** from amine **3** as free base (12-mmol scale, 69%) as a white powder; mp 169–172 °C; MS, *m/z* 265 (M^+). Anal. ($C_{15}H_{24}ClNO_3$) C, H, N, Cl.

***N*,*N*-Bis(2-hydroxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (11):** from amine **3** as free base (0.75-mmol scale, 65%) as an oil; MS, *m/z* 295 (M^+). Anal. ($C_{16}H_{25}NO_4$) C, H, N.

N-(2-Hydroxyethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (15): from amine **3** as free base (1.6-mmol scale, 70%) as an oil; MS, *m/z* 293 (M^+). Anal. ($C_{17}H_{27}NO_3$) C, H, N.

N-(2-Hydroxypropyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (20): from amine **11** (1.1-mmol scale, 67%) as an oil; MS, *m/z* 307 (M^+). Anal. ($C_{18}H_{29}NO_3$) C, H, N.

N-(2-Hydroxyethyl)-N-methyl-1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthylamine hydrochloride (23): from amine **22** as free base (0.8-mmol scale, 75%) as a white powder; mp 183–185 °C; MS, *m/z* 265 (M^+). Anal. ($C_{15}H_{24}ClNO_3$) H, Cl, N; C: calcd, 59.69; found, 59.23.

N,N-Bis(2-hydroxyethyl)-1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthylamine (25): from amine **22** as free base (0.8-mmol scale, 76%) as an oil; MS, *m/z* 295 (M^+). Anal. ($C_{16}H_{25}NO_4$) C, H, N.

N-(2-Hydroxyethyl)-N-methyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine (28): from amine **27** as free base (0.9-mmol scale, 76%) as an oil; MS, *m/z* 235 (M^+). Anal. ($C_{14}H_{21}NO_2$) H, N: C: calcd, 71.46; found, 70.99.

N-(2-Chloroethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine Hydrochloride (17). The hydroxyethyl compound **15** (0.6 g, 2.00 mmol) was dissolved in benzene (20 mL), thionyl chloride (0.28 g, 2.40 mmol) added, and the mixture stirred at room temperature for 15 h (no further reaction by TLC). The solvent was then removed under reduced pressure to leave a brown oil, which was carefully chromatographed on silica (dichloromethane–methanol, 50:1) to give the chloroethylamine as an oil (0.44 g, 69%). The amine was dissolved in ether, and addition of HCl gas gave a precipitate of the title amine hydrochloride **17**, which was recrystallized (ether–methanol, 10:1) as a white, hygroscopic powder. Anal. ($C_{17}H_{27}Cl_2NO_2$) C, H, N.

N-(2-Chloroethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine Hydrobromide (18) and the Corresponding Hydrochloride. a. N-(2-Chloroethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (**17**) as free base (0.18 g, 0.58 mmol) was dissolved in dichloromethane (10 mL) under nitrogen and the solution cooled to −5 °C. Boron tribromide in dichloromethane (1 M, 2.50 mmol) was added to the stirred solution and the mixture left at room temperature for 18 h. Dry nitrogen was then bubbled into the reaction mixture to remove excess BBr_3, and the solution was cooled to 0 °C and methanol (2 mL) added. The solvent was removed under reduced pressure and the resulting oil chromatographed on silica (CH_2Cl_2–MeOH, 8:1). Recrystallization of the product with R_f 0.5 gave the title amine hydrobromide **18** (0.151 g, 72%) as a hygroscopic powder: MS, *m/z* 283, 285 (M^+); found M^+ 285.1301, $C_{15}H_{22}{}^{37}ClNO_2$ requires M^+ 285.1311. Mass spectrometry indicated that a small amount (<5% according to NMR) of halide exchange had occurred during this reaction to give the corresponding bromide **19**.

b. N-(2-Chloroethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine (**17**) as free base (0.15 g, 0.48 mmol) was dissolved in dichloromethane (3 mL) under nitrogen, and the solution was stirred and cooled to −70 °C. A solution of boron trichloride in dichloromethane (1 M, 2.50 mmol) was added and the mixture left at room temperature for 80 h. The reaction mixture was worked up as in (a) but with omission of the chromatography to give the title amine hydrochloride (0.11 g, 72%) as a white, hygroscopic solid [MS, *m/z* 282, 285 (M^+)], which was spectroscopically identical with the product from procedure (a).

N-(2-Hydroxyethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine Hydrobromide (16). Compound **16** was prepared from the corresponding 6,7-dimethoxy compound **15** by using the BBr_3 procedure described for compound **18**. The title amine hydrobromide **16** was obtained as a yellow, oily solid from ether–methanol (10:1) (47% on a 0.68-mmol scale): MS, *m/z* 265 (M^+). Anal. ($C_{15}H_{24}BrNO_3$) C, H, N, Br.

Formation of Bromoalkylamines 6, 8, 13, 19, and 21. The precursor methoxylated N-hydroxyalkylamines or amine hydrochlorides (1 molar equiv) were dissolved in hydrobromic acid (48%, ca. 25 mL/mmol) under dry nitrogen, and the reaction mixture was refluxed for 24 h. Volatiles were removed under reduced pressure, and the resulting dark oil was treated with decolorizing charcoal in refluxing methanol. After filtration and evaporation of the methanol, the product was purified by chromatography (dichloromethane–methanol, 7:1).

N-(2-Bromoethyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (6): from amine **3** as free base (0.8-mmol scale, 81%) as a yellow hygroscopic solid; MS, *m/z* 285, 287 (M^+); found M^+ 285.0363, $C_{12}H_{16}{}^{79}BrNO_2$ requires M^+ 285.0365.

N-(2-Bromopropyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (8): from amine **7** as free base (0.75-mmol scale, 44%) as a red-brown hygroscopic solid; MS, *m/z* 299, 301 (M^+).

N,N-Bis(2-bromoethyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (13): from amine **11** (1.2-mmol scale, 49%) as a waxy, white solid; MS, *m/z* 391, 393, 395 (M^+).

N-(2-Bromoethyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (19): from amine **15** (0.7-mmol scale, 84%) as an orange oil; MS, *m/z* 327, 329 (M^+); found M^+ 327.0835, $C_{15}H_{22}{}^{79}BrNO_2$ requires M^+ 327.0835.

N-(2-Bromopropyl)-N-propyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrobromide (21): from amine **20** (0.67-mmol scale, 80%) as a light brown oil; MS (FAB), *m/z* 342, 344 ($M^+ + 1$).

Formation of Chloroalkylamines 10, 10a, 12, 24, 26, and 29. The precursor methoxylated N-hydroxyalkylamines as free bases (1 molar equiv) were dissolved in dichloromethane (ca. 10 mL/mmol). Thionyl chloride (ca. 1.2 molar equiv or 2.4 molar equiv for dihydroxy compounds) was added and the mixture refluxed until TLC indicated complete conversion (ca. 3–4 h). The volatiles were removed under reduced pressure to give the methoxylated N-chloroalkylamines. These compounds were redissolved in dichloromethane (ca. 5 mL/mmol) under nitrogen. The solution was cooled to −70 °C and stirred as a solution of BCl_3 in dichloromethane (1 M, 10–15 mL/mmol) was added. The mixture was left to warm to room temperature and stirred for 72 h. Methanol (2 mL/mmol) was added dropwise to the cooled (0 °C) reaction mixture, and the volatiles were then removed under reduced pressure. The resulting brown oil was treated with decolorizing charcoal in refluxing methanol. Following filtration and solvent removal, the oil was dissolved in methanol (2 mL/mmol) and the solution added dropwise to dry ether (60 mL/mmol). The resulting white precipitate was removed by filtration and recrystallized from methanol.

N-(2-Chloroethyl)-N-methyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrochloride (10): from amine **9** as free base (1.1-mmol scale, 61%) as a white powder; mp 121 °C; MS, *m/z* 255, 257 (M^+); found M^+ 257.0995, $C_{13}H_{18}{}^{37}ClNO_2$ requires M^+ 257.0997.

The crude product after the thionyl chloride reaction was dissolved in ether and HCl gas passed through it to precipitate a solid, which was removed by filtration and recrystallized several times from ether–methanol (10:1), giving N-(2-chloroethyl)-N-methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine hydrochloride (**10a**) as a white crystalline solid: mp 212–215 °C; MS, *m/z* 283, 285 (M^+).

N,N-Bis(2-chloroethyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrochloride (12): from amine **11** (1.4-mmol scale, 68%) as a white hygroscopic semisolid; MS, *m/z* 303, 305, 307 (M^+); found M^+ 303.0791, $C_{14}H_{19}{}^{35}Cl_2NO_2$ requires M^+ 303.0795.

N-(2-Chloroethyl)-N-methyl-1,2,3,4-tetrahydro-5,6-dihydroxy-2-naphthylamine hydrochloride (24): from amine **23** as free base (0.56-mmol scale, 63%) as a white powder; mp 228–230 °C; MS, *m/z* 255, 257 (M^+); found M^+ 257.0997, $C_{13}H_{18}{}^{37}ClO_2N$ requires M^+ 257.0996.

N,N-Bis(2-chloroethyl)-1,2,3,4-tetrahydro-5,6-dihydroxy-2-naphthylamine hydrochloride (26): from amine **25** (0.51-mmol scale, 53%) as a white hygroscopic oily solid; MS, *m/z* 303, 305, 307 (M^+); found M^+ 305.0767, $C_{14}H_{19}{}^{35}Cl^{37}ClNO_2$ requires M^+ 305.0765.

N-(2-Chloroethyl)-N-methyl-1,2,3,4-tetrahydro-6-hydroxy-2-naphthylamine hydrochloride (29): from amine **28** (0.43-mmol scale, 54%) as a white hygroscopic oily solid; MS, *m/z* 239, 241 (M^+); found M^+ 241.1046, $C_{13}H_{18}{}^{37}ClNO$ requires M^+ 241.1048.

Kinetic Studies To Determine Aziridinium Ion Formation and Decay. a. Iodine–Thiosulfate Titration Procedure.

These were carried out by using the method of Gill and Rang.[20b] The aminotetralin hydrochloride (0.04 mmol) was dissolved in ethanol (0.5 mL) and added to buffer solution (50 mL) (10.0 mM aqueous solution of potassium dihydrogen phosphate containing ethanol (20%) and adjusted to pH 7.4 with 0.1 M sodium hydroxide solution) to give a final concentration of amine hydrochloride of 0.8 mM. The solution was kept at a constant temperature of 25 °C. The time of addition of the amine salt was noted ($t = 0$). Aliquots (5.0 mL) were removed at 1–2-min intervals in the early stages of the experiment and at longer time intervals as the experiment proceeded. Immediately after removal of each aliquot, the reaction was stopped by the addition of acetic acid (0.2 M, 1.0 mL), followed by sodium thiosulfate (10.0 mM, 1.0 mL). The mixture was left to stand for ca. 20 min at room temperature. Residual thiosulfate was then measured by titration with iodine solution (4.0 mM). In this manner the amount of thiosulfate consumed in reaction with the aziridinium ion could be calculated. The accuracy of this procedure was verified by repeating Gill and Rang's kinetic experiment using benzilylcholine mustard.[20b] Comparable results were obtained.

b. ^{1}H NMR Studies. These were carried out on a Bruker CXP 200 instrument using a pulse width of 45° and digital resolution of 0.648 Hz/point by following the general procedure of Levins and Papanastassiou.[21] *N*-(2-Chloroethyl)-*N*-methyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrochloride (**10**) (ca. 10 mg) was dissolved in D_2O (0.5 mL) in an NMR tube and a solution of KOH in D_2O (10 M, >1 equiv) added to liberate the free amine. The NMR tube was placed in the probe at 25 °C and the first scan taken 30 s after mixing. Scans were then taken at 1.25-s intervals, eight scans being combined to give an averaged spectrum every 10 s. Averaged spectra were then displayed individually (Figure 4) or in a two-dimensional stacked plot (Figure 5).

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Registry No. **1**, 109529-47-7; **2**, 109529-48-8; **3**, 109529-76-2; **3**·HCl, 109529-49-9; **4**, 109529-77-3; **4**·HCl, 109529-50-2; **5**, 109529-78-4; **5**·HCl, 109529-51-3; **6**, 109529-79-5; **6**·HBr, 109529-52-4; **7**, 109529-80-8; **7**·HCl, 109529-53-5; **8**, 109529-81-9; **8**·HBr, 109529-54-6; **9**, 109529-82-0; **9**·HCl, 109529-55-7; **10**, 109529-83-1; **10**·HCl, 109529-56-8; **11**, 109529-57-9; **12**, 109529-84-2; **12**·HCl, 109529-58-0; **13**, 109529-85-3; **13**·HBr, 109529-59-1; **14**, 109529-60-4; **15**, 109529-61-5; **16**, 109529-86-4; **16**·HBr, 109529-62-6; **17**, 109529-87-5; **17**·HCl, 109529-63-7; **18**, 109529-88-6; **18**·HBr, 109529-64-8; **18**·HCl, 109529-97-7; **19**, 109529-89-7; **19**·HBr, 109529-65-9; **20**, 109529-66-0; **21**, 109529-90-0; **21**·HBr, 109529-67-1; **22**, 109529-91-1; **22**·HCl, 109529-68-2; **23**, 109529-92-2; **23**·HCl, 109529-69-3; **24**, 109529-93-3; **24**·HCl, 109529-70-6; **25**, 109529-71-7; **26**, 109529-94-4; **26**·HCl, 109529-72-8; **27**, 109529-95-5; **27**·HCl, 109529-73-9; **28**, 109529-74-0; **29**, 109529-96-6; **29**·HCl, 109529-75-1; **30**·HCl, 13917-16-3; **31**·HCl, 63307-13-1; **32**·HBr, 13575-86-5.

Evaluation of Isomeric 4-(Chlorohydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines as Dopamine D-1 Antagonists

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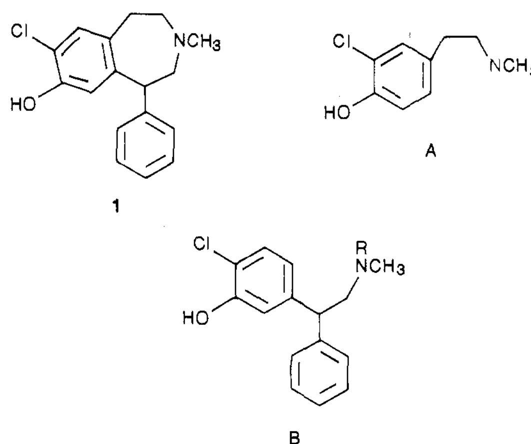
The isomeric 4-(3-chloro-4-hydroxyphenyl)- and 4-(4-chloro-3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines, the *N*-methyl derivative of the 4-(4-chloro-3-hydroxyphenyl) isomer, and 4-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline were synthesized and evaluated for dopamine D-1 antagonist activity. The 4-(3-chloro-4-hydroxyphenyl) and the 4-(3-hydroxyphenyl) isomer possessed similar potencies as D-1 antagonists. Introduction of the *N*-methyl group enhanced potency about twofold. The "pharmacophore" for selective dopamine D-1 antagonist activity appears to be a tertiary 2-(3-hydroxyphenyl)-2-phenethylamine.

SCH 23390 (**1**) is a selective antagonist for central dopamine D-1 and vascular DA_1 receptors, with weak affinity for 5-HT, α_1-adrenergic and D-2 dopamine receptors.[1-4] It blocks the conditioned avoidance response in rats and squirrel monkeys in a manner similar to that of classical antipsychotics[1] such as chloropromazine and haloperidol, which have been demonstrated to block D-2 receptors. In addition, **1** has proven to be a useful pharmacological tool in discerning the functional role and location of central dopamine D-1 receptors.[5-8]

Compound **1** may bind to the D-1 receptor in one of two different modes. It may bind as a 3-chloro-4-hydroxyphenethylamine derivative as in A or as a 2-(4-chloro-3-hydroxyphenyl)-2-phenethylamine derivative as in **B**. For **B**, the hydroxy group is oriented meta to the side chain, which is generally regarded to be a critical feature of dopamine agonists.[9] However, it may be argued that replacement of the critical *m*-OH with chlorine would give an antagonist. Further, Dandrige et al.[10] have presented a dopamine-receptor model that explicitly favors fragment A, consistent with this latter argument.



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