$\begin{array}{l} HCH_2Br, 106-95-6; CH_2 = CH(CH_2)_2Br, 5162-44-7; (CH_3)_2C = C-\\ HCH_2Br, 870-63-3; PhCH_2Br, 100-39-0; Ph(CH_2)_2Br, 103-63-9; \\ Ph(CH_2)_3Br, 637-59-2; 4-MeOC_6H_4CH_2Br, 2746-25-0; 4-t-\\ BuC_6H_4CH_2Br, 18880-00-7; 4-NO_2C_6H_4CH_2Br, 100-11-8; 4-\\ ClC_6H_4CH_2Br, 622-95-7; 4-NO_2C_6H_4(CH_2)_2Br, 5339-26-4; cyclo-\\ hexanamine hydrochloride, 4998-76-9; 1-adamantanamine hydrochloride, 10523-$ 68-9; 1-indanone, 83-33-0; cyclopropylmethyl bromide, 7051-34-5; 2-naphthylmethyl bromide, 939-26-4; 2-picolyl bromide, 55401- $97-3; 2-thiophenecarbonyl chloride, 5271-67-0; 2-furancarbonyl chloride, 527-69-5; 1-benzosuberone, 826-73-3. \\ \end{array}$

Supplementary Material Available: Tables of X-ray crystallographic data (5 pages). Ordering information is given on any current masthead page.

Spiropiperidines as High-Affinity, Selective σ Ligands

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A variety of achiral conformationally restricted spirocyclic piperidines have been prepared in an attempt to investigate the functional role of the central σ recognition site. All the compounds possessed a lipophilic N-substituent incorporating either a tetralin, indan, or benzocycloheptane skeleton. Their in vitro affinity at the σ site was assessed in radioligand displacement experiments with guinea pig cerebellum homogenates using the σ -specific radioligand [³H]-N,N'di-o-tolylguanidine ([³H]-DTG, [³H]-6). A study of the structure-activity relationships identified the N-butyl and N-dimethylallyl substituents as the optimum groups for high affinity and selectivity at the σ site (e.g., 3,4-dihydro-1'-(3-methylbut-2-enyl)spiro[1H-indene-1,4'-piperidine] (48), pIC₅₀ = 8.9 vs [³H]-6 and greater than 10 000-fold selective over the dopamine D₂ receptor). Such compounds are amongst the highest affinity σ ligands reported to date, with excellent selectivity over the dopamine D₂ receptor, and may serve as a useful tool for exploring the physiological role of the σ site.

Introduction

The functional significance of the central σ recognition site has been a focus of considerable research in recent years.^{1,2} This followed a suggestion by Martin et al. which implicated the σ site in psychosis³ and the discovery that potent neuroleptic agents, such as haloperidol (1)⁴ and perphenazine (2),^{2,5} as well as the atypical antipsychotic agents remoxipride (3)⁶ and BMY14802 (4)^{6,7} (Chart I) exhibited high affinity for this site. Since most neuroleptic agents are dopamine D₂ antagonists and have undesirable side effects associated with them, the σ site may provide a novel therapeutic target for a new class of antipsychotics. Our aim was to develop potent, selective σ ligands as tools for investigating the possible role of the σ site in psychosis.

It has been suggested by Wikström and Largent that a 3- or 4-phenylpiperidine group and a lipophilic nitrogen substituent are important features in most classes of high affinity σ ligands.^{2,8} For example, (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine (5) ((+)-3PPP), has a σ affinity of 40 nM vs [³H]-DTG ([³H]-6).⁹ As an extension of the σ ligand pharmacophore proposed by Wikström and Largent, in the current paper we report the synthesis of a series of achiral spiropiperidines 10 (Figure 1) and their in vitro affinities at the σ site. The structure-activity relationships are described, and for the highest affinity σ ligands their affinity at the dopamine D_2 receptor was

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Table I. Spirotetralins



binding data: pIC₅₀ ♠ SEM^a method of mp, °C R Х σ^{c} D_2^d microanalysis^b synthesis no (CH₃)₂C=CHCH₂ 24 Η 8.98 • 0.08 5.26 274 - 7C₁₉H₂₇N·HCl·0.6H₂O^e С C₁₈H₂₇N·HCl в 25 Н 4.96 • 0.04 245-8 CH3(CH2)3 8.92 ± 0.06 B 287-90 26 cyclohexylmethyl н 8.64 ± 0.11 5.71C₂₁H₃₁N·HCl 27 $CH_3(CH_2)_5$ 8.54 ± 0.13 C₂₀H₃₁N-HCl BBBCCBBABBBD н 5.69 266-9 C₂₂H₂₇N·HCl 28 $\frac{Ph(CH_2)_2}{CH_2=CH(CH_2)_2}$ н 272 - 4 8.30 ± 0.06 29 Н 8.18 ± 0.13 276 - 9C₁₈H₂₅N·HCl C₁₈H₂₅N·HCl·0.6H₂O cyclopropylmethyl 30 Н 7.99 ± 0.07 283 - 5CH2=CHCH2 4-CH3C6H4CH2 C17H23N.HC1.0.8H2O 31 н 7.74 • 0.10 239 - 42C22H27N·HCl·0.3H2O 32 Η 8.85 ± 0.08 6.76 • 0.15 255-8 4-CH₃OC₆H₄CH₂ C22H27NO.HCI.0.2H2O 33 н 6.92 ± 0.14 259-62 8.78 8.42 ± 0.04 34 PhCH₂ н 6.02 ± 0.13 284-6 C₂₁H₂₅N·HCl $\begin{array}{l} 4\text{-}\mathrm{ClC}_{6}\mathrm{H}_{4}\mathrm{CH}_{2} \\ 4\text{-}\mathrm{NO}_{2}\mathrm{C}_{6}\mathrm{H}_{4}\mathrm{CH}_{2} \end{array}$ C21H24CIN·HCI 35 н 8.17 ± 0.08 261-4 7.85 ± 0.07 237 - 4036 н C₂₁H₂₄N₂O₂·HCl 37 2-tetrahydrofurylmethyl Н 8.26 ± 0.14 249-52 C₁₉H₂₇NO·HCl·0.2H₂O 38 н 8.20 ± 0.12 257-60 C₁₉H₂₃NS-HCl 2-thienylmethyl D B 39 H 264 - 6C₁₉H₂₃NO·HCl 2-furylmethyl 8.02 ± 0.12 C20H24N2.2HCl-1.3H2Oh Н 214 - 740 2-picolyl 7.95 PhCH₂ C22H27N·HCl-0.2H2O 8.26 ± 0.08 A 41 6-Me 161 - 4A 264 - 742 $PhCH_2$ 6-Cl 8.17 ± 0.11 C₂₁H₂₄Cl·HCl C₂₁H₂₅NO·HCl·H₂O 7-0H 7.16 ± 0.08 164-6 43 PhCH₂ Α PhCH₂ 7-OMe 229 - 32C22H27NO+HCl-0.4H2O 7.13 ± 0.19 A 44

^a Binding results are expressed as -log₁₀ (IC₅₀) and are the mean of two to three independent determinations. Values without error limits were obtained from the mean of two independent experiments. ^b Elemental analyses for all compounds are within $\pm 0.4\%$ of the theoretical values for the indicated formula. σ binding was measured by displacement of [3H]-N,N'-di-o-tolylguanidine ([3H]-6) from guinea pig cerebellum homogenates. Haloperidol had a pIC₅₀ of 8.38 \oplus 0.05 in this assay. ^dD₂ binding was measured by displacement of [³H]-(-)sulpiride from rat striatal homogenates. "H: calcd 9.29, found 8.78. /H: calcd 8.83, found 8.14. "Lit.25a mp 285-287 °C. "H: calcd 7.41, found 6.97.



Figure 1. Proposed spirocyclic σ ligands.

evaluated.

Chemistry

A general synthetic route to the tetralin and benzo-

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cycloheptane derivatives 10 (n = 2 and 3, respectively) is presented in Scheme I.

Using a procedure described by Ainsworth et al.,¹⁰ N-

Scheme I. Synthesis of the Tetralin and Benzocycloheptane Derivatives^a



^aReagents: (i) KO-t-Bu, t-BuOH, DMSO; (ii) NH₂NH₂·H₂O, KOH, diethylene glycol, reflux; (iii) H₂, Pd(OH)₂ on C, EtOH, HCO₂H then KOH(aq).

Scheme II. Synthesis of the Spirocyclic Indans^a



^a Reagents: (i) lithium bis(trimethylsilyl)amide, THF; (ii) HCl, EtOAc; (iii) H₂, Pd on C, EtOH; (iv) Na₂CO₃(aq).

benzylbis(2-chloroethyl)amine $(13)^{11}$ was reacted with an aryl-substituted 2-tetralone $(11)^{12}$ or 2-benzosuberone $(12)^{13}$ in the presence of potassium *tert*-butoxide to afford the spiropiperidines 14. This alkylation proceeded in approximately 20% yield for the 2-tetralones and only 8% for 2-benzosuberone. The piperidine moiety was intro-

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duced exclusively at C-1, with no C-3 substituted products being isolated.

Attempts to remove the ketone function by sodium cyanoborohydride reduction of the corresponding tosylhydrazone¹⁴ proved unsuccessful. However, transformation to the saturated analogues 15 was accomplished effectively using the Huang-Minlon¹⁵ modification of the Wolff-Kishner reduction.¹⁶ When this procedure was carried out on the 7-methoxytetralin derivative 14 (n = 1, X = 7-MeO), efficient reduction of the carbonyl group proceeded with concomitant conversion of the 7-methoxy substituent to 7-hydroxy. The extent of this exchange was dependent on the time allowed for the conversion, and, if desired, by careful monitoring of the reaction, complete replacement of the methoxy group could be achieved.

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Table II. Benzocycloheptanes



		binding data: $pIC_{50} \pm SEM$				method of
no.	R	σ	D2	mp, °C	microanalysis	synthesis
46	PhCH ₂	8.17 ± 0.32	5.43 ± 0.17	273-5	C ₂₂ H ₂₇ N·HCl	Α
47	$CH_3(CH_2)_3$	8.32 ± 0.11	5.60	291-4	$C_{19}H_{29}N\cdot HCl\cdot 0.3H_2O$	В

Table III. Spiroindans



		method of				
no.	R	σ	D_2	mp, °C	microanalysis	synthesis
48	(CH ₃) ₂ C=CHCH ₂	8.93 ± 0.22	4.77 ± 0.06	264-6	C ₁₈ H ₂₅ N·HCl·1.8H ₂ O ^a	C
49	cyclohexylmethyl	8.87 ± 0.05	5.18 ± 0.12	304-6	C ₂₀ H ₂₉ N·HCl	В
50	$CH_3(CH_2)_5$	8.82 ± 0.06	5.26 ± 0.05	284-7	$C_{19}H_{29}N \cdot HCl \cdot 0.1H_2O$	В
51	$CH_3(CH_2)_3$	8.69 ± 0.09	5.40^{b}	231-4	$C_{17}H_{25}N\cdot HCl\cdot 0.1H_2O$	В
52	PhCH ₂	9.14 ± 0.15	6.05	275-7	$C_{20}H_{23}N\cdot HCl\cdot 0.1H_2O$	В
53	$Ph(CH_2)_2$	8.56 ± 0.06		287-90	C ₂₁ H ₂₅ N·HCl	В
54	4-CH ₃ OC ₆ H ₄ CH ₂	8.46 ± 0.13	6.21 ± 0.07	25 9-6 1	C ₂₁ H ₂₅ NO·HCl	В
55	4-CH ₃ C ₆ H ₄ CH ₂	8.23 ± 0.12		284-6	$C_{21}H_{25}N\cdot HCl$	В
56	2-tetrahydrofurylmethyl	8.50 ± 0.06		216-9	C ₁₈ H ₂₅ NO·HCl·0.1H ₂ O	В
57	2-picolyl	7.79 ± 0.19		20 9 –12	C ₁₉ H ₂₃ N ₂ ·HCl	В

^aH: calcd 8.65, found 9.20. ^bValue obtained from a single determination.

For the unsubstituted aryl spiropiperidines 15 (X = H), the N-benzyl group was removed using palladium-catalyzed hydrogenation in the presence of formic acid. After liberating the free base 16 subsequent alkylation was accomplished using the methods indicated in Tables I and II, and described in the Experimental Section, to give a variety of spirocyclic tetralin and benzocycloheptane derivatives 17.

The spiroindans 23 listed in Table III were prepared according to Scheme II. Indene (18) was alkylated at C-1 using lithium bis(trimethylsilyl)amide and N-(*tert*-butyloxycarbonyl)bis(2-chloroethyl)amine (19) to afford the protected spirocyclic indene 20 in 58% yield. The BOC group was quantitatively removed under acidic conditions and the resulting amine hydrochloride 21 reduced by catalytic hydrogenation to give the indan derivative 22. After liberation of the free base, alkylation, using the procedures shown in Table III, produced a range of Nsubstituted spiroindans.

Biological Evaluation Procedures

Affinity at the σ binding site was evaluated by an in vitro radioligand binding assay using homogenized guinea pig cerebellum and [³H]-DTG ([³H]-6).⁹ The highest affinity σ ligands in each series were subsequently examined for affinity at the dopamine D₂ receptor by an in vitro radioligand binding assay using rat striatal homogenates and [³H]-(-)-sulpiride. The results are presented as $-\log_{10}$ (IC₅₀) values in Tables I–III and the procedures described in detail in the Experimental Section.

Results and Discussion

The radioligand binding results for the tetralin analogues are shown in Table I. There are several examples (24-28, 32-34) which exhibit comparable σ binding to some of the



Figure 2. trans-Octahydrobenz[f]isoquinoline derivatives.

highest affinity σ ligands currently known, including haloperidol (pIC₅₀, 8.4) and 1*S*,2*R*-(-)-*cis*-*N*-methyl-*N*-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine [(-)-7] (pIC₅₀, 8.9).¹⁷

An examination of simple N-alkyl-substituted derivatives 24-31 identified the N-dimethylallyl (24) (pIC₅₀, 9.0) and N-butyl (25) (pIC₅₀, 8.9) substituents as optimum for σ binding. Further increases in the size of the lipophilic nitrogen substituent to hexyl (27) or phenethyl (28) failed to produce an increase in affinity, whereas a small decrease in chain length to the cyclopropylmethyl (30) and allyl (31) spiropiperidines resulted in a significant decrease in σ binding affinity. The 17-fold increase in σ affinity when replacing allyl with dimethylallyl is analogous to the result observed in the benzomorphan series in which (+)-pentazocine (9) displays a 15-fold preference for the σ site compared to (+)-SKF 10,047 (8).⁹

Benzyl-substituted derivatives 32-36 also had good affinity for the σ site, with the *p*-methyl (32) and *p*-methoxy (33) analogues displaying a marginal increase in σ affinity

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compared to the unsubstituted compound 34. However, as was described by Russell et al.,¹⁸ the *p*-nitro (36) substituent proved detrimental to binding. In fact, the structure-activity relationships described throughout this paper are remarkably similar to those reported by Russell et al. for the *trans*-octahydrobenz[*f*]isoquinoline derivatives 45 (Figure 2) and confirms the observation by Largent et al.²⁸ that, up to a certain size, σ binding affinity increases with increasing lipophilicity of the nitrogen substituent. A few N-heteroalkyl-substituted derivatives (37-40) were also examined and found to possess comparably good σ affinity.

The effect of introducing an aryl substituent into the tetralin moiety was also investigated. The results demonstrate that such groups offer no advantage over the unsubstituted analogue 34. While the 6-methyl (41) and 6-chloro (42) compounds had equivalent σ affinity to 34, the 7-hydroxy (43) and 7-methoxy (44) derivatives lost more than 10-fold affinity for the σ site.

Those ligands which had a pIC₅₀ greater than 8.3 at the σ site were then submitted for the dopamine D₂ binding assay. In each case excellent selectivity for the σ site was observed. The dimethylallyl (24) and butyl (25) derivatives exhibited an outstanding preference for σ over the D₂ receptor (greater than 5000- and 9000-fold, respectively). The least selective spiropiperidine was the *p*-methoxybenzyl analogue 33 which displayed some 70-fold preference for the σ site.

The radioligand binding results for spiropiperidines 46 and 47, possessing a benzocycloheptane nucleus, are shown in Table II. While these compounds retained good affinity for the σ recognition site, neither displayed improved binding compared to its tetralin counterpart (cf. 34 and 25). The benzocycloheptanes exhibited high selectivity for the σ site over the D₂ receptor (47, 520-fold; 46, 550-fold).

A variety of spirocyclic indans 48–57 were synthesized which incorporated the optimal nitrogen substituents established in the tetralin series. These compounds have very high affinity for the σ site, comparable to that of their tetralin analogues. The benzyl derivative 52 was identified as the highest affinity spirocyclic σ ligand, with a pIC₅₀ of 9.1. Generally, compared to the analogous tetralins and benzocycloheptanes, the indans had improved selectivity for the σ site over the D₂ receptor. In most cases examined, selectivity for the σ site was greater than 1,000-fold.

In conclusion, a series of achiral spirocyclic piperidines have been identified as high-affinity σ ligands. The effective σ binding displayed by many of these derivatives has demonstrated that this site is tolerant of large variations in the identity of the nitrogen substituent. This observation is comparable to that reported by Scherz et al. for the N,N'-di-o-tolylguanidine analogues,¹⁹ when describing the structural insensitivity of the σ site. The spiropiperidines also exhibited excellent selectivity for the σ site over the dopamine D₂ receptor. In particular, the N-dimethylallyl-substituted derivative 48 had greater than 10 000-fold preference for the σ binding site and may serve as a useful tool for exploring the physiological role of this site.

Experimental Section

General Methods. Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. Proton NMR spectra were obtained using either a Bruker AM360 or a Bruker AC250 spectrometer. Chemical shifts are reported in parts per million relative to Me₄Si as an internal standard. Mass spectra (MS) were recorded on a VB70-250 instrument operating either in the electron impact (EI) or chemical ionization (CI) mode as indicated. Elemental analyses for carbon, hydrogen, and nitrogen were performed by CHN Analysis Ltd. (Leicester) or Butterworth Laboratories Ltd. (Teddington) and are within $\pm 0.4\%$ of the theoretical values for the given formulas. Analytical thin-layer chromatography was conducted on precoated silica gel 60 F₂₅₄ plates (Merck). Flash chromatography was conducted on silica gel 60, 220-440 mesh (Fluka). HPLC analyses were performed on a Waters WISP 710B instrument, using a μ Bondapak C18 column (Waters), eluting on a 30-min gradient from 5 to 95% acetonitrile/water (containing 0.1% trifluoroacetic acid) and detecting on a Waters Lambda-Max 481LC spectrophotometer at 254 nm. Solutions were evaporated under reduced pressure on a Büchi rotary evaporator. Solvents were either reagent or HPLC grade. Starting materials were commercially available and used as received, unless otherwise indicated. Petroleum ether refers to that fraction having a boiling point range of 60-80 °C. All reactions were carried out under an atmosphere of nitrogen, unless stated otherwise.

Method A. 1'-Benzyl-3,4-dihydrospiro[naphthalene-1-(2H),4'-piperidine] (34).²⁰ A solution of 1'-benzyl-3,4-dihydro-2-oxospiro[naphthalene-1(2H),4'-piperidine] (14, n = 1, X= H)²¹ (0.73 g, 2.4 mmol), KOH (0.48 g, 8.6 mmol), and hydrazine hydrate (0.4 mL, 8.6 mmol) in diethylene glycol (6 mL) was heated at reflux for 2 h. After this time the reflux condenser was replaced with an air condenser and the mixture heated at 200 °C for a further 2 h. Finally, the solution was heated at reflux for 3 h and then allowed to cool to ambient temperature. EtOAc (100 mL) was added and the mixture partitioned with water (70 mL). The organic layer was separated and the aqueous phase extracted with EtOAc $(2 \times 50 \text{ mL})$. The organic layers were combined, washed with brine (100 mL), dried (MgSO4), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether-Et₂O (1:1) as the eluent, to afford 34 (0.42 g, 60%) as a white solid. The hydrochloride salt was prepared using ethereal hydrogen chloride and recrystallized from EtOAc-EtOH: mp 284-286 °C (lit.^{20a} mp 285-287 °C); ¹H NMR (D₂O) δ 1.76 (6 H, m), 2.24 (2 H, td, J = 10 and 4 Hz), 2.80 (2 H, t, J = 5 Hz), 3.28 $(2 \text{ H}, \text{td}, J = 10 \text{ and } 3 \text{ Hz}), 3.42 (2 \text{ H}, \text{m}), 4.40 (2 \text{ H}, \text{s}, CH_2Ph),$ 7.20-7.60 (9 H, m, ArH); MS (CI, NH₃) m/z 292 (M + 1 of free base). Anal. $(C_{21}H_{25}N\cdot HCl) C, H, N.$

1'-Benzyl-3,4-dihydro-6-methylspiro[naphthalene-1-(2H),4'-piperidine] (41). Prepared in the same way as that described for 34, using 1'-benzyl-3,4-dihydro-6-methyl-2-oxospiro[naphthalene-1(2H),4'-piperidine] (14, n = 1, X = 6-Me)²¹ (84 mg, 0.26 mmol), hydrazine hydrate (46 μ L, 0.95 mmol), KOH (53 mg, 0.95 mmol), and diethylene glycol (3 mL). The residue was purified by flash chromatography on silica gel, using petroleum ether-Et₂O (1:1) as the eluent, to afford the title compound 41 (28 mg, 35%) as a pale yellow oil. Hydrochloride salt: mp 161-164 °C (sublimed); ¹H NMR (MeOH- d_4) δ 1.73-1.91 (6 H, m), 2.25 (5 H, m), 2.72 (2 H, t, J = 6 Hz), 3.31 (4 H, m), 4.35 (2 H, s, NCH₂Ph), 6.98 (1 H, s, ArH), 7.06 (1 H, d, J = 8 Hz, ArH), 7.29 (1 H, d, J = 8 Hz, ArH), 7.54 (5 H, s, ArH); MS (EI) m/z 305 (M⁺ of free base). Anal. (C₂₂H₂₇N·HCl·0.2H₂O) C, H, N.

1'-Benzyl-6-chloro-3,4-dihydrospiro[naphthalene-1-(2H),4'-piperidine] (42). Prepared in the same way as that

⁽¹⁸⁾ Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. Benz[f]isoquinoline Analogues as High Affinity σ Ligands. J. Med. Chem., previous paper in this issue.

⁽¹⁹⁾ Scherz, M. W.; Fialeix, M.; Fischer, J. B.; Reddy, N. L.; Server, A. C.; Sonders, M. S.; Tester, B. C.; Weber, E.; Wong, S. T.; Keana, J. F. W. Synthesis and Structure-Activity Relationships of N,N'-Di-o-Tolylguanidine Analogues, High-Affinity Ligands for the Haloperidol-Sensitive σ Receptor. J. Med. Chem. 1990, 33, 2421-2429.

⁽²⁰⁾ An alternative procedure for the preparation of 1'-benzyl-3,4dihydrospiro[naphthalene-1(2H),4'-piperidine] is described by: (a) Janssen, C. Procedé de Préparation de N-(3,3-Diphenyl-3alcanoyl)-propylspiro-(tétraline 1,4'-piperidines). Fr. Patent 1,335,331, 1964. (b) Hashigaki, K.; Hiramatsu, K.; Yamato, M.; Tasaka, K. Synthesis and Structure-Activity Relationship of Spiro[isochromanpiperidine]Analogs for Inhibition of Histamine Release IV. Chem. Pharm. Bull. 1984, 32, 3561-3568.

⁽²¹⁾ Prepared using N-benzylbis(2-chloroethyl)amine¹¹ (13) and the appropriately substituted aryl tetralone, using the procedure described in ref 10.

described for 34, using 1'-benzyl-6-chloro-3,4-dihydro-2-oxo-spiro[naphthalene-1(2H),4'-piperidine] (14, n = 1, X = 6-Cl)²¹ (1.1 g, 3.3 mmol), hydrazine hydrate (0.6 g, 15.3 mmol), KOH (0.86 g, 15.3 mmol), and diethylene glycol (50 mL). The residue was purified by flash chromatography on silica gel, using petroleum ether-Et₂O (1:1) as the eluent, to afford 42 (410 mg, 38%) as a white solid. Hydrochloride salt: mp 264-267 °C (sublimed); ¹H NMR (DMSO- d_6) δ 1.67 (4 H, m), 1.85 (2 H, m), 2.43 (2 H, m), 2.70 (2 H, t, J = 6 Hz), 3.18 (4 H, m), 4.33 (2 H, d, J = 5 Hz, NCH₂Ph), 7.13 (1 H, s, ArH), 7.23 (1 H, d, J = 9 Hz, ArH), 7.47 (4 H, m, ArH), 7.63 (2 H, m, ArH); MS (EI) m/z 325 (M⁺ of free base). Anal. (C₂₁H₂₄ClN·HCl) C, H, N.

1'-Benzyl-3.4-dihydro-7-methoxyspiro[naphthalene-1-(2H),4'-piperidine] (44) and 1'-Benzyl-3,4-dihydro-7hydroxyspiro[naphthalene-1(2H),4'-piperidine] (43). A solution of 1'-benzyl-3,4-dihydro-7-methoxy-2-oxospiro[naphthalene-1(2H),4'-piperidine] (14, n = 1, X = 7-OMe)²¹ (400 mg, 1.2 mmol), KOH (0.3 g, 5.3 mmol), and hydrazine hydrate (0.2 mL, 4.3 mmol) in diethylene glycol (4 mL) was heated at reflux for 1.5 h. After this time the reflux condenser was replaced with an air condenser and the mixture heated at 210 °C for a further 2 h. Finally, the solution was heated at reflux for 3 h and then allowed to cool to ambient temperature. EtOAc (30 mL) was added and the mixture partitioned with water (30 mL). The organic layer was separated and the aqueous phase extracted with EtOAc $(2 \times 30 \text{ mL})$. The organic layers were combined, washed with brine (100 mL), dried (MgSO₄), and evaporated. The residue was purified on silica gel, using petroleum ether-EtOAc (1:1) as the eluent, to afford 44 (185 mg, 49%) $(R_f 0.4)$ as a colorless oil and 43 (124 mg, 35%) (R_f 0.3) as a white solid. Hydrochloride salt of 43: mp 164-166 °C; 1H NMR (D₂O) & 1.69-1.89 (6 H, m), 2.18 (2 H, t, J = 11 Hz), 2.68 (2 H, t, J = 6 Hz), 3.29 (2 H, t, J= 13 Hz), 3.42 (2 H, m), 4.37 (2 H, s, NCH₂Ph), 6.72 (1 H, dd, J = 8 and 2 Hz, ArH), 6.88 (1 H, s, ArH), 7.05 (1 H, d, J = 8 Hz, ArH), 7.55 (5 H, m, ArH); MS (EI) m/z 307 (M⁺ of free base). Anal. $(C_{21}H_{25}NO\cdot HCl\cdot H_2O)$ C, H, N.

Hydrochloride salt of 44: mp 229–232 °C; ¹H NMR (MeOH- d_4) δ 1.75–1.87 (4 H, m), 1.95 (2 H, m), 2.34 (2 H, td, J = 12 and 3 Hz), 2.71 (2 H, t, J = 7 Hz), 3.32 (4 H, m), 3.75 (3 H, s, OCH₃), 4.37 (2 H, s, NCH₂Ph), 6.70 (1 H, dd, J = 9 and 1 Hz, ArH), 6.92 (1 H, s, ArH), 6.97 (1 H, d, J = 9 Hz, ArH), 7.54 (5 H, m, ArH); MS (EI) m/z 321 (M⁺ of free base). Anal. (C₂₂H₂₇NO·HCl-0.4H₂O) C, H, N.

Method B. 3,4-Dihydrospiro[naphthalene-1(2H),4'piperidine] (16, n = 1).^{20a} A solution of 1'-benzyl-3.4-dihydrospiro[naphthalene-1(2H),4'-piperidine] (34) (0.85 g, 2.9 mmol) and formic acid (2 mL) in EtOH (20 mL) was hydrogenated at 50 psi, in the presence of palladium hydroxide on carbon (Pearlman's catalyst) (0.22 g, 25% (w/w)), for 18 h. The catalyst was filtered off and the solvent evaporated. The residue was partitioned between EtOAc (50 mL) and aqueous KOH (50 mL of a 5% (w/v)solution) and the organic phase separated. The aqueous layer was extracted once more with EtOAc (20 mL), and the combined organic layers were dried (MgSO₄). The solvent was removed to afford the title amine (0.37 g, 64%) as a white solid. Hydrochloride salt: mp 278-280 °C; ¹H NMR (D₂O) δ 1.76-1.98 (6 H, m), 2.22 (2 H, td, J = 10 and 4 Hz), 2.82 (2 H, t, J = 5 Hz), 3.35 (4 H, m),7.20–7.54 (4 H, m, ArH); MS (CI, NH₃) m/z 202 (M + 1 of free base). Anal. $(C_{14}H_{19}N\cdot HCl\cdot 0.2H_2O)$ C, H, N.

1'-Cyclohexylmethyl-3,4-dihydrospiro[naphthalene-1-(2H),4'-piperidine] (26). To a stirred solution of 3,4-dihydrospiro[naphthalene-1(2H),4'-piperidine] (176 mg, 0.87 mmol) in DMF (10 mL) was added K₂CO₃ (145 mg, 1.1 mmol) and cyclohexylmethyl bromide (146 μ L, 1.1 mmol). The mixture was heated at 100 °C for 1 h and then allowed to cool to room temperature. The solvent was evaporated and the residue taken up in Et_2O (20 mL) and then washed with water $(2 \times 20 \text{ mL})$. The organic layer was separated, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether- $Et_2O(1:1)$ as the eluent, to give the desired amine 26 (158 mg, 61%) as a colorless oil. Hydrochloride salt: mp 287-290 °C; ¹H NMR (D_2O) δ 1.07 (2 H, m), 1.28–1.98 (15 H, m), 2.33 (2 H, td, J = 11 and 2 Hz), 2.80 (2 H, t, J = 6 Hz), 3.03 (2 H, d, J =7 Hz), 3.25 (2 H, m), 3.51 (2 H, m), 7.22-7.30 (3 H, m, ArH), 7.48 $(1 \text{ H}, d, J = 8 \text{ Hz}, \text{ArH}); \text{ MS (CI, NH}_3) m/z 298 (M + 1 \text{ of free})$ base). Anal. $(C_{21}H_{31}N\cdot HCl) C, H, N.$

Method C. 3,4-Dihydro-1'-(3-methylbut-2-enyl)spiro-[naphthalene-1(2H),4'-piperidine] (24). To a stirred solution of 3,4-dihydrospiro[naphthalene-1(2H),4'-piperidine] (0.14 g, 0.69 mmol) in CH₂Cl₂ (10 mL) was added 4-bromo-2-methyl-2-butene (0.1 g, 0.69 mmol). After 3 h the solution was partitioned between CH₂Cl₂ (20 mL) and saturated aqueous NaHCO₃ (20 mL). The organic layer was separated, dried (MgSO4), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with CH_2Cl_2 -MeOH (93:7) to produce the title compound 24 (75 mg, 40%) as a white solid. Hydrochloride salt: mp 274-277 °C; ¹H NMR (D₂O) δ 1.75–1.96 (12 H, m), 2.25 (2 H, td, J = 15 and 4 Hz), 2.80 (2 H, t, J = 6 Hz), 3.23 (2 H, t, J = 13 Hz), 3.47 (2 H, m), 3.77 (2 H, d, J = 8 Hz), 5.35 (1 H, t, J = 8 Hz, CH), 7.21-7.32 (3 H, m, ArH), 7.46 (1 H, d, J = 8 Hz, ArH); MS (EI) m/z 269 (M⁺ of free base); high-resolution MS (EI) m/z 269.2125 $(269.2144 \text{ calcd for } C_{19}H_{27}N)$. Anal. $(C_{19}H_{27}N\cdot HCl\cdot 0.6H_2O) C_{19}H_{27}N\cdot HCl\cdot 0.6H_2O)$ H, N.

Method D. 1'-(2-Furylmethyl)-3,4-dihydrospiro[naphthalene-1(2H),4'-piperidine] (39). A solution of 3,4-dihydrospiro[naphthalene-1(2H),4'-piperidine] (0.2 g, 1 mmol), triethylamine (0.35 mL, 2.5 mmol), and 2-furoyl chloride (0.2 mL, 2 mmol) in CH₂Cl₂ (9 mL) was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue partitioned between Et₂O (20 mL) and water (20 mL). The organic layer was separated and the aqueous phase extracted with Et₂O (20 mL). The combined ethereal layers were dried (MgSO₄) and evaporated.

The residue was dissolved in THF (15 mL), and to the stirred solution was added, dropwise, a solution of lithium aluminum hydride in THF (3 mL of a 1 M solution, 3 mmol). After 2 h, EtOAc (2 mL) was added, followed by saturated aqueous ammonium chloride (6 mL). The mixture was filtered and the filtrate dried (MgSO₄) and evaporated. The crude residue was purified by flash chromatography on silica gel, eluting with petroleum ether-Et₂O (1:1), to afford **39** (103 mg, 37%) as a colorless oil. Hydrochloride salt: mp 264-266 °C; ¹H NMR (D₂O) δ 1.76 (2 H, m), 1.92 (4 H, m), 2.26 (2 H, m), 2.79 (2 H, t, J = 6 Hz), 3.40 (4 H, m), 4.43 (2 H, s), 6.57 (1 H, dd, J = 3 and 2 Hz, H^{4"}), 6.75 (1 H, d, J = 3 Hz, ArH), 7.68 (1 H, d, J = 2 Hz, H^{5"}); MS (EI) m/z 281 (M⁺ of free base). Anal. (C₁₉H₂₃NO·HCl) C, H, N.

1'-Benzyl-6,7,8,9-tetrahydrospiro[5*H*-benzocycloheptene-5,4'-piperidine] (46). 1'-Benzyl-6,7,8,9-tetrahydro-6oxospiro[5*H*-benzocycloheptene-5,4'-piperidine] (14, n = 2, X =H) was reacted with hydrazine hydrate and KOH, using the same procedure as that described for 34, to afford the title amine 46 as a pale yellow oil (57%). Hydrochloride salt: mp 273-275 °C; ¹H NMR (MeOH- d_4) δ 1.67 (2 H, m), 1.88 (4 H, m), 2.24 (4 H, m), 2.98 (2 H, m), 4.32 (2 H, s, CH₂Ph), 7.15 (3 H, m, ArH), 7.29 (1 H, d, J = 8 Hz, ArH), 7.50 (5 H, m, ArH); MS (EI) m/z 305 (M⁺ of free base). Anal. (C₂₂H₂₇N·HCl) C, H, N.

N-(tert-Butyloxycarbonyl)bis(2-chloroethyl)amine (19). Triethylamine (74 mL, 0.58 mol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (125 g, 0.57 mol) and bis-(2-chloroethyl)amine hydrochloride (85 g, 0.48 mol) in CH₂Cl₂ (600 mL). After 1 h more triethylamine (6 mL, 0.04 mol) was added and the mixture stirred overnight. The solvent was evaporated and the resulting oil taken up in Et₂O (500 mL) and washed with water (500 mL). The organic phase was separated and the aqueous layer extracted once more with Et₂O (500 mL). The ethereal layers were combined, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether-Et₂O (1:1) as the eluent to give 19 (102 g, 88%) as a pale yellow oil: ¹H NMR (CDCl₃) δ 1.48 (9 H, s, (CH₃)₃), 3.64 (8 H, m, (CH₂CH₂)₂); MS (CI, NH₃) m/z 242/244 (M + 1).

1'-(tert -Butyloxycarbonyl)spiro[1H-indene-1,4'piperidine] (20). To a stirred solution of indene (18) (5.1 mL, 0.04 mol) in THF (15 mL), at 0 °C, was added lithium bis(trimethylsilyl)amide (82 mL of a 1 M solution in THF, 0.08 mol) over 15 min. The mixture was stirred for a further 30 min and then added dropwise to a stirred solution of N-(tert-butyloxycarbonyl)bis(2-chloroethyl)amine (19) (9.9 g, 0.04 mol) in THF at 0 °C. After 2 h the mixture was allowed to warm to ambient temperature, then the solvent was removed. The resulting oil was purified by flash chromatography on silica gel, using petroleum ether-Et₂O (5:1) as the eluent, to give 20 (7.1 g, 58%) as a pale

Spiropiperidines

yellow solid: mp 129–131 °C; ¹H NMR (CDCl₃) δ 1.28 (2 H, d, J = 12 Hz), 1.50 (9 H, s, (CH₃)₃), 2.00 (2 H, td, J = 12 and 4 Hz), 3.13 (2 H, td, J = 12 and 2 Hz), 4.20 (2 H, m), 6.79 (1 H, d, J = 6 Hz, CH), 6.84 (1 H, d, J = 6 Hz, CH), 7.30 (4 H, m, ArH); MS (EI) m/z 285 (M⁺). Anal. (C₁₈H₂₃NO₂) C, H, N.

Spiro[1*H*-indene-1,4'-piperidine] Hydrochloride (21). Hydrogen chloride was bubbled through a stirred solution of 20 (3.0 g, 0.01 mol) in EtOAc (150 mL) at 0 °C for 30 min. The mixture was evaporated to dryness and then azeotroped with EtOAc (3 × 100 mL). The solid residue was stirred with Et₂0 (200 mL) and filtered to afford the desired amine hydrochloride 21 (2.3 g, 99%) as a pale yellow solid: mp 291-294 °C; ¹H NMR (D₂O) δ 1.54 (2 H, d, J = 14 Hz), 2.31 (2 H, td, J = 14 and 4 Hz), 3.57 (2 H, td, J = 13 and 2 Hz), 3.66 (2 H, m), 6.95 (1 H, d, J = 6 Hz, CH), 6.99 (1 H, d, J = 6 Hz, CH), 7.31-7.52 (4 H, m, ArH); MS (EI) m/z 185 (M⁺ of free base). Anal. (C₁₃H₁₅N-HCl-0.2H₂O) C, H, N.

3,4-Dihydrospiro[1*H*-indene-1,4'-piperidine] Hydrochloride (22).^{20a} A solution of spiro[1*H*-indene-1,4'-piperidine] hydrochloride (21) (1.9 g, 8.6 mmol) in EtOH (50 mL) was hydrogenated at 50 psi for 1 h, in the presence of 10% palladium on carbon (0.3 g, 16% (w/w)). The catalyst was filtered off and the EtOH evaporated. The remaining solid was recrystallized from EtOAc-EtOH (4:1) to produce 22 (0.81 g, 43%) as a white crystalline solid: mp 288-290 °C (lit.^{20a} mp 288-290 °C); ¹H NMR (D₂O) δ 1.79 (2 H, d, J = 14 Hz), 2.06 (2 H, td, J = 14 and 4 Hz), 2.14 (2 H, t, J = 7 Hz), 2.98 (2 H, t, J = 7 Hz), 3.25 (2 H, td, J= 14 and 2 Hz), 3.48 (2 H, m), 7.33 (4 H, m, ArH); MS (EI) m/z187 (M⁺ of free base). Anal. (C₁₃H₁₇N·HCl) C, H, N.

3,4-Dihydro-1'-(2-phenylethyl)spiro[1*H*-indene-1,4'piperidine] (53). 3,4-Dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride (22) was partitioned between EtOAc and aqueous Na₂CO₃ to liberate the free base. This was then reacted with 2-phenylethyl bromide, using the same procedure as that described for 26, to give 53 as a pale yellow oil (68%). Hydrochloride salt: mp 287-290 °C; ¹H NMR (DMSO-d₆) δ 1.67 (2 H, d, J = 14 Hz), 2.07 (2 H, t, J = 7 Hz), 2.26 (2 H, m), 2.90 (2 H, t, J = 7 Hz), 3.12 (4 H, m), 3.31 (2 H, m), 3.57 (2 H, d, J = 11 Hz), 7.24 (9 H, m, ArH), 10.82 (1 H, brs, NH⁺); MS (CI, NH₃) m/z 292 (M + 1 of free base). Anal. (C₂₁H₂₅N-HCl) C, H, N.

Radioligand Binding Assays. Radioligand binding assays

were performed using crude P_2 pellets from guinea pig cerebellum (σ) or rat striatum (dopamine D_2).

For full experimental details see the preceding paper by Russell et al.¹⁸ and references cited therein.

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Registry No. 6, 106916-81-8; 11 (X = H), 530-93-8; 11 (X = 6-Cl), 17556-18-2; 11 (X = 7-OMe), 4133-34-0; 11 (X = 6-CH₃), 31706-57-7; 12, 34663-15-5; 13, 55-51-6; 14 (n = 1, X = H), 134697-63-5; 14 $(n = 1, X = 6-CH_3)$, 134697-66-8; 14 (n = 1, X)= 7-OMe), 134697-67-9; 14 (n = 1, X = 6-Cl), 134697-65-7; 14 (n= 2, X = H), 137730-68-8; 16 (n = 1), 134697-64-6; 16 (n = 2), 137730-69-9; 19, 118753-70-1; 20, 137419-24-0; 21, 137730-67-7; 22, 96651-85-3; 23 (R = H), 428-38-6; 24, 134697-99-7; 24-HCl, 134698-00-3; 25, 134697-69-1; 25-HCl, 134697-70-4; 26, 134697-83-9; 26·HCl, 134697-84-0; 27, 134697-91-9; 27·HCl, 134697-92-0; 28, 134697-81-7; 28·HCl, 134697-82-8; 29, 134697-93-1; 29·HCl, 134697-94-2; 30, 134697-97-5; 30-HCl, 134697-98-6; 31, 134697-95-3; 31.HCl, 134697-96-4; 32, 134697-75-9; 32.HCl, 134697-76-0; 33, 134697-73-7; 33·HCl, 134697-74-8; 34, 95417-67-7; 34·HCl, 95417-61-1; 35, 134697-87-3; 35-HCl, 134697-88-4; 36, 134697-85-1; 36.HCl, 134697-86-2; 37, 134697-89-5; 37.HCl, 134697-90-8; 38, 134698-03-6; 38-HCl, 134698-04-7; 39, 134698-01-4; 39-HCl, 134698-02-5; 40, 134697-71-5; 40-2HCl, 140468-29-7; 41, 134698-07-0; 41·HCl, 134698-12-7; 42, 134698-05-8; 42·HCl, 134698-06-9; 43, 134698-13-8; 43-HCl, 134698-08-1; 44, 134697-79-3; 44-HCl, 134697-80-6; 46, 137730-62-2; 46·HCl, 140468-30-0; 47, 137730-63-3; 47.HCl, 137730-82-6; 48, 137730-58-6; 48.HCl, 137730-78-0; 49, 137730-54-2; 49·HCl, 137730-72-4; 50, 137730-65-5; 50·HCl, 137730-74-6; 51, 137730-64-4; 51·HCl, 137730-70-2; 52, 137730-52-0; 52.HCl, 102981-00-0; 53, 137730-66-6; 53.HCl, 137730-77-9; 54, 137730-55-3; 54·HCl, 137730-73-5; 55, 137730-53-1; 55·HCl, 137730-71-3; 56, 137730-57-5; 56·HCl, 137730-76-8; 57, 137730-56-4; 57.HCl, 137730-75-7; NH(CH₂CH₂Cl)₂.HCl, 821-48-7; indene, 95-13-6.