histamine) administration. Three concentrations of acetylcholine and histamine were applied, each being repeated once, in a random sequence. A 10 μM concentration of disopyramide was applied to bath 1 and a similar concentration of the dealkylated metabolite to bath 2. The tissues were left in contact with the drug for 20 min. The cycle of acetylcholine and histamine doses was then repeated, with disopyramide and the metabolite being added to the bath after each wash of the tissues. At the completion of the dose cycle, the tissues were washed frequently for 60 min before the control cycle of acetylcholine and histamine doses was repeated. Then, 10 μM disopyramide was applied to bath 2 and 10 μM metabolite was applied to bath 1. After 20 min in contact with the drug, the acetylcholine and histamine dose cycle was again repeated, with the drug or metabolite readministered after each wash.

Dose–response curves were constructed by plotting the percentage inhibition of contractile tension against the $\log_{10}$ of the cumulative concentration of the isomer in the bath. The concentration which resulted in 50% inhibition of contractile tension (IC_{50}) was determined from the plots after the slope and intercept of the linear portions were obtained by log-linear least-squares regression analysis. The statistical significance of the difference between the IC_{50} values of the two isomers in inhibiting electrically stimulated contractions were evaluated with a Wilcoxon test. No statistical analysis was performed on the two strips where the relative potencies of the metabolite and disopyramide were evaluated.

For the acetylcholine and histamine studies, contraction heights were measured for each response to both compounds in the presence and absence of racemic disopyramide and monodealkylated disopyramide. Dose ratios were calculated as the ratio of stimulant concentration required to give a defined effect in the presence of drug (disopyramide or metabolite) to the equivalent concentration in the absence of drug. From the dose ratio, an estimate of the antagonist dissociation concentration was determined [K_D = antagonist concentration/(dose ratio)].

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Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidines] as Potential Central Nervous System Agents. 6. Synthesis, ^{13}C NMR, and Biological Evaluation of *cis*- and *trans*-4-Amino-3′-arylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] Derivatives[1]

Lawrence L. Martin,* Manfred Worm,[2] Marc N. Agnew,

Chemical Research Department

Hansjoerg Kruse,[2] Jeffrey C. Wilker, and Harry M. Geyer III

Deparment of Pharmacology, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876.
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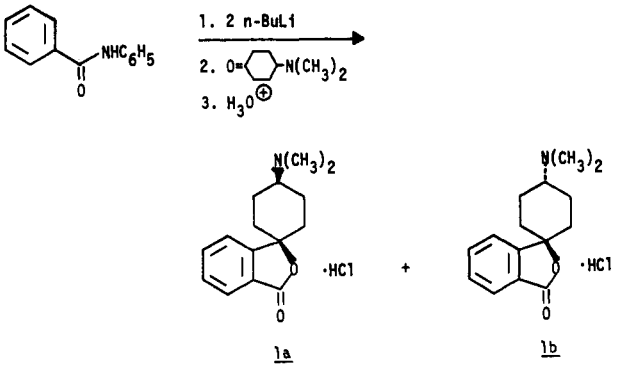
4-(Dimethylamino)- and 4-(methylamino)-3′-arylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] derivatives were prepared as analogues of previously reported 3-arylspiro[isobenzofuran-1(3*H*),4′-piperidines]. Metalation of benzanilide with *n*-butyllithium, addition of 4-(dimethylamino)cyclohexanone, and acidification afforded a mixture of *cis*- and *trans*-4-(dimethylamino)spiro[cyclohexane-1,1′(3′*H*)-isobenzofuran]-3′-ones (**1a,b**), which were separated by fractional crystallization. Addition of aryllithium or aryl Grignard reagents to **1a,b** and formic acid reduction afforded *cis*- and *trans*-4-(dimethylamino)-3′-arylspiro[cyclohexane-1,1′(3′*H*)-isobenzofurans] **3a–f**, which were converted to secondary amine analogues **5a–e**. Tentative stereochemical assignments are based on chemical arguments and are supported by ^{13}C NMR chemical shift data. Marked inhibition of tetrabenazine-induced ptosis is a property of most antidepressants, and significant antitetrabenazine activity is observed for several of these compounds. Optimal antitetrabenazine activity is associated with the *cis*-3′-phenyl series, and the cis secondary amine **5a** is approximately twice as potent as the cis tertiary amine **3a**. The various compounds are relatively weak with respect to potentiation of L-5-hydroxytryptophan-induced seizures.

We previously reported the synthesis, pharmacology, and biochemical properties of 3-arylspiro[isobenzofuran-1(3*H*),4′-piperidines] and conformationally mobile analogues.[1,3–13] Many of these compounds display strong activity in biochemical and pharmacological assays which suggest potential utility as antidepressant or antipsychotic

Scheme I



(1) Has been presented in part; see "Abstracts of Papers", 178th Meeting of the American Chemical Society, Washington, DC, Sept 10–13, 1979; American Chemical Society: Washington, DC, 1979, Abstr MEDI 25.
(2) Visiting Scientist, Hoechst AG, Frankfurt-Höchst, West Germany.
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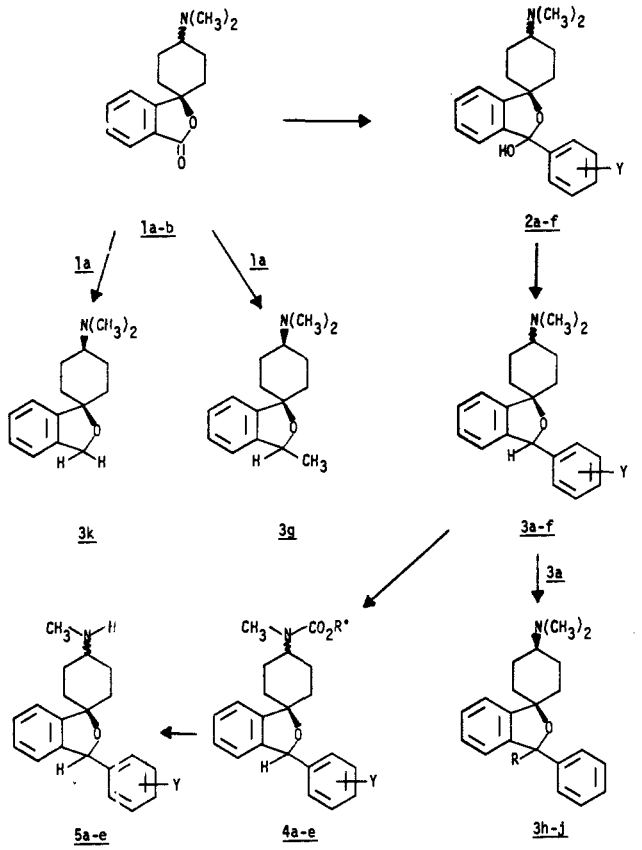
Scheme II[a]



[a] Cis N/O: Y = H (a), 2-CH_3 (c), 4-F (d), 4-Cl (e), 4-CH_3 (f). Trans N/O: Y = H (b). R = CH_3 (3h), C_2H_5 (3i), n-C_3H_7 (3j); R' = C_2H_5 (4a), C_6H_5 (4b-e).

agents. Reports of potential central nervous system activity for *cis*- and *trans*-4-arylcyclohexylamine derivatives[14] prompted investigation of *cis*- and *trans*-4-amino-3'-arylspiro[cyclohexane-1,1'(3'*H*)-isobenzofuran] derivatives as analogues of the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperdines].

Chemistry. Low-temperature metalation of benzanilide with *n*-butyllithium, addition of 4-(dimethylamino)cyclohexanone, and aqueous acidic quenching with concomitant lactonization afforded a 3:1 mixture of cis (**1a**) and trans (**1b**) lactones, which were separated by fractional crystallization of the hydrochloride salts (Scheme I, Table II). Treatment of **1a,b** with phenyllithium or aryl Grignard reagents afforded phthalanols **2a–f** (Scheme II, Table II), which were reduced by refluxing with formic acid to spiro[cyclohexane-1,1'(3'*H*)-isobenzofurans] **3a–f** (Table I). Addition of methylmagnesium chloride to **1a** gave phthalanol **2g** (Table II). $LiAlH_4$ reduction of **2g** afforded a diol intermediate which cyclized under acidic conditions to **3g** (Table I). Low-temperature alkylation of the lithium salt of **3a** with dimethyl sulfate or an alkyl halide gave **3h–j** (Table I). Borane reduction of **1a** afforded **3k** (Table I). N-Demethylation of **3a–e** with ethyl or phenyl chloroformate afforded carbamates **4a–e** (Table II), which were hydrolyzed under alkaline conditions to provide secondary amines **5a–e** (Table I).

Stereochemical assignments are based on chemical arguments and ^{13}C NMR chemical shift data. Preferred equatorial addition of phenyllithium to 4-*tert*-butylcyclohexanone is observed,[15] and the equatorial addition of an aryllithium reagent to 4-(dimethylamino)cyclohexanone should analogously afford a *cis*-1-aryl-4-(dimethylamino)cyclohexanol derivative as the major product. Presumably, lactonization of the addition product from benzanilide and 4-(dimethylamino)cyclohexanone and subsequent modifications should not affect the stereochemistry at the spiro center.

The technique of ^{13}C NMR is very sensitive to the conformation of aminocyclohexane systems, and an axial amino group deshields the ring carbon less than an equatorial amino group in sterically noncrowded cyclohexane derivatives.[16] Using the ^{13}C NMR chemical shift assignments in Table III and *cis*- and *trans*-4-*tert*-butyl-*N,N*-dimethylaminocyclohexane[17] (**6a,b**) as models, the conformation at C-4 of the spiro derivatives may be assigned. The equatorial to axial chemical shift difference of the amino-substituted ring carbon for model compounds **6a,b** is 3.29 ppm and varies from 0.88 (**1a,b**; HCl salts; Me_2SO-d_6) to 3.04 ppm (**5a,b**; bases) at C-4 for the compounds of interest (**1a,b**, **3a,b**, and **5a,b**). For each isomeric pair, C-4 is consistently deshielded less for the minor isomer. Assignment of the dimethylamino or methylamino group as axial or equatorial for the minor (**1b**, **3b**, and **5b**) and major (**1a**, **3a**, and **5a**) isomers, respectively, by the chemical shift of C-4 is, thus, in accordance with the ^{13}C NMR literature[16] and with the conformation at C-4 which was tentatively assigned by chemical arguments.

Loomes and Robinson reported that the ^{13}C NMR chemical shifts of the N-CH_3 group may be used to determine the conformation at C-1 of (dimethylamino)-cyclohexane derivatives and that an equatorial N-CH_3 is shielded relative to an axial N-CH_3.[16] For our compounds the shift of the N-CH_3 group is very reproducible in both the salt and base forms for the dimethylamino derivatives (Table III). The equatorial to axial shift difference of the N-CH_3 for model compounds **6a,b** is −2.08 ppm and varies only from −2.02 (**3a,b**) to −2.29 ppm (**1a,b**; bases). These data for **1a,b** and **3a,b** are also consistent with the literature[16] for assignment of the C-4 dimethylamino group as equatorial or axial. However, methylamino derivatives **5a,b** apparently do not adhere to any obvious rules (+0.77 ppm, bases; −0.89 ppm, salts).[18]

Results and Discussion

The tertiary and secondary amines summarized in Table I were evaluated for activity with respect to antagonism of tetrabenazine-induced ptosis (TBZ) in mice and potentiation of L-5-hydroxytryptophan-induced seizures (HTP) in rats. Three compounds belonging to the cis series (**3a,d** and **5a**) exhibited moderate to potent activity in TBZ, which suggests antidepressant-like properties. The activity of these compounds in each case is, however, several fold less potent than the antitetrabenazine activity of previously reported spiro[isobenzofuran-1(3*H*),4'-piperidine] analogues.[3] Introduction of an alkyl group at C-3' (**3h–j**) or aromatic substitutents other than 4-F in **3d**

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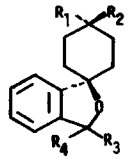
(18) To confirm the tentatively assigned configuration of the spiro center, **5b** has been submitted for X-ray crystallographic analysis.

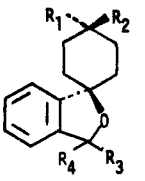
Table I. Spiro[cyclohexane-1,1'(3'*H*)-isobenzofurans][a]



compd	R_1	R_2	R_3	R_4	starting material	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	TBZ[f]	HTP[g]
3a	H	$(CH_3)_2N$	C_6H_5	H	2a	131.5–132.5	61	E	$C_{21}H_{25}NO$	C, H, N	3.7 (3.4–4.1)	50
3b	$(CH_3)_2N$	H	C_6H_5	H	2b	83.5–85	66	A	$C_{21}H_{25}NO$	C, H, N	>20	0
3c	H	$(CH_3)_2N$	2-$CH_3C_6H_4$	H	2c	118.5–119.5	74	E	$C_{22}H_{27}NO$	C, H, N	>20	0
3d	H	$(CH_3)_2N$	4-FC_6H_4	H	2d	104–106	30	A	$C_{21}H_{24}FNO$	C, H, F, N	8.4[h] (6.9–10.7)	50
3e	H	$(CH_3)_2N$	4-ClC_6H_4	H	2e	251–253	21	G	$C_{21}H_{24}ClNO\cdot HCl\cdot H_2O$	C, H, N	>20	0
3f	H	$(CH_3)_2N$	4-$CH_3C_6H_4$	H	2f	243–244	80	F-D	$C_{22}H_{27}NO\cdot HCl$	C, H, Cl, N	>20	33
3g	H	$(CH_3)_2N$	CH_3	H	2g	210–212	95	F-D	$C_{16}H_{23}NO\cdot HCl$	C, H, Cl, N	~20	0
3h	H	$(CH_3)_2N$	C_6H_5	CH_3	3a	176–178	60	F-D	$C_{22}H_{27}NO\cdot C_2H_2O_4$	H, N; C[i]	>20	0
3i	H	$(CH_3)_2N$	C_6H_5	C_2H_5	3a	266–267	83	B-D	$C_{23}H_{29}NO\cdot HCl$	C, H, Cl, N	>20	0
3j	H	$(CH_3)_2N$	C_6H_5	n-C_3H_7	3a	218–219.5	57	B-D	$C_{24}H_{31}NO\cdot HCl$	C, H, Cl, N	>20	0
3k	H	$(CH_3)_2N$	H	H	1a	248–249	65	B-D	$C_{15}H_{21}NO\cdot HCl$	C, H, Cl, N	>20	0
5a	H	CH_3NH	C_6H_5	H	4a	268–272	49	B-D	$C_{20}H_{23}NO\cdot HCl$	C, H, Cl, N	2.0 (1.8–2.2)	0
5b	CH_3NH	H	C_6H_5	H	4b	286–290 dec	45	C	$C_{20}H_{23}NO\cdot HCl$	C, H, Cl, N	>20	50
5c	H	CH_3NH	2-$CH_3C_6H_4$	H	4c	275–277.5	54	G	$C_{21}H_{25}NO\cdot HCl$	C, H, Cl, N	>20	50
5d	H	CH_3NH	4-FC_6H_4	H	4d	263–267	54	G	$C_{20}H_{22}FNO\cdot HCl\cdot 0.5H_2O$	C; H[j]	~20	0
5e	H	CH_3NH	4-ClC_6H_4	H	4e	275–277 dec	46	B	$C_{20}H_{22}ClNO\cdot HCl$	C, H, N	>20	0
amitriptyline											1.5 (1.4–1.6)	7.1[k] (3.0–9.1)
desipramine											0.30 (0.28–0.32)	

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material; yields were not optimized. [d] A = acetonitrile; B = absolute ethanol; C = 95% ethanol; D = ether; E = *n*-hexane; F = methanol; G = 2-propanol; H = toluene. [e] Analytical results within ±0.4% of theoretical values unless otherwise noted. [f] ED_{50}, mg/kg ip (mouse), to reverse tetrabenazine ptosis (TBZ). [g] Percent potentiation of 5-hydroxytryptophan-induced head twitching at 10 mg/kg ip (rat) (HTP). [h] Administered per os. [i] C: calcd, 70.05; found, 69.38. [j] H: calcd, 6.25; found, 6.82. [k] ED_{50}, mg/kg ip.

Table II. Intermediate Spiro[cyclohexane-1,1′(3′*H*)-isobenzofurans][a]



compd	R_1	R_2	R_3	R_4	starting material	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]
1a	H	$(CH_3)_2N$	=O			275-276	39	G	$C_{15}H_{19}NO_2 \cdot HCl$	C, H, Cl, N
1b	$(CH_3)_2N$	H	=O			275-283	14	F	$C_{15}H_{19}NO_2 \cdot HCl$	C, H
2a	H	$(CH_3)_2N$	C_6H_5	OH	1a	184-185.5	32	H-E	$C_{21}H_{25}NO_2$	C, H, N
2b	$(CH_3)_2N$	H	C_6H_5	OH	1b	184-188	73	H	$C_{21}H_{25}NO_2$	C, H, N
2c	H	$(CH_3)_2N$	2-$CH_3C_6H_4$	OH	1a	161-163	50	G	$C_{22}H_{27}NO_2$	C, H, N
2d	H	$(CH_3)_2N$	4-FC_6H_4	OH	1a	140-158	54	C	$C_{21}H_{24}FNO_2 \cdot 0.5H_2O$	H, F, N; C[f]
2e	H	$(CH_3)_2N$	4-ClC_6H_4	OH	1a	164-168	9	A	$C_{21}H_{24}ClNO_2$	C, H, Cl, N
2f	H	$(CH_3)_2N$	4-$CH_3C_6H_4$	OH	1a	196-197	61	H-E	$C_{22}H_{27}NO_2$	C, H, N
2g	H	$(CH_3)_2N$	CH_3	OH	1a	140.5-141.5	60	H-E	$C_{16}H_{23}NO_2$	C, H, N
4a	H	$C_2H_5OC(=O)NCH_3$	C_6H_5	H	3a	96-98	27	E	$C_{23}H_{27}NO_3$	C, H, N
4b	$C_6H_5OC(=O)NCH_3$	H	C_6H_5	H	3b	127-134	37	C	$C_{27}H_{27}NO_3$	C, H, N
4c	H	$C_6H_5OC(=O)NCH_3$	2-$CH_3C_6H_4$	H	3c	122-125.5	66	E	$C_{28}H_{29}NO_3$	C, H, N
4d	H	$C_6H_5OC(=O)NCH_3$	4-FC_6H_4	H	3d	133-137	73	C	$C_{27}H_{26}FNO_3$	C, H, N
4e	H	$C_6H_5OC(=O)NCH_3$	4-ClC_6H_4	H	3e	127-133	53	C	$C_{27}H_{26}ClNO_3$	C, H

[a-e] See corresponding footnotes to Table I. [f] C: calcd, 71.98; found, 71.52.

leads to significantly reduced antitetrabenazine activity (**3c,e,f** and **5c–e**). The C-3′ phenyl group is apparently required for good activity (**3a** vs. **3g,k**). Enhancement of serotonergic systems, a property of some antidepressant agents, is assessed in HTP. The compounds of Table I are relatively weak at 10 mg/kg ip in this assay. Representative examples of each structural type summarized in Table II did not display significant activity in these assays (**1a,b**, **2a**, and **4a**).

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOL C60HL; tetramethylsilane) spectra. ^{13}C NMR spectra were determined at 15.03 MHz on a JEOL FX 60 Fourier transform spectrometer. All chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, IL. Results are within ±0.4% of theoretical values unless otherwise noted in the tables. Reactions with organometallic reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents.

***cis*- (1a) and *trans*-4-(Dimethylamino)spiro[cyclohexane-1,1′(3′*H*)-isobenzofuran]-3′-one Hydrochloride (1b).** A stirred chilled (−45 °C) suspension of 295.9 g (1.5 mol) of benzanilide and 4.0 L of anhydrous tetrahydrofuran was treated with 1.36 L of 2.2 M *n*-butyllithium in hexane, during which the temperature was maintained below −20 °C. The solution was then stirred for 1 h at 0 °C, chilled to −40 °C, and a solution of 105.9 g (0.75 mol) of 4-(dimethylamino)cyclohexanone[19] and 50 mL of anhydrous tetrahydrofuran was added over 0.5 h. The turbid mixture was stirred for 0.75 h at −40 °C and for 1 h at 0 °C. The reaction was quenched with 300 mL of water, diluted with 1.0 L of dichloromethane, and acidified with 1.5 L of 3.3 N hydrochloric acid with cooling. After the solution stirred overnight at ambient temperature, the phases were separated and the organic phase was washed with water (3 L). The aqueous phase was basified with 50% sodium hydroxide and extracted with dichloromethane (2.5 L). The dried (Na_2SO_4) organic phase was concentrated to an oil, which was subjected to vacuum distillation at 100 °C to remove aniline and 4-(dimethylamino)cyclohexanone. The residual oil was dissolved in 200 mL of dichloromethane, diluted with 2.0 L of anhydrous ether, filtered, and treated with etheral hydrogen chloride to afford 158.6 g of crude **1a** and **1b**. Recrystallization from 500 mL of methanol afforded 29.6 g of **1b**. Evaporation of the mother liquor to dryness and recrystallization of the residue from 1.7 L of 2-propanol afforded 81.7 g of **1a**, which was contaminated with a trace of **1b**. Analytical samples were prepared by several recrystallizations from 2-propanol (**1a**) and methanol (**1b**). Properties of **1a** and **1b** are included in Table II.

(±)-*cis*-4-(Dimethylamino)-3′-hydroxy-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (2a). A solution of 7.36 g (0.03 mol) of **1a** free base and 100 mL of anhydrous tetrahydrofuran was added dropwise at −30 °C to 30 mL of stirred 2.1 M phenyllithium in 70:30 benzene–ether. The solution was then stirred for 1 h at 0 °C, quenched with water, and extracted with ether. The organic phase was washed with water, dried (Na_2SO_4), and concentrated to an oil, which was triturated with cyclohexane to give 4.96 g of crude material. Recrystallization from toluene–hexane provided 3.12 g of **2a** as colorless crystals. Properties of **2a**, and of **2b–g** prepared in similar manner from the appropriate aryl or alkyl Grignard reagent, are included in Table II.

(±)-*cis*-4-(Dimethylamino)-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (3a). A solution of 0.5 g (0.01 mol) of **2a** and 10 mL of 97% formic acid was heated for 2 h under conditions similar to those described by Martin et al.[3] (method H). Properties of **3a**, and of **3b–f** prepared in similar manner, are included in Table I.

(±)-*cis*-4-(Dimethylamino)-3′-methylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (3g). $LiAlH_4$ reduction of 3.68 g (11 mmol) of **2g** under conditions similar to those described by Martin et al.[3] (method E) afforded 3.28 g (88.6%) of (±)-*cis*-1-[2-(1-hydroxyethyl)phenyl]-4-(dimethylamino)cyclohexanol, mp 146–148 °C (ether–hexane). Refluxing 1.94 g (7.4 mmol) of the cyclohexanol derivative with 30 mL of glacial acetic acid and 4

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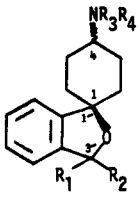
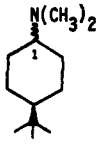
Table III. ^{13}C NMR Chemical Shift Data[a]





6a-b

compd[b]	salt	stereochem[c] at C-4	solvent[d]	R_1	R_2	R_3	R_4	chemical shift C-4	chemical shift N-CH_3	chemical shift C-1,1′	chemical shift C-3′
1a		e	C	=O		CH_3	CH_3	62.20	41.21	86.12	169.87
1b		a	C	=O		CH_3	CH_3	59.66	43.50	87.23	170.01
1a	HCl	e	C	=O		CH_3	CH_3	62.94	39.02	84.41	169.54
1a	HCl	e	D	=O		CH_3	CH_3	61.76	38.67	84.58	168.60
1b	HCl	a	D	=O		CH_3	CH_3	60.88	40.83	85.19	168.60
3a		e	C	H	C_6H_5	CH_3	CH_3	63.05	41.35	86.02	83.75
3b		a	C	H	C_6H_5	CH_3	CH_3	61.15	43.37	86.67	83.36
3g	HCl	e	C	H	CH_3	CH_3	CH_3	64.03	39.17	83.58	77.84
3k	HCl	e	C	H	H	CH_3	CH_3	63.99	39.14	84.80	71.13
5a		e	C	H	C_6H_5	H	CH_3	57.73	33.53	85.90	83.58
5b		a	C	H	C_6H_5	H	CH_3	54.69	32.76	86.68	83.47
5a	HCl	e	D	H	C_6H_5	H	CH_3	55.63	29.33	84.36	82.76
5b	HCl	a	D	H	C_6H_5	H	CH_3	53.58	30.22	84.85	82.64
6a	HCl	e	C					63.93[e]	41.68		
6b	HCl	a	C					60.64[e]	43.76		

[a] ^{13}C NMR spectra were determined at 15.03 MHz on a JEOL FX60 Fourier transform spectrometer. All chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. [b] A supplemental table listing ^{13}C NMR chemical shift data for 3c,d,f,h,i and 5c is available; see paragraph at end of paper concerning supplementary material. [c] e = equatorial; a = axial. [d] C = $CDCl_3$; D = Me_2SO-d_6. [e] Chemical shift of C-1.

mL of concentrated hydrochloric acid under conditions similar to those described by Martin et al.[3] (method G) afforded **3g**. Properties of **3g** are included in Table I.

(±)-*cis*-4-(Dimethylamino)-3′-methyl-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] oxalate (3h) was prepared from 4.61 g (0.015 mol) of **3a** and 1.87 g of dimethyl sulfate under conditions similar to those described by Martin et al.[3] Properties of **3h**, and **3i,j** prepared in similar manner from **3a** and ethyl bromide and *n*-propyl iodide, are included in Table I.

***cis*-4-(Dimethylamino)spiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] Hydrochloride. (3k)**. A stirred chilled (0 °C) solution of 4.63 g (0.02 mol) of **1a** free base and 50 mL of anhydrous tetrahydrofuran was treated dropwise with 50 mL of 1 M borane in tetrahydrofuran. The solution was then stirred for 0.5 h at ambient temperature, followed by heating overnight under reflux. The chilled (0 °C) solution was treated with 19 mL of 6 N hydrochloric acid, heated for 5 h under reflux, concentrated, diluted with water, basified, and extracted with ether. The dried (Na_2SO_4) organic phase was concentrated to an oil, which was converted to the hydrochloride salt. Recrystallization from absolute ethanol–ether afforded 3.48 g of **3k** as colorless crystals. Properties of **3k** are included in Table I.

(±)-*cis*-4-[*N*-(Ethoxycarbonyl)-*N*-methylamino]-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (4a) was prepared from 15.7 g (0.051 mol) of **3a**, 10 mL of ethyl chloroformate, and 150 mL of dichloromethane under conditions similar to those described by Martin et al.[3] (method M). Properties of **4a** are included in Table II.

(±)-*trans*-4-[*N*-Methyl-*N*-(phenoxycarbonyl)amino]-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] (4b) was prepared from 4.61 g (0.015 mol) of **3b**, 2.82 g (0.018 mol) of phenyl chloroformate, and 35 mL of dichloromethane under conditions similar to those described by Martin et al.[3] (method N). Properties of **4b**, and of **4c–e** prepared in similar manner, are included in Table II.

(±)-*cis*-4-(Methylamino)-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] hydrochloride (5a) was prepared by KOH–ethylene glycol hydrolysis of 7.9 g (0.022 mol) of **4a** under similar conditions, as described by Shutske et al.[6] Properties of **5a** are included in Table I.

(±)-*trans*-4-(Methylamino)-3′-phenylspiro[cyclohexane-1,1′(3′*H*)-isobenzofuran] Hydrochloride (5b). A stirred suspension of 5.82 g (0.014 mol) of **4b**, 2.5 mL of water, 58 mL of 1-propanol, and 8.25 g of potassium hydroxide pellets was heated overnight under reflux. The cooled solution was concentrated, and the residue was diluted with water and extracted with dichloromethane (2 × 125 mL). The dried (Na_2SO_4) organic phase was concentrated to an oil, which was converted to the hydrochloride salt. Recrystallization from 95% ethanol afforded 2.07 g of **5b** as colorless crystals. Properties of **5b**, and of **5c–e** prepared in similar manner, are included in Table I.

Tetrabenazine Assay. The test compound was adminstered by intraperitoneal injection to male mice (Charles Rivers CD-1) in groups of five. Tetrabenazine methanesulfonate (40 mg/kg, ip) was administered 30 min later, and after another 30 min the mice were placed in individual containers. Ptosis was then evaluated on a three-point scale: eyes closed = 2; eyes half open = 1; eyes open = 0. A linear regression analysis of the ptosis scores was used to evaluate ED_{50} values and 95% confidence intervals. Data for the reference standards amitriptyline and desipramine are included in Table I.

L-5-Hydroxytryptophan Seizure Potentiation. Groups of six male Wistar rats received 75 mg/kg of pargyline hydrochloride by subcutaneous injection 4 h prior to testing. Thirty minutes before testing, the test drug was administered ip in a dosage volume of 10 mL/kg. L-5-Hydroxytryptophan was administered at 1 mg/kg ip in distilled water. Five minutes later, the animals were observed for head motion and coarse tremors. A compound was considered to potentiate 5-HTP activity if the animals exhibited continuous forelimb clonus. Potentiation was expressed as normalized percent potentiation relative to vehicle control. ED_{50} values and 95% confidence limits for reference standards were determined by Probit analysis using ten animals per group.

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Supplementary Material Available: Table listing ^{13}C NMR chemical shift data for **3c,d,f,h,i** and **5c** (1 page). Ordering information is given on any current masthead page.