Synthesis of Spiro[isobenzofuran-1(3*H*),4'-piperidines] as Potential Central Nervous System Agents. 1[1]

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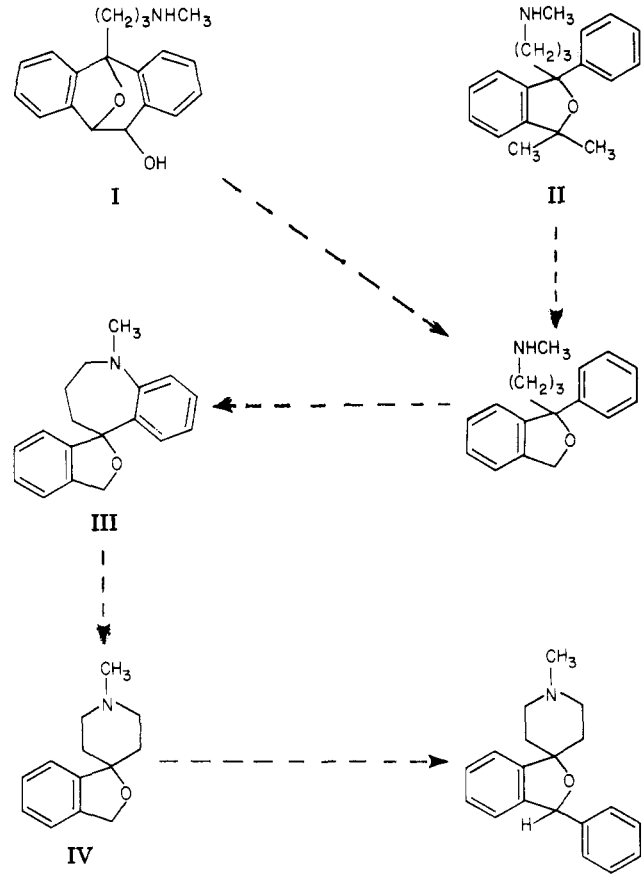
Synthesis of 1'-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (**7a**, HP 365) and the demethyl analogue **9a** (HP 505) was prompted by recognition of an aminoalkyl(aryl)isobenzofuran moiety common to the antidepressants talopram (Lu 3-010) and *trans*-10,11-dihydro-5,10-epoxy-5-[3-(methylamino)propyl]-5*H*-dibenzo[*a*,*d*]cyclohepten-11-ol (MK-940). Convenient laboratory synthesis of **7a** was provided by lithiation of 2-bromobenzhydryl methyl ether, followed by addition of 1-methyl-4-piperidone and acid-catalyzed cyclization. N-Dealkylation by standard methods afforded **9a**. Synthesis of analogues was stimulated by discovery of marked inhibition of tetrabenazine-induced ptosis for lead compounds **7a** and **9a**. Optimal antitetrabenazine activity is associated with the 3-phenylspiro-[isobenzofuran-1(3*H*),4'-piperidine] moiety where nitrogen is basic. Modification of this moiety by introduction of large nitrogen substituents or a C-3 substituent > H significantly reduced antitetrabenazine activity. A series of analogues with aromatic substituents was investigated; however, few of these compounds were significantly more active than **7a** and **9a**. Compound **9a** was selected for additional studies.

The search for novel antidepressants continues to be stimulated by factors such as the slow onset of therapeutic action with the tricyclic antidepressants and monoamine oxidase inhibitors,[2] the frequent occurrence of untoward effects with both the tricyclics (anticholinergic[3,4] and cardiovascular[5,6] effects) and monoamine oxidase inhibitors (hypotension[3]), and the gradual recognition of the multifaceted etiology of depression.[7] Perception of a recurring structural element in several reference drugs has frequently stimulated synthesis of novel compounds with, hopefully, improved biological properties. Synthesis of spiro[isobenzofuran-1(3*H*),4'-piperidines] as potential central nervous system (CNS) agents was prompted as shown in Scheme I by recognition of an aminoalkyl-(aryl)isobenzofuran moiety as a recurring structural element in the antidepressants, *trans*-10,11-dihydro-5,10-epoxy-5-[3-(methylamino)propyl]-5*H*-dibenzo-[*a*,*d*]cyclohepten-11-ol (I) and talopram (II, an antidepressant representing a major structural departure from the tricyclics[2]). *N*-Aryl bond formation would give the novel spiro[isobenzofuranbenzazepine] III, which on further simplification to facilitate synthesis would afford IV. Incorporation of a pendant phenyl group to maintain molecular bulk gives the series of 3-arylspirophthalans (Table I) which constitute the subject of this paper.[8]

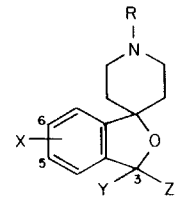
Scheme I



Chemistry. Our initial approach to 3-phenylspiro-[isobenzofuran-1(3*H*),4'-piperidines] was based on the carboxyl protection studies of Meyers and Temple.[11] By this route the carboxyl group of 2-bromobenzoic acid was protected as oxazoline derivative **2a** (Scheme II). Grignard addition (method A) of **2a** to 1-methyl-4-piperidone gave piperidinol **3a** in 21% yield. Significant improvement in yield (59%) of **3a** was achieved by low-temperature conversion of **2a** to the lithium reagent with *n*-butyllithium, followed by piperidone addition (method B). Similar addition of oxazolines **2a–c** to *N*-alkyl(aralkyl)piperidones gave **3b–f** (Table II). Acid hydrolysis of **3a–f** and concomitant lactonization afforded phthalides **4a–f** (Table III). Addition of an aryllithium (method C) or an arylmagnesium halide (method D) reagent to **4a–e** gave phthalanols **5a–h** (Table IV). $LiAlH_4$ reduction of **5a–g** to diols **6a–g** (method E, Table V) and acid-catalyzed cyclization (methods G, H) of **6a–f** gave spirophthalans **7a–f** (Table I). N-Dealkylation of **7a–e** with ethyl or phenyl chloroformate[12] (methods M and N, respectively) gave carbamates **8a–f** (Table VI) which were hydrolyzed (method O) to **9a–d** (Table I). Alternatively, **7b** was catalytically debenzylated to **9a** (method P). Compound **9o** was prepared from **6g** (methods G, M, O) without full characterization of intermediates.

The need to provide analogues and sufficient quantities of lead compounds **7a** and **9a** for extensive pharmacological evaluation prompted investigation of more efficient syntheses. The synthesis of spirophthalans from 2-bromobenzyl alcohol and alicyclic ketones reported by Parham and Egberg[13] suggested a possible alternative route to **7** via **6** (Scheme III). Simple modification of this synthesis by metalation of 2-bromobenzhydrol (**10a**) with

Table I. Spiro[isobenzofuran-1(3*H*),4′-piperidines][a]



Compd	R	X	Y	Z	Starting material	Method	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]	Tetrabenazine ptosis,[f] ED_{50}, mg/kg ip (mouse)
7a	CH_3	H	H	C_6H_5	6a, 8a, 11a	G-J	123-124[g]	51-98	L	$C_{19}H_{21}NO$	C, H, N	1.1 (0.6-1.8)
7b	$C_6H_5CH_2$	H	H	C_6H_5	6b, 11a	G, I	137-138	50	M	$C_{25}H_{25}NO$	C, H, N	>15
7c	CH_3	5-CH_3O	H	C_6H_5	6c	H	78-80	72	L	$C_{20}H_{23}NO_2$	C, H, N	6.4 (4.1-8.4)
7d	CH_3	H	H	4-$CH_3OC_6H_4$	6d	G	127-128	71	L	$C_{20}H_{23}NO_2$	C, H, N	1.1 (0.9-1.4)
7e	$C_6H_5CH_2$	H	H	4-FC_6H_4	6e, 11i	G, I	111-113	56	M	$C_{25}H_{24}FNO$	C, H, F, N	6.3 (5.6-7.0)
7f	$C_6H_5(CH_2)_2$	H	H	C_6H_5	6f	G	257-261	36[h]	M	$C_{26}H_{27}NO$·HCl	C, H, Cl, N	>50
7g	CH_3	H	H	4-HOC_6H_4	7d	L	273-276 dec	63	G	$C_{19}H_{21}NO_2$	H, N; C[i]	1.0 (0.3-1.7)
7h	CH_3	H	H	4-FC_6H_4	6i	G	126-127	95	E	$C_{19}H_{20}FNO$	C, H, F, N	1.4 (1.1-1.7)
7i	CH_3	H	H	4-ClC_6H_4	11h	I	133-135	37	K	$C_{19}H_{20}ClNO$	C, H, Cl, N	0.4 (0.2-0.5)
7j	CH_3	H	H	4-$CH_3C_6H_4$	8h	J	135-136	75	E	$C_{20}H_{23}NO$	C, H, N	2.2 (1.7-2.7)
7k	CH_3	H	H	4-$CF_3C_6H_4$	6k	G	239	44	B	$C_{20}H_{20}F_3NO$·HCl	H, Cl, N; C[j]	>10
7l	CH_3	H	H	3-$CH_3C_6H_4$	11e	I	78-80	67	L	$C_{20}H_{23}NO$	C, H, N	6.3 (5.4-7.1)
7m	CH_3	H	H	3-$CH_3OC_6H_4$	11f[k]	I	108-109	42	F	$C_{20}H_{23}NO_2$	C, H, N	10.7 (9.7-11.6)
7n	CH_3	H	H	3-FC_6H_4	6j	G	81-84	69	L	$C_{19}H_{20}FNO$	C, H, N	0.6 (0.4-0.8)
7o	CH_3	6-CH_3O	H	C_6H_5	6l	H	82-85	85	L	$C_{20}H_{23}NO_2$	H, N; C[l]	6.6 (5.4-8.1)
7p	CH_3	6-HO	H	C_6H_5	7o	K	207-212	44	I	$C_{19}H_{21}NO_2$	C, H, N	>25
7q	CH_3	6-F	H	C_6H_5	11d	I	127-129	26	F	$C_{19}H_{20}FNO$	C, H, N	1.5 (1.2-1.9)
7r	CH_3	5-HO	H	C_6H_5	7c	K	193-200	58	I	$C_{19}H_{21}NO_2$	C, H, N	27.5 (24-33)
7s	CH_3	H	H	3,4-$(CH_3O)_2$-C_6H_3	6h	H	67-71	70	L	$C_{21}H_{25}NO_3$	C, H, N	10.0 (9.0-11.2)
7t	CH_3	5,6-(C_2H_3O)$_2$	H	C_6H_5	6m	H	165-168	61	C-L	$C_{21}H_{25}NO_3$	C, H, N	>25
7u	CH_3	6-F	H	4-FC_6H_4	6n	G	134-135	85	E	$C_{19}H_{19}F_2NO$	C, H, F, N	2.0 (1.7-2.4)
7v	CH_3	6-CH_3O	H	4-FC_6H_4	8n	J	235 dec	62	M	$C_{20}H_{22}FNO_2$·HBr	C, H, Br, N	18.4 (14.6-25.5)
7w	$C_6H_5CH_2$	H	H	4-$CH_3C_6H_4$	11g	I	98-99	46	M	$C_{26}H_{27}NO$	C, H, N	nt
7x	$C_6H_5CH_2$	6-CH_3O	H	4-FC_6H_4	11c	I	86-88	3	K	$C_{26}H_{26}FNO_2$	H, N; C[m]	nt
7y	CH_3	H	H	H			76-77[n]	33	L	$C_{13}H_{17}NO$	C, H, N	4.7 (4.2-5.3)
9a	H	H	H	C_6H_5	7b, 8a,b	O, P	121-122	97, 83	E	$C_{18}H_{19}NO$	C, H, N	0.5 (0.3-0.7)
9b	H	5-CH_3O	H	C_6H_5	8c	O	104-106	68	L	$C_{19}H_{21}NO_2$	C, H, N	15.7 (11.2-19.4)
9c	H	H	H	4-$CH_3OC_6H_4$	8d	O	101-103	77	L	$C_{19}H_{21}NO_2$	C, H, N	2.6 (2.2-3.1)
9d	H	H	H	4-FC_6H_4	8f	O	98-100	78	F	$C_{18}H_{18}FNO$	H, F, N; C[o]	0.6 (0.4-0.7)
9e	H	H	H	4-HOC_6H_4	9c	L	255 dec	50	G	$C_{18}H_{19}NO_2$	C, H, N	0.7 (0.5-0.9)
9f	H	H	H	4-ClC_6H_4	8g	O	90-92	13	F	$C_{18}H_{18}ClNO$	H, N; C[p]	0.4 (0.3-0.5)
9g	H	H	H	4-$CH_3C_6H_4$	8h	O	116-117	51	E	$C_{19}H_{21}NO$	C, H, N	0.8 (0.6-1.0)
9h	H	H	H	3-$CH_3C_6H_4$	8i	O	228 dec	32	H	$C_{19}H_{21}NO$·HBr	C, H, N	5.3 (4.7-6.1)
9i	H	H	H	3-$CH_3OC_6H_4$	8j	O	195-198 dec	73	H	$C_{19}H_{21}NO_2$·HCl	C, H, N	1.0 (0.8-1.2)
9j	H	6-CH_3O	H	C_6H_5	8k	O	88-91	60	L	$C_{19}H_{21}NO_2$	C, H, N	0.5 (0.4-0.6)
9k	H	6-HO	H	C_6H_5	9j	K	274-276 dec	50	H	$C_{18}H_{19}NO_2$·HBr	C, H, Br, N	6.2 (4.1-8.0)
9l	H	5-HO	H	C_6H_5	9b	K	202-208	31	G	$C_{18}H_{19}NO_2$·$(CH_3)_2SO$	C, H, N, S	22.7 (19-28)
9m	H	H	H	3,4-$(CH_3O)_2$-C_6H_3	8l	O	212-218	37	N-I	$C_{20}H_{23}NO_3$·HCl	C, H, Cl, N	3.0 (2.5-3.9)
9n	H	6-F	H	4-FC_6H_4	8m	O	111-112	56	L	$C_{18}H_{17}F_2NO$	C, H, N	0.76 (0.7-0.8)

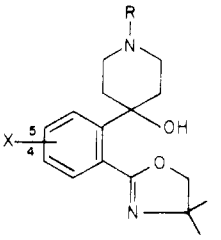
9o	H	5-CH_3O	H	4-FC_6H_4	6g	G, M, O	275 dec	31	H	$C_{19}H_{20}FNO_2$·HCl	C, H, Cl, F, N	6.6 (5.7–7.7)
9p	H	H	H	H			84–86[q]	67	L	$C_{12}H_{15}NO$	H, N; C[r]	2.9 (2.0–3.8)
13a	C_2H_5	H	H	C_6H_5	12a	V	113–115	58	D	$C_{20}H_{23}NO$	C, H, N	1.5 (0.9–2.1)
13b	n-C_3H_7	H	H	C_6H_5	12b	V	98–100	35	I	$C_{21}H_{25}NO$	C, H, N	nt
13c	n-C_4H_9	H	H	C_6H_5	12c	V	102–103	48	I	$C_{22}H_{27}NO$	C, H, N	⩾10
13d	i-C_4H_9	H	H	C_6H_5	12d	V	117–119	78	H	$C_{22}H_{27}NO$	C, H, N	>25
13e	CH_2-c-C_3H_5	H	H	C_6H_5	12e	V	97–99	50	I	$C_{22}H_{25}NO$	C, H, N	4.8 (3.9–6.3)
13f	CH_2-c-C_3H_5	H	H	4-FC_6H_4	12f	V	233–235	72	H	$C_{22}H_{24}FNO$·HBr	H, N; C[s]	1.5 (1.2–1.8)
13g	CH_2-c-C_4H_7	H	H	C_6H_5	12g	V	119–121	75	H	$C_{23}H_{27}NO$	C, H, N	>25
13h	i-C_3H_7	H	H	C_6H_5	9a	W	121–124	53	H	$C_{21}H_{25}NO$	C, H, N	8.3 (7.3–9.3)
13i	$CH_2CH=CH_2$	H	H	C_6H_5	9a	W	127–130	16	L	$C_{21}H_{23}NO$	C, H, N	nt
13j	$CH_2CH=C(CH_2)_2$	H	H	C_6H_5	9a	W	119–121	36	H	$C_{23}H_{27}NO$	C, H, N	>25
14a	CH_3	H	CH_3	C_6H_5	7a		122–125 dec	42	J	$C_{20}H_{23}NO$·HBr	C, H, Br, N	9.5 (8–11.6)
14b	CH_3	H	C_2H_5	C_6H_5	7a		107–108	41	L	$C_{21}H_{25}NO$	C, H, N	>25
14c	CH_3	H	n-C_3H_7	C_6H_5	7a		205–206	65	A-I	$C_{22}H_{27}NO$·HCl	C, H, Cl, N	>25
14d	CH_3	H	n-C_4H_9	C_6H_5	7a		203–204	67	A	$C_{23}H_{29}NO$·HCl	H, Cl, N; C[t]	>25
Imipramine												1.3 (0.9–1.7)
Desipramine												0.8 (0.6–0.9)

[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 = acetone; B = acetonitrile; C = benzene; D = chloroform; E = cyclohexane; F = diisopropyl ether; G = dimethyl sulfoxide; H = ethanol; I = ether; J = ethyl acetate; K = heptane; L = hexane; M = 2-propanol; N = methanol; O = petroleum ether (bp 30–60 °C); P = toluene; Am = amorphous. [e] Analytical results within ±0.4% of theoretical values unless otherwise noted. [f] nt = not tested. Compounds 13b and 13i were available in insufficient quantity; compounds 7w and 7x were prepared as intermediates. [g] Lit.[10] mp 120–123 °C (cyclohexane). [h] Calculated from 5f. [i] C: calcd, 77.26; found, 76.28. [j] C: calcd, 62.58; found, 61.92. [k] Crude oil. [l] C: calcd, 77.62; found, 77.09. [m] C: calcd, 77.39; found, 76.84. [n] Lit.[10] mp 281–282 °C (as HCl salt). [o] C: calcd, 76.30; found, 75.54. [p] C: calcd, 72.11; found, 71.66. [q] Lit. mp 208.5–209.5 °C (HCl salt; ethanol–ether);[9] mp 200–202 °C (HCl salt, acetonitrile).[10] [r] C: calcd, 76.16; found, 75.68. [s] C: calcd, 63.16; found, 62.72. [t] C: calcd, 74.26; found, 73.76.

Scheme II

2 equiv of n-butyllithium, followed by addition of 1-methyl-4-piperidone and aqueous quenching, afforded **6a**, generally in low yield (method F). Substitution of 2-bromobenzhydryl methyl ether (**11a**) (method I) halved the n-butyllithium requirement and significantly increased overall yield of **7a** (30 and 51% from **10a** and **11a**, respectively). Attempts to isolate the methyl ether intermediate of method I were generally unsuccessful due to ease of cyclization to **7**. Convenient laboratory synthesis of **7a–e,h–o,q,s–x** and **9a–d,f–j,m,n** was provided from 2-bromobenzhydrol or 2-bromobenzhydryl methyl ether derivatives. Bromobenzhydrols **10a–r** (Table VII) were prepared by Friedel–Crafts aromatic ketone synthesis and borohydride reduction of the intermediate benzophenones (methods Q, S) or by Grignard addition of an aryl halide to an appropriately substituted 2-bromobenzaldehyde (method R). Methyl ethers **11a–i** (Table VII) were prepared by refluxing the corresponding benzhydrols with methanolic HCl (method T) or by treatment of a benzhydrol with sodium methoxide and dimethyl sulfate (method U). Phenolic spirophthalans **7g,p,r** and **9e,k,l** were obtained by cleavage of the methyl ethers with 48% HBr (method K) or sodium thioethoxide[14] (method L). Amides **12a–h** (Table VI) were synthesized by treatment of **9** with acid chlorides. $LiAlH_4$ reduction of **12a–g** gave tertiary amines **13a–g** (method V), while treatment of **9a** with alkyl halides afforded **13h–j** (method W) (Table I). Alkylation of **7a** at C-3 by treatment with n-butyllithium

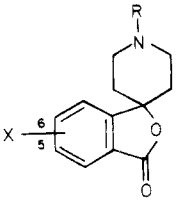
Table II. 4-[2-(4,4-Dimethyl-2-oxazolin-2-yl)aryl]-4-piperidinols[a]



Compd	R	X	Starting material	Method	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
3a	CH_3	H	2a	A, B	162-163[f]	21, 59	H	$C_{17}H_{24}N_2O_2$	C, H, N
3b	$C_6H_5CH_2$	H	2a	A, B	109-112[g]	78, 54	C	$C_{23}H_{28}N_2O_2$	C, H, N
3c	$C_6H_5CH_2$	4-CH_3O	2b	A	157-165	15[h]		$C_{21}H_{30}N_2O_3 \cdot 2HCl$	
3d	CH_3	4-CH_3O	2b	A	154-156	9	C	$C_{18}H_{26}N_2O_3$	C, H, N
3e	$C_6H_5(CH_2)_2$	H	2a	A	130-132	19	E	$C_{24}H_{30}N_2O_2$	C, H, N
3f	$C_6H_5CH_2$	4,5-(CH_3O)$_2$	2c	A	Oil	81[i]		$C_{25}H_{32}N_2O_4$	

[a-e] See corresponding footnotes to Table I. [f] Lit.[10] mp 158-160 °C (acetone). [g] Lit.[10] mp 97-100 °C (benzene). [h] Yield of crude salt which was converted without purification to 4c. [i] Yield of crude 3f which was converted without purification to 4f.

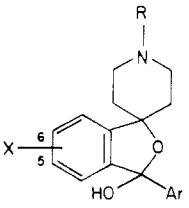
Table III. Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones[a]



Compd	R	X	Starting material	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
4a	CH_3	H	3a	147-148[f]	76	C	$C_{13}H_{15}NO_2$	C, H, N
4b	$C_6H_5CH_2$	H	3b	104-106[g]	76	F	$C_{19}H_{19}NO_2$	C, H, N
4c	$C_6H_5CH_2$	5-CH_3O	3c	163-164	14	C-E	$C_{20}H_{21}NO_3$	C, H, N
4d	CH_3	5-CH_3O	3d	123-125	57	C-E	$C_{14}H_{17}NO_3$	C, H, N
4e	$C_6H_5(CH_2)_2$	H	3e	101-104	59	C-L	$C_{20}H_{21}NO_2$	C, H, N
4f	$C_6H_5CH_2$	5,6-(CH_3O)$_2$	3f	143-144	8	C-E	$C_{21}H_{23}NO_4$	C, H, N

[a-e] See corresponding footnotes to Table I. [f] Lit.[10] mp 147-148 °C (ether). [g] Lit. mp 105-106 °C (ether-methanol);[9] 103-104 °C (cyclohexane).[10]

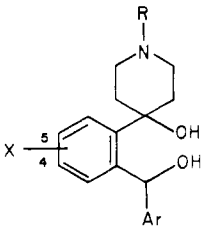
Table IV. 3-Hydroxy-3-arylspiro[isobenzofuran-1(3*H*),4′-piperidines][a]



Compd	R	X	Ar	Starting material	Method	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
5a	CH_3	H	C_6H_5	4a	C	182-183[f]	96	H	$C_{19}H_{21}NO_2$	C, H, N
5b	$C_6H_5CH_2$	H	C_6H_5	4b	C	87-90	44	H	$C_{25}H_{25}NO_2 \cdot C_2H_5OH$	C, H, N
5c	CH_3	5-CH_3O	C_6H_5	4d	C	208-210	83	M	$C_{20}H_{23}NO_3$	C, H, N
5d	CH_3	H	4-CH_3-OC_6H_4	4a	D	123-124[g]	77	H	$C_{20}H_{23}NO_3$	H, N; C[h]
5e	$C_6H_5CH_2$	H	4-FC_6H_4	4b	D	60	45	Am	$C_{25}H_{24}FNO_2$	C, H, N
5f	C_6H_5-$(CH_2)_2$	H	C_6H_5	4e	C	146-150	21	M	$C_{26}H_{27}NO_2$	H, N; C[i]
5g	$C_6H_5CH_2$	5-CH_3O	4-FC_6H_4	4c	D	70	61	Am	$C_{26}H_{26}FNO_3$	C, H, N; F[j]
5h	$C_6H_5CH_2$	H	4-CH_3-OC_6H_4	4d	D	63	2	Am	$C_{26}H_{27}NO_3$	C, H, N

[a-e] See corresponding footnotes to Table I. [f] Lit.[10] mp 170-172 °C (EtOAc). [g] Lit.[10] mp 158-161 °C (EtOAc). [h] C: calcd, 73.82; found, 74.23. [i] C: calcd, 81.01; found, 80.56. [j] F: calcd, 4.53; found, 4.11.

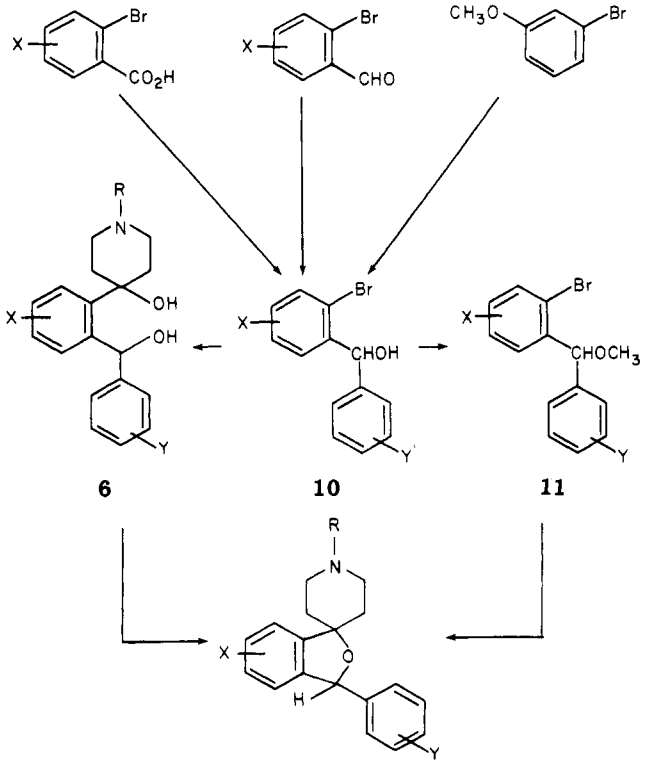
Table V. 4-(α-Hydroxy-α-aryl-2-tolyl)-4-piperidinols[a]



Compd	R	X	Ar	Starting material	Method	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
6a	CH_3	H	C_6H_5	5a, 10a	E, F	190-191	94, 30	P	$C_{19}H_{23}NO_2$	C, H, N
6b	$C_6H_5CH_2$	H	C_6H_5	5b, 10a	E, F	55	92	F	$C_{25}H_{27}NO_2$[f]	C, H, N
6c	CH_3	4-CH_3O	C_6H_5	5c, 10d	E, F	196-197	47, 45	P	$C_{20}H_{25}NO_3$	C, H, N
6d	CH_3	H	4-$CH_3OC_6H_4$	5d, 10b	E, F	214-215	65, 24	P	$C_{20}H_{25}NO_3$	C, H, N
6e	$C_6H_5CH_2$	H	4-FC_6H_4	5e	E	55	96	Am	$C_{25}H_{26}FNO_2$	H, F, N; C[g]
6f	C_6H_5-$(CH_2)_2$	H	C_6H_5	5f	E	Oil	43[h]		$C_{26}H_{29}NO_2$	
6g	$C_6H_5CH_2$	4-CH_3O	4-FC_6H_4	5g	E	65	94	Am	$C_{26}H_{28}FNO_3$	C, H, F, N
6h	CH_3	H	3,4-$(CH_3O)_2$-C_6H_3	10l	F	178-180	14	P	$C_{21}H_{27}NO_4$	C, H, N
6i	CH_3	H	4-FC_6H_4	10i	F	166-167	33	P	$C_{19}H_{22}FNO_2$	C, H, F, N
6j	CH_3	H	3-FC_6H_4	10k	F	187-189	14	P	$C_{19}H_{22}FNO_2$	C, H, N
6k	CH_3	H	4-$CF_3C_6H_4$	10j	F	178-180	24	P	$C_{20}H_{22}F_3NO_2$	C, H, N
6l	CH_3	5-CH_3O	C_6H_5	10f	F	182-184	11	P	$C_{20}H_{25}NO_3$	C, H, N
6m	CH_3	4,5-$(CH_3O)_2$	C_6H_5	10n	F	196-197	48	P	$C_{21}H_{27}NO_4$	C, H, N
6n	CH_3	5-F	4-FC_6H_4	10o	F	167-169	10	Am	$C_{19}H_{21}F_2NO_2$	C, H, N

[a-e] See corresponding footnotes to Table I. [f] Complexed with 0.33 mol of diisopropyl ether per mole of 6b. [g] C: calcd, 76.70; found, 75.51. [h] Yield of crude oil.

Scheme III



7, R = CH_3, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$
9, R = H

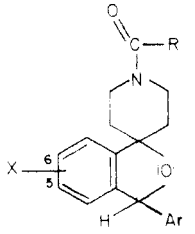
and addition of dimethyl sulfate or an alkyl halide gave **14a–d** (Table I). Spirophthalans **7y** and **9p** were prepared by literature methods.[9]

Structure–Activity Relationships. Tetrabenazine methanesulfonate induces a reserpine-like behavorial depression with concomitant ptosis which is antagonized by antidepressant agents. Evaluation of lead compounds **7a** and **9a** in a battery of pharmacological assays revealed marked antitetrabenazine activity and suggested a unique profile of activity for these compounds with respect to standard antidepressants. Antitetrabenazine activity has been most actively pursued and data (Table I) for the various analogues permit preliminary structure–activity correlations.

Representative examples of the intermediate oxazolines (**2**), piperidinols (**3**), phthalides (**4**), phthalanols (**5**), and diols (**6**) had marginal or no antitetrabenazine activity. Thus, antitetrabenazine activity is apparently associated with the spiro[isobenzofuran-1(3*H*),4'-piperidine] moiety; however, a basic nitrogen is required as the intermediate carbamates **8** and amides **12** are essentially devoid of activity. Optimal antitetrabenazine activity is conferred by a C-3 phenyl group as indicated by the significantly enhanced activity of **7a** and **9a** vs. **7y** and **9p**, respectively. Optimal antitetrabenazine activity is also associated with analogues where the nitrogen substituent is H (**9a**), small alkyl (**7a, 13a**), and cyclopropylmethyl (**13e**), whereas significantly reduced activity is associated with larger nitrogen substituents (**7b,f, 13c,d,g,h**) (Table I). Antitetrabenazine activity is also greatly reduced by introduction of a second C-3 substituent (Y > H) (**5a–d,f, 14a–d**).

The effect of aromatic substituents on antitetrabenazine activity is not clearly defined, although 18 tertiary amines (**7c,d,g–v**) and 14 secondary amines (**9b–o**) were evaluated (Table I). Generalizations with respect to the effect of aromatic substituents must be regarded with caution as only a limited number of substituents were evaluated at any single position, with possible exception of the 3-(4-XC_6H_4) series. The matter is further complicated by the observation that an aromatic substituent frequently does

Table VI. 1′-Alkoxycarbonyl(acyl)-3-arylspiro[isobenzofuran-1(3*H*),4-piperidines][a]



Compd	R	X	Ar	Starting material	Method	Mp,[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
8a	C_2H_5O	H	C_6H_5	7a,b	M	121-123	51, 92	H	$C_{21}H_{23}NO_3$	C, H, N
8b	C_6H_5O	H	C_6H_5	7a,b	N	179-183	33, 75	C-L	$C_{25}H_{23}NO_3$	C, H, N
8c	C_6H_5O	5-CH_3O	C_6H_5	7c	N	181-185	81	C-L	$C_{26}H_{25}NO_4$	H, N; C[f]
8d	C_2H_5O	H	4-$CH_3OC_6H_4$	5h	E, G, M	113-115	72[g]	H	$C_{22}H_{25}NO_4$	C, H, N
8e	C_6H_5O	H	4-$CH_3OC_6H_4$	7d	N	163-165	95	H	$C_{26}H_{25}NO_4$	C, H, N
8f	C_2H_5O	H	4-FC_6H_4	7e	M	104-106	82	L	$C_{21}H_{22}FNO_3$	H, F, N; C[h]
8g	C_6H_5O	H	4-ClC_6H_4	7i	N	183-185	65	H	$C_{25}H_{22}ClNO_3$	C, H, N
8h	C_2H_5O	H	4-$CH_3C_6H_4$	7w	M	106-108	83	H	$C_{25}H_{25}NO_3$	C, H, N
8i	C_6H_5O	H	3-$CH_3C_6H_4$	7l	N	156-158	77	H	$C_{26}H_{25}NO_3$	C, H, N
8j	C_6H_5O	H	3-$CH_3OC_6H_4$	7m	N	129-131	86	H	$C_{26}H_{25}NO_4$	C, H, N
8k	C_2H_5O	6-CH_3O	C_6H_5	7o	M	178-180	65	N	$C_{22}H_{25}NO_4$	C, H, N
8l	C_6H_5O	H	3,4-$(CH_3O)_2$-C_6H_3	7s	N	170-172	71	H	$C_{27}H_{27}NO_5$	C, H, N
8m	C_2H_5O	6-F	4-FC_6H_4	11b	I, M	123-126	46[i]	H	$C_{21}H_{21}F_2NO_3$	H, N; C[j]
8n	C_2H_5O	6-CH_3O	4-FC_6H_4	7x	M	168-170	89	H	$C_{22}H_{24}FNO_4$	C, H, N
8o	C_6H_5O	H	4-$CF_3C_6H_4$	7k	N	201-203	62	I[k]	$C_{26}H_{22}F_3NO_3$	C, H, N
8p	C_6H_5O	H	4-$C_6H_5OC(=O)OC_6H_4$	7g	N	173-175	38	H[l]	$C_{32}H_{27}NO_6$	H, N; C[m]
12a	CH_3	H	C_6H_5	9a		128-130	65	D	$C_{20}H_{21}NO_2$	C, H, N
12b	C_2H_5	H	C_6H_5	9a		116-119	80	I	$C_{21}H_{23}NO_2$	C, H, N
12c	n-C_3H_7	H	C_6H_5	9a		110-112	65	I	$C_{22}H_{25}NO_2$	H, N; C[n]
12d	i-C_3H_7	H	C_6H_5	9a		112-114	72	L	$C_{22}H_{25}NO_2$	C, H, N
12e	c-C_3H_5	H	C_6H_5	9a		133-135	67	I	$C_{22}H_{23}NO_2$	H, N; C[o]
12f	c-C_3H_5	H	4-FC_6H_4	9d		149-152	83	F	$C_{22}H_{22}FNO_2$	C, H, N
12g	c-C_4H_7	H	C_6H_5	9a		126-130	75	L	$C_{23}H_{25}NO_2$	C, H, N
12h	$C_6H_5CH_2$	H	C_6H_5	9a		174-176	57	D	$C_{26}H_{25}NO_2$	C, H, N

[a-e] See corresponding footnotes to Table I. [f] C: calcd, 75.15; found, 74.27. [g] Based on crude 1′-benzyl-3-(4-methoxyphenyl)spiro[isobenzofuran-1(3*H*),4′-piperidine]. [h] C: calcd, 70.97; found, 71.60. [i] Based on crude 1′-benzyl-6-fluoro-3-(4-fluorophenyl)spiro[isobenzofuran-1(3*H*),4′-piperidine]. [j] C: calcd, 67.55; found, 67.09. [k] Crude solid washed with ether. [l] Crude solid washed with ethanol. [m] C: calcd, 73.69; found, 72.52. [n] C: calcd, 78.77; found, 78.27. [o] C: calcd, 79.24; found, 78.51.

not influence antitetrabenazine activity of the tertiary and secondary amines in a similar manner (e.g., **7d > 7j, 9c < 7g; 7m < 7l, 9i > 9h**). This observation suggests, a priori, possible differences in absorption, distribution, metabolism, or drug–receptor interaction for tertiary vs. secondary amines.

Compounds which are approximately equipotent with **7a** and **9a** generally belong to the 3-(4-XC_6H_4) series (Table I). The enhanced antitetrabenazine activity of chloro analogue **7i**, and possibly **9f**, suggests a $+\pi$ (where π is the Hansch hydrophobic substituent parameter) or $+\sigma$ (where σ is the Hammett substituent parameter) dependence or blockade of metabolism for the 3-(4-XC_6H_4) series. However, the lower antitetrabenazine activity of trifluoromethyl analogue **7k** and the approximate equipotency of methoxy and phenolic analogues **7d,g** and **9e** with respect to **7a** and **9a** do not support a $+\pi$ or $+\sigma$ dependence. Halogen blockage (**7h,i, 9d,f**) of metabolism is also not supported since phenols **7g** and **9e** represent potential metabolites and are approximately equipotent with **7a** and **9a**, respectively.

A limited number of other aromatic analogues were evaluated. For analogues belonging to the 3-(3-XC_6H_4) series (**71–n, 9h,i**) lower antitetrabenazine activity was generally observed with possible exception of fluoro analogue **7n**. Introduction of C-5 or C-6 substituents (**7c,o–r, 9b,j–l**) also significantly reduced antitetrabenazine activity with the exception of the 6-fluoro analogue **7q** and the 6-methoxy analogue **9j** which are approximately equipotent with **7a** and **9a**, respectively. Incorporation of two aromatic substituents (**7s–v, 9m–o**) also resulted in reduction of antitetrabenazine activity with the possible exception of difluoro analogues **7u** and **9n**.

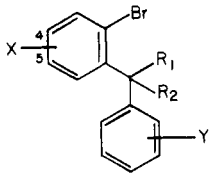
Although the scope of this paper is limited to antitetrabenazine activity, the various structural modifications also resulted in alteration of other pharmacological properties for several members of this series. Work is in progress to more completely elucidate the pharmacological profiles for a number of these compounds.

Experimental Section

The structures of all compounds are supported by their ir (Perkin-Elmer 457) and ^1H NMR (JEOLCO C6OHL) (tetramethylsilane) spectra. Melting points were taken on a Thomas-Hoover capillary melting point apparatus. All melting and boiling points are uncorrected. Elemental analyses were performed by Micro-Tech Labs., Skokie, Ill. Results are within ±0.4% of theoretical values unless otherwise noted in the tables. Organolithium reagents were obtained from Alfa Chemical Co. Reactions with organometallic reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents.

2-Bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide (1a) was prepared in a similar manner as described by Marxer et al.[10] Recrystallization from ethanol gave 85% of colorless crystals: mp

Table VII. 2-Bromobenzophenones, 2-Bromobenzhydrols, and 2-Bromobenzhydryl Methyl Ethers[a]



Compd	R_1	R_2	X	Y	Method	Mp or bp (mm),[b] °C	Yield,[c] %	Recrystn solvent[d]	Formula	Analyses[e]
10a	H	HO	H	H	Q,[f] R	57-59	75, 80	C-L	$C_{13}H_{11}BrO$	
10b	H	HO	H	4'-CH_3O	Q,[g] R	64-65	88	E	$C_{14}H_{13}BrO_2$	C, H, Br
10c	O		5-CH_3O	H	Q[h]	42-44	52	O	$C_{14}H_{11}BrO_2$	C, H, Br
10d	H	HO	5-CH_3O	H	Q	67-68	59	O	$C_{14}H_{13}BrO_2$	C, H, Br
10e	O		4-CH_3O	H	S	83-84	49	E	$C_{14}H_{11}BrO_2$	C, H, Br
10f	H	HO	4-CH_3O	H	S	160 (0.05)	83		$C_{14}H_{13}BrO_2$	C, H, Br
10g	H	HO	H	4'-CH_3	R	70-72	43	E	$C_{14}H_{13}BrO$	C, H
10h	H	HO	H	4'-Cl	R	145 (0.05)	56		$C_{13}H_{10}BrClO$	C, H
10i	H	HO	H	4'-F	R	76-79	46	E	$C_{13}H_{10}BrFO$	C, H
10j	H	HO	H	4'-CF_3	R[i]	155 (0.1)	37		$C_{14}H_{10}BrF_3O$	C, H
10k	H	HO	H	3'-F	R	135 (0.25)	48		$C_{13}H_{10}BrFO$	C, H
10l	H	HO	H	3',4'-$(CH_3O)_2$	Q	60-64	93[j]	L	$C_{15}H_{15}BrO_3$	C, H, Br
10m	O		4,5-$(CH_3O)_2$	H	Q[k]	76-77	31	H	$C_{15}H_{13}BrO_3$	C, H, Br
10n	H	HO	4,5-$(CH_3O)_2$	H	Q	82-85	75	C-E	$C_{15}H_{15}BrO_3$	C, H, Br
10o	H	HO	4-F	4'-F	R[l]	78-80	55	E	$C_{13}H_9BrF_2O$	C, H
10p	O		4-CH_3O	4'-F	S	79-81	25	H	$C_{14}H_{10}BrFO_2$	C, H
10q	H	HO	4-CH_3O	4'-F	S	Oil	100[m]		$C_{14}H_{12}BrFO_2$	C, H
10r	H	HO	4-F	H	R[l]	110 (0.5)	47		$C_{13}H_{10}BrFO$	
11a	H	CH_3O	H	H	T, U	125-128 (0.2)	97-100		$C_{14}H_{13}BrO$	C, H
11b	H	CH_3O	4-F	4'-F	T	105 (0.5)	93		$C_{14}H_{11}BrF_2O$	C, H
11c	H	CH_3O	4-CH_3O	4'-F	T	105 (0.5)	100[n]		$C_{15}H_{14}BrFO_2$	C, H
11d	H	CH_3O	4-F	H	T	105 (0.5)	92		$C_{14}H_{12}BrFO$	
11e	H	CH_3O	H	3'-CH_3	R, T	115 (0.1)	68[o]		$C_{15}H_{15}BrO$	
11f	H	CH_3O	H	3'-CH_3O	R, T	139 (0.2)	45		$C_{15}H_{15}BrO_2$	
11g	H	CH_3O	H	4'-CH_3	T	125 (0.25)	91		$C_{15}H_{15}BrO$	C, H
11h	H	CH_3O	H	4'-Cl	T	135 (0.02)	73		$C_{14}H_{12}BrClO$	H; C[p]
11i	H	CH_3O	H	4'-F	T	110 (0.8)	88		$C_{14}H_{12}BrFO$	C, H

[a-e] See corresponding footnotes to Table I. [f] 2-Bromobenzophenone was prepared according to the ref 16. [g] 2-Bromo-4'-methoxybenzophenone was prepared according to the ref 17. [h] Prepared from 2-bromo-5-methoxybenzoic acid.[18] [i] A mixture of 2-bromo-4'-trifluoromethylbenzophenone and 2-bromo-4'-trifluoromethylbenzhydrol was obtained and reduced with $NaBH_4$. [j] Yield of crude product. [k] Prepared from 6-bromoveratric acid.[19] [l] 2-Bromo-4-fluorobenzaldehyde, mp 65-68 °C, was prepared from 2-bromo-4-fluorotoluene (PCR Inc.) in 62% yield by CrO_3-$(CH_3CO)_2O$ oxidation and acid hydrolysis.[19,20] [m] Yield of crude product. [n] Yield of crude product. [o] Yield calculated from 2-bromo-3'-methylbenzhydrol. [p] C: calcd, 53.96; found, 54.37.

143-144 °C (lit.[10,11] mp 142-144 and 135-136 °C, respectively).

Prepared in a similar manner from 2-bromo-5-methoxybenzoic acid[18] was 2-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)-5-methoxybenzamide (**1b**): mp 131-133 °C (dichloromethane) (46%). Anal. ($C_{12}H_{16}BrNO_3$) C, H, N.

Prepared in a similar manner from 6-bromoveratric acid[19] was 2-bromo-4,5-dimethoxy-*N*-(2-hydroxy-1,1-dimethylethyl)-benzamide (**1c**): mp 106-108 °C (acetone-cyclohexane) (15%). Anal. ($C_{13}H_{18}BrNO_4$) C, H, Br, N.

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline (2a). To a stirred suspension of 54.4 g (0.2 mol) of **1a** and 500 ml of toluene was added, dropwise at 0° during 30 min, 17 ml (0.21 mol) of thionyl chloride. During addition, the solid dissolved and then a precipitate began to form. The mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. Filtration and washing the filter cake with toluene provided 55 g of **2a**·HCl as colorless crystals: mp 129-131 °C (lit.[10,11] 118-120 and 108-110 °C, respectively).

The free base was prepared by stirring the filter cake for 10 min at 0 °C with 300 ml of 10% sodium hydroxide and extracting with ether. The ether solution was dried (K_2CO_3) and concentrated to an oil. Trituration with 30 ml of cold hexane gave 46.4 g (92%) of colorless crystals: mp 38-40 °C. Recrystallization from hexane provided **2a** as colorless crystals: mp 39-40 °C (lit.[10] mp 38-39 °C). Anal. ($C_{11}H_{12}BrNO$) C, H, Br, N.

Prepared in a similar manner from **1b** was 2-(2-bromo-5-methoxyphenyl)-4,4-dimethyl-2-oxazoline (**2b**): mp 57-59 °C (hexane) (64%). Anal. ($C_{12}H_{14}BrNO_2$) C, H, Br, N.

Prepared in a similar manner from **1c** was 2-(2-bromo-4,5-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (**2c**): mp 49-51 °C (cyclohexane) (86%). Anal. ($C_{13}H_{16}BrNO_3$) C, H, Br, N.

4-[2-(4,4-Dimethyl-2-oxazolin-2-yl)phenyl]-1-methyl-4-piperidinol (3a). Method A. The Grignard reagent was prepared by dropwise addition of a solution of 53.3 g (0.21 mol) of **2a** and 500 ml of anhydrous tetrahydrofuran to a refluxing stirred mixture of 6.2 g of Mg shavings and 100 ml of tetrahydrofuran. The mixture was refluxed for 2 h, after which a solution of 25 ml of 1-methyl-4-piperidone and 25 ml of tetrahydrofuran was added dropwise. The solution was refluxed for 2 h and cooled, and 25 ml of saturated ammonium chloride solution was added. The mixture was filtered and the filter cake washed with benzene. The combined organic solution was diluted with benzene, washed with water and saturated sodium chloride solution, dried (K_2CO_3), and concentrated to an oil. Crystallization from ethanol gave 13.0 g (21%) of **3a** as colorless crystals. Properties of **3a**, and of **3b-f** prepared in a similar manner, are included in Table II.

Method B. A cold (-30 °C) stirred solution of 70.0 g (0.27 mol) of **2a** and 500 ml of anhydrous tetrahydrofuran was treated dropwise under nitrogen with 140 ml of 2.1 M *n*-butyllithium in hexane. The dark red solution was stirred at -30 °C for 45 min, and a solution of 30.5 g (0.27 mol) of 1-methyl-4-piperidone and 100 ml of tetrahydrofuran was added dropwise, maintaining the temperature at -30 °C. The mixture was stirred overnight at room

temperature, diluted with 1.5 l. of water, and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and concentrated to a solid. Trituration with hexane gave 47 g (59%) of **3a** as a colorless solid. Properties of **3a**, and of **3b** prepared in a similar manner, are included in Table II.

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (4a) was prepared from **3a** in a similar manner as described by Marxer et al.[10] Recrystallization from benzene gave 78% of **4a** as colorless crystals. Properties of **4a**, and of **4b–f** prepared in a similar manner, are included in Table III.

3-Hydroxy-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (5a). Method C. A solution of 5.7 g (26 mmol) of **4a** and 150 ml of dry tetrahydrofuran was added dropwise during 30 min to 30 ml of cold, stirred 2.0 M phenyllithium in 70:30 benzene–ether. The solution was stirred at 0 °C for 1 h, diluted with water, and extracted with benzene. The benzene solution was dried (K_2CO_3) and concentrated to an oil. Trituration with hexane followed by recrystallization from ethanol provided 7.3 g (96%) of **5a** as colorless crystals. Properties of **5a**, and of **5b,c,f** prepared in a similar manner, are included in Table IV.

3-Hydroxy-3-(4-methoxyphenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (5d). Method D. To a stirred solution of 2.6 g (12 mmol) of **4a** and 35 ml of anhydrous tetrahydrofuran was added dropwise, during 15 min, 18 ml (18 mmol) of 1 N 4-methoxyphenylmagnesium bromide in tetrahydrofuran. The mixture was stirred 2 h, diluted with 300 ml of water, and extracted with benzene. The organic solution was dried (K_2CO_3) and concentrated to a solid. Two recrystallizations from ethanol provided 3.0 g (77%) of **5d** as colorless crystals. Properties of **5d**, and of **5e,g,h** prepared in a similar manner, are included in Table IV.

4-(α-Hydroxy-α-phenyl-2-tolyl)-1-methyl-4-piperidinol (6a). Method E. A solution of 8.5 g (29 mmol) of **5a** in 150 ml of anhydrous tetrahydrofuran was added dropwise during 30 min to a stirred suspension of 2.0 g of $LiAlH_4$ in 150 ml of tetrahydrofuran. The mixture was stirred for 30 min at room temperature and 1 h at 50 °C, cooled, diluted cautiously with water, and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and concentrated to a solid. Recrystallization from benzene provided 8.1 g (94%) of **6a** as colorless crystals. Properties of **6a**, and of **6b–g** prepared in a similar manner, are included in Table V.

Method F. To a cold (−20 °C) stirred solution of 30 g (0.11 mol) of **10a**, 85 ml of anhydrous tetrahydrofuran, and 21 ml of hexane was added dropwise during 75 min 131 ml (0.26 mol) of 2.0 M *n*-butyllithium in hexane. After 3 h, a solution of 14.8 g (0.13 mol) of 1-methyl-4-piperidone in 50 ml of tetrahydrofuran was added dropwise during 10 min at −15 °C. After stirring 2 h at −15 °C and overnight at room temperature, the mixture was quenched at 0 °C with 170 ml of saturated ammonium chloride solution. The phases were separated, and the aqueous phase was extracted with chloroform, combining the extracts with the organic phase. The organic solution was dried (Na_2SO_4) and concentrated to a solid. Recrystallization from benzene gave 10.2 g (30%) of **6a** as colorless crystals. Properties of **6a**, and of **6b–d,h–n** prepared in a similar manner, are included in Table V.

1′-Methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (7a). Method G. A solution of 8.1 g (27 mmol) of **6a**, 50 ml of glacial acetic acid, and 10 ml of concentrated hydrochloric acid was heated under reflux for 10 min, cooled to 0 °C, diluted with water, made basic with 50% sodium hydroxide solution, and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and concentrated to a solid. Recrystallization from hexane gave 7.4 g (98%) of **7a** as colorless crystals. Properties of **7a**, and **7b,d–f,h,k,n,u** prepared in a similar manner, are included in Table I.

Method H. A solution of 89.1 g (0.3 mol) of **6a** and 390 ml of 88% formic acid was heated under reflux for 2 h. The solution was diluted with 800 ml of water, made alkaline by addition of 50% sodium hydroxide with cooling, and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and concentrated to a solid. Recrystallization from hexane gave 72.1 g (86%) of **7a** as colorless crystals. Properties of **7a**, and **7c,o,s,t** prepared in a similar manner, are included in Table I.

Method I. A stirred solution of 27.7 g (0.1 mol) of **11a** in 38 ml of anhydrous tetrahydrofuran and 14 ml of hexane was treated at −50 °C under nitrogen with 53 ml (0.11 mol) of 2.1 M *n*-butyllithium in hexane. The solution was stirred at −60 °C for 2 h and a solution of 10.7 g (0.1 mol) of 1-methyl-4-piperidone was added over 5 min. The resultant suspension was stirred at −60 °C for 2 h and at room temperature overnight. Ice (50 g) was added in portions and the organic phase was removed. The aqueous phase was extracted with chloroform, combining the extracts with the organic phase and drying (Na_2SO_4). The organic solution was evaporated to an oil which was diluted to 200 ml with benzene. A 50-ml aliquot was extracted twice with 15 ml of 3 N HCl. A suspension of crystals was obtained in each aqueous phase, which was combined, heated under reflux for 10 min, and evaporated to dryness. The residue was heated under reflux for 10 min with 60 ml of glacial acetic acid and 15 ml of concentrated hydrochloric acid. The cooled solution was diluted with 500 g of ice and made alkaline with 40% sodium hydroxide with cooling. The precipitate was collected and recrystallized from hexane to give 3.6 g (51% based on aliquot proportions) of **7a** as colorless crystals. Properties of **7a**, and **7b,e,i,l,m,q,w,x** prepared in a similar manner, are included in Table I.

1′-Methyl-3-(4-tolyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] (7j). Method J. To a suspension of 0.4 g (10.6 mmol) of $LiAlH_4$ in 75 ml of anhydrous tetrahydrofuran was added 3.5 g (10.0 mmol) of **8h** under nitrogen. The mixture was heated under reflux for 1 h, cooled to 0 °C, and decomposed by dropwise addition of water. The mixture was diluted with 1.2 l. of water and extracted with benzene. The organic phase was dried (Na_2SO_4) and evaporated to a solid. Recrystallization from cyclohexane afforded 2.2 g (75%) of **7j** as colorless crystals. Properties of **7j**, and of **7a,v** prepared in a similar manner, are included in Table I.

5-Hydroxy-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (7r). Method K. A solution of 4.0 g (13 mmol) of **7c** and 64 ml of 48% HBr was held in a 160 °C bath for 15 min. The solution was decanted into 64 ml of ice water and made alkaline with 60 ml of concentrated ammonium hydroxide. The precipitate was collected by filtration, washed with water, suspended in 150 ml of chloroform, and washed with three 70-ml portions of 7% sodium bicarbonate. The chloroform solution was dried (Na_2SO_4) and concentrated to a foam which was dissolved in excess ether. Concentration afforded 2.2 g (58%) of **7r** as a cream-colored solid. Properties of **7r**, and of **7p** and **9k,l** prepared in a similar manner, are included in Table I.

3-(4-Hydroxyphenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (7g). Method L. Sodium thioethoxide was prepared by addition of 4.8 g (78 mmol) of ethanethiol to a stirred suspension of 3.0 g of NaH (57% dispersion in mineral oil) and 100 ml of anhydrous dimethylformamide. A solution of **7d** (3.0 g, 9.6 mmol) and 20 ml of anhydrous dimethylformamide was added and the mixture was heated under reflux for 3 h. The cooled mixture was diluted with 1 l. of water, adjusted to pH 1 with concentrated HCl, and extracted with methylene chloride. The aqueous phase was made basic with 50% NaOH, extracted with methylene chloride, and then adjusted to pH 7 with dilute HCl. The precipitate was collected, washed with water and ether, and dried. Recrystallization from dimethyl sulfoxide gave 1.8 g (63%) of **7g** as colorless crystals. Properties of **7g**, and of **9e** prepared in a similar manner, are included in Table I.

1′-Ethoxycarbonyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (8a). Method M. To a solution of 106.7 g (0.3 mol) of **7a** and 600 ml of benzene was added 35.8 g (0.33 mol) of ethyl chloroformate. The solution was heated under reflux for 18 h, cooled to room temperature, and stirred for 30 min with 10% sodium hydroxide. The mixture was diluted with water and extracted with ether. The ether layer was dried (Na_2SO_4) and concentrated to an oil. Trituration with hexane followed by recrystallization from ethanol provided 93.1 g (92%) of **8a** as colorless crystals. Properties of **8a**, and of **8d,f,h,k,m,n** prepared in a similar manner, are included in Table VI.

1′-Phenoxycarbonyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (8b). Method N. A solution of 0.56 g (2.0 mmol) of **7a** and 5 ml of anhydrous dichloromethane was treated with a solution of 0.35 g (2.2 mmol) of phenyl chloroformate and 5 ml of dichloromethane. The solution was stirred 24 h at room

temperature and concentrated to a solid. Trituration with ether and recrystallization from benzene–hexane afforded 0.25 g (33%) of **8b** as colorless crystals. Properties of **8b**, and **8c,e,g,i,j,l,o,p** prepared in a similar manner, are included in Table VI.

3-Phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (9a). Method O. A solution of 84.4 g (0.25 mol) of **8a**, 900 ml of ethanol, and 600 ml of 20% aqueous sodium hydroxide was heated under reflux for 18 h under nitrogen. The ethanol was distilled under reduced pressure, and the residue was diluted with water and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and concentrated to an oil. Crystallization from cyclohexane provided 64.6 g (97%) of **9a** as colorless crystals. Properties of **9a**, and of **9b–d,f–j,m–o** prepared in a similar manner, are included in Table I.

Method P. A mixture of 100 g (0.28 mol) of **7b**, 500 ml of toluene, 250 ml of 2-propanol, and 10.0 g of 10% palladium on charcoal was hydrogenated for 5 h at 75 °C and 48 psi and then cooled and filtered. The filtrate was concentrated to a colorless solid. Recrystallization from cyclohexane provided 61.4 g (83%) of **9a** as colorless crystals.

2-Bromobenzhydrol (10a). Method Q. To a stirred suspension of 7.6 g (0.2 mol) of $NaBH_4$ and 200 ml of absolute ethanol was added over 1.5 h with cooling a solution of 52.0 g (0.2 mol) of 2-bromobenzophenone[16] and 150 ml of absolute ethanol. The mixture was maintained at 75 °C for 3 h, cooled, diluted with 1 l. of water, and adjusted to pH 6 with 1 N HCl. An oil separated and was extracted with benzene. The dried ($MgSO_4$) organic phase was evaporated to give 49.5 g of a colorless oil which crystallized. Recrystallization from 70:30 benzene–hexane gave 39.6 g (75%) of **10a** as colorless crystals. Properties of **10a**, and of **10b–d,l–n** prepared in a similar manner, are included in Table VII.

Method R. A solution of 75.0 g (0.41 mol) of 2-bromobenzaldehyde in 100 ml of anhydrous tetrahydrofuran was added over 1.5 h to 0.45 mol of freshly prepared phenylmagnesium bromide and 200 ml of tetrahydrofuran with stirring and cooling. The mixture was heated under reflux for 15 min, cooled, and quenched with 2.0 l. of saturated ammonium chloride solution, and the aqueous supernatant was decanted. The oil was dissolved in chloroform, and the solution was washed with water, dried (Na_2SO_4), and concentrated to an oil which crystallized on standing. Recrystallization from benzene–heptane gave 86 g (80%) of **10a** as colorless crystals. Properties of **10a**, and of **10b,g–k,o,r** prepared in a similar manner, are included in Table VII.

2-Bromo-4-methoxybenzhydrol (10f). Method S. To a cold stirred solution of 93.5 g (0.5 mol) of *m*-bromoanisole, 112 g (0.8 mol) of benzoyl chloride, and 200 ml of carbon disulfide was added during 30 min 106 g (0.8 mol) of aluminum chloride. The solution was stirred at 0 °C for 1 h and at room temperature for 1 h and then heated under reflux for 1 h. The mixture was poured onto a mixture of 1000 ml of ice and 250 ml of concentrated hydrochloric acid, followed by benzene extraction. The benzene solution was washed with 10% sodium hydroxide solution and water, dried (K_2CO_3), and concentrated to an oil which solidified on trituration with cyclohexane. Recrystallization from cyclohexane gave 71.5 g (49%) of **10e** as colorless crystals (Table VII). A stirred solution of 42.4 g (0.14 mol) of **10e**, 4.0 g of sodium borohydride, and 300 ml of ethanol was heated under reflux for 1 h, followed by stirring overnight at room temperature. Acetone (10 ml) was added and the solution was stirred 24 h at room temperature; then 100 ml of water and 10 ml of glacial acetic acid were added. The mixture was extracted with chloroform; the extracts were dried (K_2CO_3) and concentrated to an oil. Distillation provided 35.4 g (83%) of **10f** as a colorless oil. Properties of **10f**, and of **10p,q** prepared in a similar manner, are included in Table VII.

2-Bromobenzhydryl Methyl Ether (11a). Method T. A solution of 730 g (2.8 mol) of **10a** and 2.5 l. of methanol was slowly heated to reflux during 2 h, during which time a gentle stream of HCl was bubbled through the solution. The solution was heated under reflux for 24 h and concentrated to an oil. Distillation gave 747 g (97%) of **11a** as a pale yellow liquid. Properties of **11a**, and of **11b–i** prepared in a similar manner, are included in Table VII.

Method U. To a solution of 15.9 g (0.28 mol) of solid sodium methoxide in 35.7 g of methanol was added 66 g (0.25 mol) of **10a** in 300 ml of toluene. The solution was heated under reflux, removing the methanol with a Dean-Stark apparatus. Dimethyl sulfate (30 g, 0.25 mol) was added dropwise at reflux, followed by refluxing for 4 h. The mixture was cooled, 250 ml of H_2O added, and the organic phase removed. The organic solution was washed with water and concentrated to an oil. Vacuum distillation of the crude oil gave 70 g (100%) of **11a** as a colorless oil. Properties of **11a** are included in Table VII.

1'-Acetyl-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (12a). To a cold stirred solution of 6.0 g (23 mmol) of **9a**, 2.4 g of triethylamine, and 50 ml of chloroform was added dropwise a solution of 2.0 g of acetyl chloride and 50 ml of chloroform. The mixture was stirred for 2 h at room temperature, washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystallized from chloroform to provide 4.5 g (65%) of **12a** as colorless crystals. Properties of **12a**, and of **12b–h** prepared in a similar manner, are included in Table VI.

1'-Ethyl-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (13a). Method V. To a stirred suspension of 0.53 g of lithium aluminum hydride in 50 ml of tetrahydrofuran was added dropwise a solution of 2.20 g (7 mmol) of **12a** in 50 ml of tetrahydrofuran. The mixture was heated under reflux for 2 h, cooled, quenched cautiously with water, and extracted with ether. The ether solution was dried (Na_2SO_4) and concentrated to a solid. Recrystallization from chloroform gave 1.2 g (58%) of **13a** as colorless crystals. Properties of **13a**, and of **13b–g** prepared in a similar manner, are included in Table I.

1'-Isopropyl-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (13h). Method W. A mixture of 2.65 g (10 mmol) of **9a**, 3.0 g of anhydrous potassium carbonate, 1.87 g (11 mmol) of isopropyl iodide, and 40 ml of anhydrous dimethylformamide was heated at 75 °C with stirring for 21 h. The mixture was diluted with benzene and washed with water, and the organic phase was dried (Na_2SO_4) and concentrated. Crystallization of the residue from ethanol gave 1.62 g (53%) of **13h** as colorless crystals. Properties of **13h**, and of **13i,j** prepared in a similar manner from allyl bromide and 1-bromo-3-methyl-2-butene, respectively, are included in Table I.

1',3-Dimethyl-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (14a). To a cold (−50 °C) stirred solution of 1.4 g (5 mmol) of **7a** and 20 ml of anhydrous tetrahydrofuran was added dropwise 4 ml of 2.0 M *n*-butyllithium in hexane under nitrogen. After 30 min, a solution of 0.9 g of dimethyl sulfate in 10 ml of tetrahydrofuran was slowly added. The mixture was stirred at −10 °C for 1 h and at room temperature for 15 h, diluted with ice and water, and extracted with ether. The ether solution was dried (K_2CO_3) and concentrated to an oil. The oil was converted to a hydrobromide salt which was recrystallized from ethyl acetate to provide 0.79 g (42%) of **14a** as colorless crystals. Properties of **14a**, and of **14b–d** prepared in a similar manner from **7a** and the appropriate alkyl bromide, are included in Table I.

Tetrabenazine Assay. The test compound was administered 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 reference standards imipramine and desipramine are included in Table I.

Acknowledgment. The authors wish to express their appreciation to Marc N. Agnew, Lee J. O'Donnel, Romana H. Fedasiuk, Michael Ruberto, Yorum R. Shatz, and Irene W. Tsina for spectral data and to Susan A. Dowling, James G. Kiley, Jr., Barbara Kirby, Kathleen H. Morrison, and Susan C. Rediske for performing pharmacological assays. We also gratefully acknowledge June D. Baird and Ann Van Dine for library research, Daniel E. Aultz and Eugene C. Dombrowski for synthetic assistance, and Kathleen M. Huppert for assistance in preparation of the manuscript.

References and Notes

(1) Presented in part at the First Chemical Congress of the North American Continent, Mexico City, Mexico, Nov 30–Dec 5, 1975, BMPC section.

(2) J. H. Biel, "Principles of Psychopharmacology", Clark and Giudice, Ed., Academic Press, New York, N.Y., 1970, p 269.
(3) C. Kaiser and C. L. Zirkle, "Medicinal Chemistry", A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, Chapter 55.
(4) B. Blackwell, J. O. Lipkin, J. H. Meyer, R. Kuzma, and W. V. Boulter, *Psychopharmacologia*, **25**, 205 (1972).
(5) J. C. Ballin, *J. Am. Med. Assoc.*, **231**, 1369 (1975).
(6) J. Vohra and G. B. Burrows, *Drugs*, **8**, 432 (1974).
(7) B. Bopp and J. H. Biel, *Life Sci.*, **14**, 415 (1974).
(8) While this work was in progress both a patent[9] and a paper[10] appeared, covering in part the scope of our investigation.
(9) W. J. Houlihan and J. Nadelson, U.S. Patent 3 745 165 (1974).
(10) A. Marxer, H. R. Rodriguez, J. M. McKenna, and H. M. Tsai, *J. Org. Chem.*, **40**, 1427 (1975).
(11) A. I. Meyers and D. L. Temple, Jr., *J. Am. Chem. Soc.*, **92**, 6646 (1970).
(12) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).
(13) W. E. Parham and D. C. Egberg, *J. Org. Chem.*, **37**, 1545 (1972).
(14) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970).
(15) The general pharmacology of **7a** and **9a** will constitute the subject of a future paper.
(16) E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).
(17) H. A. Fahim, F. G. Baddar, and M. A. Galaby, *J. Chem. Soc.*, 317 (1955).
(18) C. A. Bunton, G. W. Kenner, M. J. T. Robinson, and B. R. Webster, *Tetrahedron*, **19**, 1001 (1963).
(19) L. C. Raiford and R. P. Perry, *J. Org. Chem.*, **7**, 354 (1942).
(20) S. V. Lieberman and R. Connor, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 441.
(21) T. Nishimura in ref 20, Collect. Vol. IV, 1963, p 713.

Lipid Solubility and Affinity for N-Demethylation of Dansylamides in Isolated Rat Hepatocytes

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Isolated hepatocytes carry out the N-demethylation of dansylamide at near linear rates for up to 8 h. This reaction was measured by following the release of tritium into water on hydroxylation of ^{3}H-labeled methyl groups. The competitive inhibition of dansylamide by dansylated amino acids was studied in this system as an example of competing drug metabolism in a series of compounds which are identical around the site of metabolism and different remote to that site. A correlation between lipid solubility and the K_i was not found over the entire range of substrate analogues. While most of the high K_m inhibitors seem to correlate with lipid solubility, the highly lipophilic derivatives of the leucines and phenylalanine are in a separate group. Lipid solubilities of the dansylated amino acids were little affected by changes in pH and thus behaved as "essential nonelectrolytes".

Liver parenchymal cells have been recognized as the main locus of drug metabolism via microsomal hydroxylation pathways. Teleologically this process is necessary to excrete foreign materials in the kidney. Excretion is facilitated after introduction or uncovering of polar groups in an otherwise lipid-soluble xenobiotic, which would be reabsorbed in the latter part of the nephron. The degree of lipid solubility, as a rule, determines to a large extent the susceptibility of a xenobiotic to P-450-mediated reactions[1] in a system which otherwise shows very little substrate specificity. Binding of substrates precedes the metabolic transformation. Jefcoate et al.[2] have shown that the binding energy for the interaction of *n*-alkylamines with P-450 is linearly related with alkyl chain length, providing evidence for a hydrophobic cavity in the heme region of P-450 sufficient to accommodate large, hydrophobic substrates.

In this communication we are trying to investigate the utility of isolated hepatocytes for a study of the potential correlation between lipid solubility and the K_i of competitive substrates (inhibitors) of the metabolism of a radioactive parent molecule. Similar studies have been done before; however, the variations on the molecule to be metabolized were on the actual site of hydroxylation. An example of this approach was reported in 1963 by McMahon et al.[3] These authors reported that oxidative O-dealkylation of a series of alkyl and arylalkyl *p*-nitrophenyl esters in rat liver microsomes was dependent on the size of the alkyl groups. For saturated alkyl groups, the K_m and V_{max} values decreased with increasing length of the groups, which resulted in an overall decrease of the reaction rate for a given concentration. In vivo dealkylation rates correlated well with in vitro results. Creaven et al.[4] and Davies and Creaven,[5] studying a series of substituted hydroxybiphenyl derivatives, showed progressively decreasing rates of microsomal O-dealkylation as the alkyl substituent was increased from methyl through *n*-butyl but did not determine K_m and V_{max}.

We were particularly interested in whether lipid solubility would be the only variable in determining the effectiveness of structurally similar inhibitors in cases where the variation in the molecule was far distant from the site of hydroxylation and consisted of more than a chain-length alteration. For these experiments a series of dansylated amino acids was employed. The inhibition of [*N-methyl*-^{3}H]dansylamide N-demethylation by different dansylamino acids was measured and compared with the relative lipid solubility of the various derivatized amino acids. From the measured effectiveness of dansylamide N-demethylation, we have calculated the K_i values. Theoretically, if classical Michaelis–Menten enzyme kinetics are obeyed, one would predict the K_m of an inhibitor's own metabolism to be identical with its K_i in the competitively inhibited reaction. To study the relevance of lipid solubility as a singular determinant of drug metabolism in a series of similar compounds under conditions close to the in vivo situation, but in the absence of biological variation, a minimal requirement is an intact cellular system.

Despite the advantages of liver cells as compared to microsomes, there have been relatively few attempts to utilize this system to study drug metabolism. Berry[6] has successfully used isolated hepatocytes to study the action of pyruvate on ethanol metabolism. Holtzman et al.[7] have