solution was refluxed for 3 hr. After cooling, a few drops of a saturated solution of sodium sulfate were added, and the white solid was removed by filtration. The solid was washed with acetone, then extracted with chloroform in a Soxhlet for 48 hr. From the filtrate and the chloroform extract a total of 51 mg of **7a** was obtained: mp 176–178°; ν_{max} (KBr) 3400, 1050 cm^{-1}. The tetrol **7a** was acetylated (pyridine–acetic anhydride, 16 hr, room temperature) and the triacetate **7b** was recovered in the conventional manner. The product was crystallized from methanol: mp 143–144°; ν_{max} (KBr) 3510 (sharp), 1730, 1725, and 1248 cm^{-1}; NMR 126.5 (acetate), 121 (two acetates), 50 (19-Me), and 46 Hz (18-Me).

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.45; H, 8.82.

Acknowledgment. We thank Professor Jerrold Meinwold, Department of Chemistry, Cornell University, Ithaca, N.Y., for the high-resolution mass spectra. We are indebted to Dr. T. A. Wittstruck of this laboratory for the computer LAOCOON II NMR calculations.

Registry No.—**1a,** 521-18-6; **2,** 54642-80-7; **3a,** 54632-41-6; **3b,** 54632-42-7; **4a,** 54642-81-8; **4b,** 54632-43-8; **4c,** 54632-44-9; **5,** 54632-45-0; **6a,** 54632-46-1; **6b,** 54632-47-2; **6c,** 54632-48-3; **6d,** 54632-49-4; **7a,** 54632-50-7; **7b,** 54632-51-8; **8b,** 54632-52-9; **8c,** 54632-53-0; **9b,** 54632-54-1; **10a,** 1165-38-4; **10b,** 1169-77-3; **11,** 54632-55-2; **12b,** 54632-56-3; **13,** 54632-57-4; **14b,** 54632-58-5; **15b,** 54632-59-6; **16,** 2010-48-2; **17,** 2429-68-7; **18a,** 54632-60-9; **18b,** 54632-61-0; 1,4-dichlorobut-2-yne, 831-10-3; 2-butyne-1,4-diol, 110-65-6; pregnenolone, 145-13-1; 3β,17β-dihydroxy-5α-androstan-7-one, 28375-34-0; 3β-hydroxyandrost-5-en-17-one, 53-43-0.

References and Notes

(1) This investigation was supported by National Institutes of Health Grants CA-07137, CA-13369, and CA-K3-16614.
(2) (a) Postdoctoral Fellow, 1964–1966. Assistant Drugs Controller, South Zone, Custom House, Madras-1, India. (b) Postdoctoral Fellow, 1970–1971.
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Spiro Piperidines. I. Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidines] and Spiro[isobenzofuran-1(3*H*),3′-piperidines]

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General synthetic methods for the preparation of 3,3-disubstituted aminoalkyl phthalides are described. Their specific use in the synthesis of spiro[isobenzofuran-1(3*H*),4′-piperidines] and spiro[isobenzofuran-1(3*H*),3′-piperidines] is elaborated. The chemistry of these heterocycles is also discussed.

Although the chemistry of phthalides in general is quite extensive,[1] careful examination of the literature reveals that there are few papers concerning the synthesis of phthalides containing an aminoalkyl side chain in the 3 position.[2a-g] The most general method reported consists in condensation of phthalaldehydic acids with nitroalkanes followed by reduction of the 3-nitroalkyl phthalides produced either electrolytically,[2a] catalytically,[2b] or by dissolving metals.[2c] A lesser used method is the hydrolysis of 3-alkylidene phthalides, formation of the corresponding isonitroso ketones, and catalytic reduction to the 3-aminoalkyl phthalides.[2d] Other approaches are of limited synthetic utility.[2e,f] A serious drawback of most of these methods is that their nature precludes formation of 3,3-disubstituted aminoalkyl phthalides and therefore this class of compounds is essentially unknown.[2g,h]

The recent work of Meyers[3] and Hauser[4] utilizing aryl organometallics containing a masked carboxylic acid in the ortho position suggested the possibility of obtaining a simple, general synthesis of just such phthalides. Accordingly, we report herein this method and its application to the synthesis of the hitherto unknown[2h] spiran systems spiro[isobenzofuran-1(3*H*),4′-piperidines] and spiro[isobenzofuran-1(3*H*),3′-piperidines].[5]

Spiro[isobenzofuran-1(3*H*),4′-piperidines]. The first synthetic approach (method A) made use of the method of Meyers.[3] Reaction of the magnesium derivative of 2-(2-bromophenyl)-4,4-dimethyloxazoline (1) with *N*-alkylpiperidones **2a,b** gave the expected piperidinols **3a,b,** albeit in low yield (~35%). Subsequent acid hydrolysis led to the desired phthalides **4a,b.** Investigation of the side products of the Grignard reactions revealed starting piperidones **2a,b**

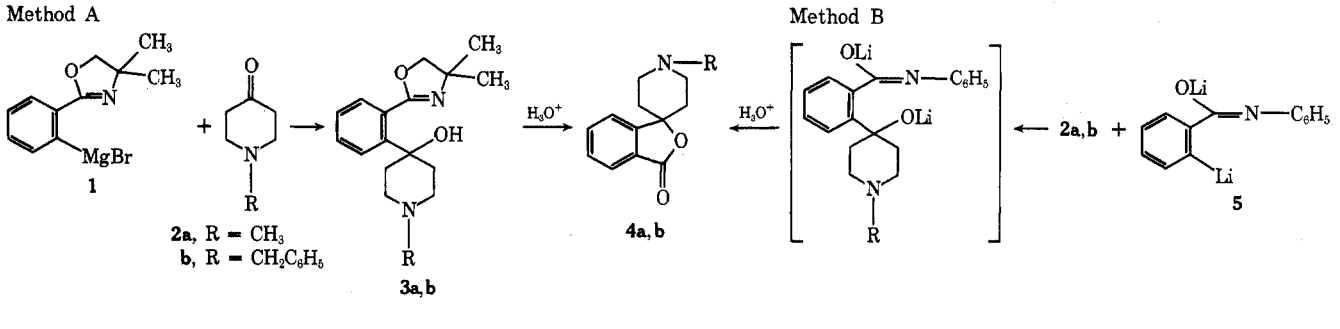
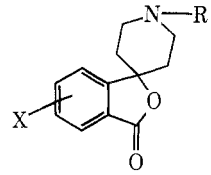


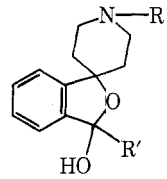
Table I
Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones[a-c]



Registry no.	X	R	Yield, %	Method	Mp or bp, °C[d,e]	Solvent of crystn
54595-70-9	H	CH_3	31.7	A	147–148	Ether
			49.6	B	149–150	Ether
37663-42-6	H	$CH_2C_6H_5$	26.6	A	103–104[f]	Cyclohexane
			41.5	B	102–103	Cyclohexane
54595-71-0	6-Cl	CH_3	25.2	B	209–213	Ether
54595-72-1	6-Cl	$CH_2C_6H_5$	17.3	B	196–202 (0.01)	
54595-73-2	6-F	CH_3	45.0	B	176–179	THF
54595-74-3	4-OCH_3	CH_3	23.7	B	177–180	Benzene–cyclohexane
54595-75-4	6-OCH_3	CH_3	38.9	B	161–166 (0.05)	
54595-76-5	7-OCH_3	CH_3	19.0	B	141–144 (0.10)	

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] All compounds exhibited absorption in the ir typical of phthalides[14] (1755–1758 cm^{-1}). [c] All compounds exhibited NMR spectra consistent with assigned structures. [d] All melting points and boiling points are uncorrected. Boiling points are expressed in °C (mmHg). [e] Hydrochlorides of all compounds were prepared in the usual manner. The melting point (solvent of crystallization) listed in the order of the table are as follows: 270–272° (EtOAc–MeOH), 280–283° (CH_3CN–MeOH), 265–268° (H_2O), 284–287° (H_2O), 254–255° (EtOAc–MeOH), 238–241° (EtOAc–EtOH), 236–238° (EtOAc–EtOH), 248–250° (EtOAc–EtOH). [f] Lit.[2h] mp 105–106°.

Table II
3-Alkyl-(aryl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols[a,b]



Registry no.	Compd no.	R	R′	Yield, %[c]	Mp, °C[d]	Solvent of crystn
54595-77-6	**11e**	CH_3	C_6H_5	92.0	170–172	EtOAc
54595-78-7	f	CH_3	*p*-FC_6H_4	64.7	168–170	EtOAc
54595-79-8	g	CH_3	*p*-$CH_3OC_6H_4$	80.5	158–161	EtOAc
54595-80-1	h	CH_3	2-Thienyl	41.0	194–196	EtOAc
54595-81-2	i	CH_3	CH_3	69.5	155–157	Ether
54595-82-3	j	CH_3	C_2H_5	87.5	158–161	Ether
54595-83-4	k	CH_3	*i*-C_3H_7	61.0	163–166	Ether
54595-84-5	l	CH_3	c-C_6H_{11}	77.0	135–137	Petroleum ether
54595-85-6	m	CH_3	$CH_2C_6H_5$	68.2	127–129	EtOAc
54595-86-7	n	CH_3	$(C_6H_5)_2CH$	66.1	168–170	Ether
54595-87-8	o	$CH_2C_6H_5$	$CH_2C_6H_5$	91.0	149–151	Cyclohexane
54595-88-9	p	CH_3	$CH_2CH_2C_6H_5$	75.3	93–96	Ether–petroleum ether

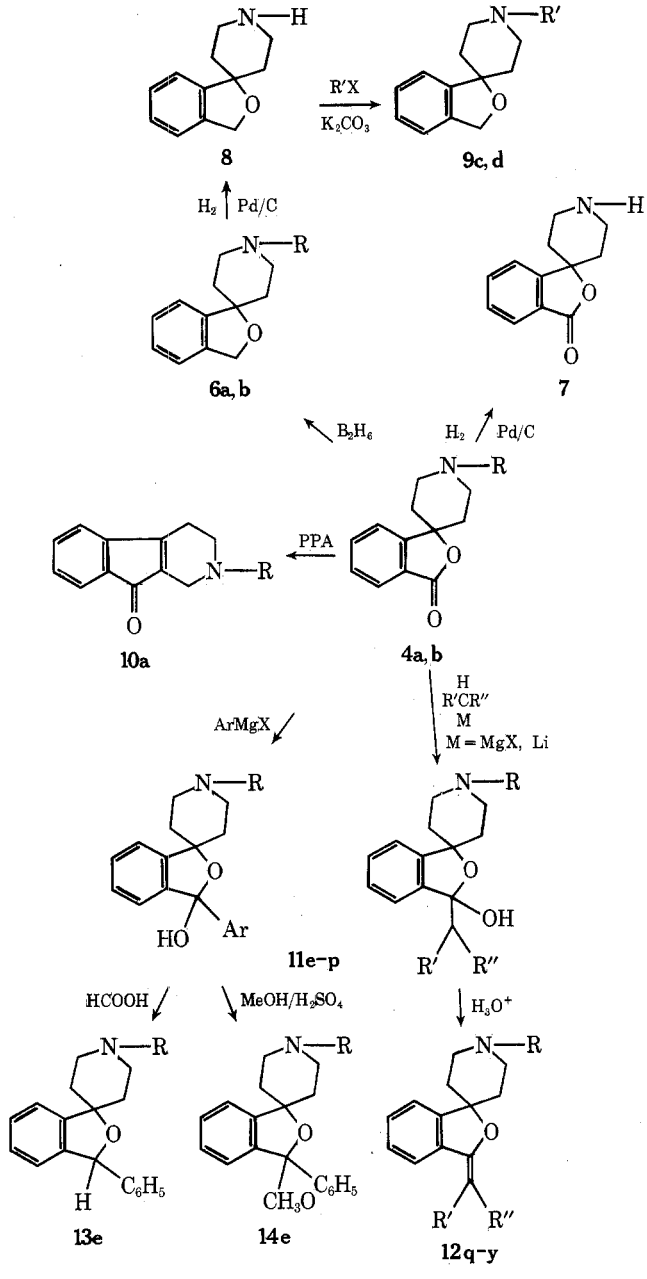
[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] All compounds exhibited NMR spectra consistent with assigned structures. [c] No attempt was made to optimize yields. [d] All melting points are uncorrected.

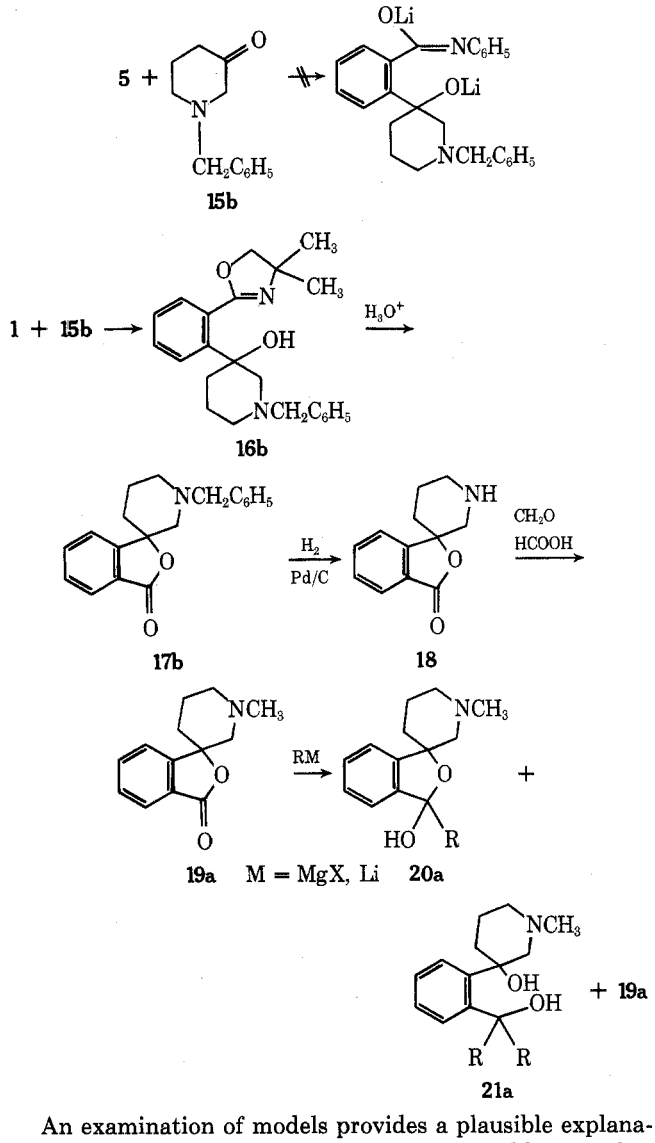
and 4,4-dimethyl-2-phenyloxazoline exclusively under a variety of reaction conditions. These results strongly suggested that the main competing reaction was enolization of **2a,b** by the Grignard reagents.[6] We therefore explored the known tendency of lithium aryls to be more reactive toward carbonyl additions with less attendant enolization of substrate.[7] Circumstances were particularly favorable in this instance, since Hauser's[4] ortho-lithiated benzamide species could be utilized.

It was determined that reaction of 2-lithio-*N*-phenylbenzamide (**5**),[8] prepared by a modification of Hauser's procedure[4] (see Experimental Section) with **2a,b,** led directly on acidic work-up[9] to phthalides **4a,b** in moderate yields (50 and 42%, respectively). This approach (method B) proved not only to be shorter and higher yielding (see Table I) but also more versatile in that a wider variety of benzo-substituted compounds (Table I) could be prepared, since the correspondingly functionalized benzoic acids are generally more accessible than the substituted 2-bromobenzoic acids. Of course the functional groups chosen were, perforce, limited to those stable to *n*-butyllithium, but in no case was there evidence of lithiation other than ortho to the amide moiety.[10a,b]

A study of some of the reactions of this ring system was next undertaken. Reduction of **4a,b** to the corresponding phthalans **6a,b** proceeded smoothly with diborane. Reductive cleavage of the benzyl group either in **4** or **6b** gave the parent NH derivatives **7** and **8.** Reaction of **8** with a variety of alkylating agents gave new *N*-alkyl derivatives **9c,d** in moderate yield. Treatment of **4a** with PPA yielded the novel indenone **10a.**

It has been reported that reaction of 3,3-dialkyl-





phthalides with Grignard reagents proceeds in a discrete manner to obtain monoadducts.[11] This was also found to be the case with this ring system. Treatment of **4a,b** with a wide variety of aryl and alkyl Grignards as well as lithium aryls and alkyls led to the corresponding phthalanols **11e–p** (Table II). Where possible structurally, these derivatives dehydrated readily to give the vinyl ethers **12q–y** (Table III).[12] 3-Aryl phthalanols such as **11e** could either be reduced with refluxing formic acid to phthalan **13e** or solvolyzed to phthalanol ether **14e** with cold MeOH–H_2SO_4.

Spiro[isobenzofuran-1(3*H*),3′-piperidines]. In contrast to **2b,** the isomeric 1-benzyl-3-piperidone (**15b**) gave evidence (ir absorption) of formation of practically no phthalide when treated with **5.** Fortuitously, application of the Meyers[3] approach, i.e., treatment of **1** with **15b,** yielded the corresponding piperidinol **16b** (47%). Acid hydrolysis gave the desired phthalide **17b.** Hydrogenolysis of **17b** gave the NH derivative **18,** which in turn yielded the NCH_3 derivative **19a** when treated with formaldehyde and formic acid. Contrary to the results obtained with **4a,** reaction of **19a** with a variety of organometallic reagents led to complex mixtures consisting of monoadducts **20a,** diadducts **21a,** and starting material.[13]

An examination of models provides a plausible explanation of this difference in behavior, i.e., monoadduct **20a** has the possibility of chelate formation via a favorable 1,3-diaxial interaction.[15] In this form the adduct is in the ketonic mode, which can then further react to yield diol **21a.** However, monoadducts from **4a** have no such option since

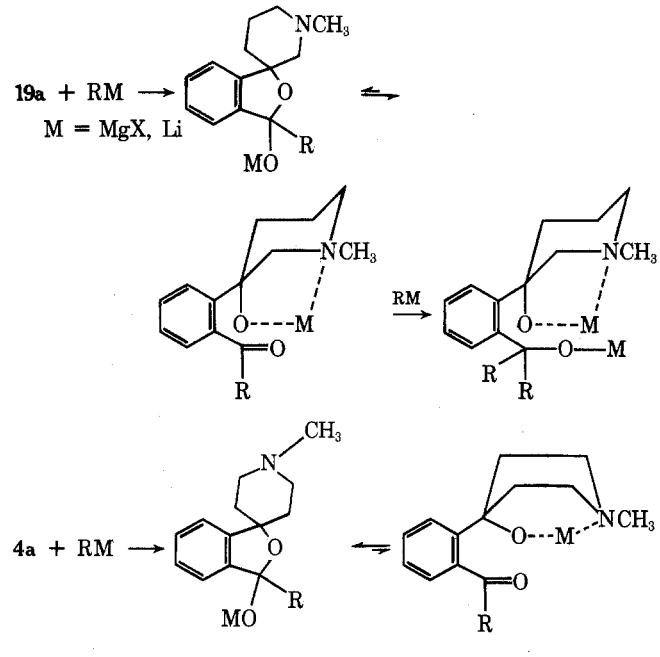
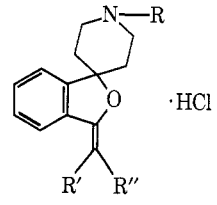


Table III
3-Alkylidenespiro[isobenzofuran-1(3*H*),4′-piperidines][a-c]



Registry no.	Compd no.	R	R′	R″	Yield, %[d]	Mp, °C[e]	Solvent of crystn
54595-89-0	12q	CH_3	H	CH_3	62.1	287–289	CH_3CN
54595-90-3	r	CH_3	CH_3	CH_3	57.0	293–295	CH_3CN–MeOH
54595-91-4	s	CH_3		c-C_5H_{10}	32.3	260–262	EtOAc
54595-92-5	t	CH_3	H	C_6H_5	68.0	289–291	CH_3CN–MeOH
54595-93-6	u	CH_3	C_6H_5	C_6H_5	98.5	>315	EtOH
54595-94-7	v	CH_3	H	$CH_2C_6H_5$	58.5	231–233	EtOAc
54595-95-8	w	CH_3	H	3-Methyl-5-isoxazolyl	38.3	>315	CH_3CN–MeOH
54595-96-9	x	CH_3	H	4-Pyridyl	44.7	155–157[f]	Cyclohexane
54595-97-0	y	$CH_2C_6H_5$	H	C_6H_5	93.5	284–286	CH_3CN–MeOH

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all the compounds listed in the table. [b] All compounds exhibited NMR spectra consistent with assigned structures. [c] Compounds in which R″ is either aryl or heterocyclyl exhibited uv spectra consistent with the trans stilbene type structure. [d] No attempt was made to optimize yields. [e] All melting points are uncorrected. [f] This melting point is for the free base.

a chelate can form only through the unfavorable boat 1,4 interaction.[16] These monoadducts are therefore locked into the phthalanol mode and as such are stable to further reaction under these conditions.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 521 grating infrared spectrophotometer. Spectra were obtained as Nujol mulls unless otherwise specified. Absorption bands are reported in reciprocal centimeters. Ultraviolet spectra were obtained on a Carey 14 spectrophotometer in MeOH solution. NMR spectra were recorded on a Varian A-60 spectrometer. Spectra were obtained in deuteriochloroform solution unless otherwise specified with tetramethylsilane as the internal standard. The chemical shifts are reported in parts per million (δ). Melting points were determined on a Thomas-Hoover melting point apparatus. All melting points and boiling points are uncorrected.

All solvents were dried over molecular sieves. Reactions with organometallic reagents were maintained under a N_2 atmosphere. Solutions of reaction work-ups were dried either over K_2CO_3 (basic products) or Na_2SO_4 (neutral products).

Grignard reagents and organolithium reagents were obtained from Alfa Chemical Co. except for *n*-butyllithium, which was supplied by Foote Mineral Co. Diborane solutions and the Mg chips utilized for preparation of Grignards were also obtained from Alfa Chemical Co. All other reagents were supplied by Aldrich Chemical Co.

2-Bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide. To a cooled solution of 2-amino-2-methyl-1-propanol (458 g, 5.15 mol) in 1.10 l. of CH_2Cl_2 was added a solution of 2-bromobenzoyl chloride (575 g, 2.50 mol) in 1.10 l. of CH_2Cl_2 at such a rate as to maintain the temperature at 0°. After addition was complete, stirring was continued for 4 hr at the same temperature. The mixture was filtered and the filtrate was washed with 3 *N* HCl and water, dried, and evaporated in vacuo. Trituration with ether gave 624 g (88%) of colorless crystals: mp 142–144° (lit.[3] mp 135–136°); ir 3240, 3190, 3070 (OH, NH), 1630 cm^{-1} (C=O); NMR (DMSO) δ 7.1–7.9 (m, 4, ArH), 4.80 (t, 1, OH), 3.50 (d, 2, CH_2), 1.33 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.57; H, 5.19; N, 5.15. Found: C, 48.47; H, 5.09; N, 5.02.

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline. Thionyl chloride (800 ml) was added to 2-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide (200 g, 0.73 mol) with stirring at room temperature. The resulting solution was allowed to stand overnight and was then poured into 3 l. of ether. The mixture was filtered and washed well with ether to yield 186 g (87%) of colorless crystals: mp 118–120° (lit.[3] mp 108–110°); ir 1640 cm^{-1} (C=N); NMR (TFA) 11.4 (s, 1, H), 7.5–8.2 (m, 4, ArH), 5.02 (s, 2, CH_2), 1.84 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{12}BrNO \cdot HCl$: C, 45.56; H, 4.17; N, 4.83. Found: C, 45.28; H, 4.54; N, 4.61.

The free base was prepared by dissolution of the hydrochloride in a minimum amount of ice-cold water, layering with ether, and adjustment of the aqueous layer to pH 10 by the addition of cold 20% NaOH. The layers were then separated and the aqueous phase was extracted with ether. The combined extracts were washed once with cold water, dried, and evaporated in vacuo to yield a colorless solid, mp 36–38°. Distillation in vacuo gave 148 g (91%) of analytically pure material: bp 93–95° (0.7 mm); mp 38–39°; ir 1640 cm^{-1} (C=O); NMR δ 7.1–7.9 (m, 4, ArH), 3.97 (s, 2, CH_2), 1.33 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{12}BrNO$: C, 52.01; H, 4.76; N, 5.51. Found: C, 52.11; H, 4.70; N, 5.39.

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (4a). Method A. Freshly cut Mg (7.2 g, 0.30 g-atom) was placed in a dry flask. A small crystal of I_2 was added and just enough THF to cover the Mg. The mixture was then refluxed on a steam bath until the color had disappeared (~10 min). Approximately 10% of a solution of 2-(2-bromophenyl)-4,4-dimethyloxazoline (72.0 g, 0.284 mol) in 900 ml of THF was added all at once and reflux was continued until a brown coloration appeared. The remainder of the solution was added dropwise with continued reflux. After addition was complete heating was maintained for 2 hr, at which point almost all of the Mg had dissolved. The solution of 1 was then cooled to 0° and 1-methyl-4-piperidone (**2a**, 32.5 g, 0.33 mol) was added dropwise with stirring. The reaction mixture was stirred overnight at room temperature and poured over a mixture of ether and water. The layers were separated and the aqueous layer was extracted with ether. The combined extracts were washed with water, dried, evaporated in vacuo, and crystallized from acetone to give 28.0 g (34%) of **3a** as a colorless solid: mp 158–160°; ir 3150 cm^{-1} (OH); NMR δ 7.2–7.8 (m, 4, ArH), 3.29 (s, 2, OCH_2), 2.28 (s, 3, NCH_3), 2.0–3.5 (m, 8, CH_2), 1.30 (s, 6, CCH_3).

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 71.03; H, 8.25; N, 9.64.

A solution of **3a** (23.0 g, 0.80 mol) in 480 ml of 3 *N* HCl was refluxed for 5 hr and then evaporated in vacuo to yield a colorless solid. This was layered between $CHCl_3$ and water and the pH of the aqueous layer was adjusted to 10 with saturated KOH solution. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed with water, dried, and evaporated in vacuo to give an oil which was crystallized from ether to yield 16.0 g (93%) of colorless crystals of **4a:** mp 147–148°; ir 1758 cm^{-1} (C=O); NMR δ 7.2–8.0 (m, 4, ArH), 2.38 (s, 3, NCH_3), 1.4–3.0 (m, 8, CH_2).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.52; H, 6.89; N, 6.50.

Method B. To a solution of *N*-phenylbenzamide (148 g, 0.75 mol) in 1.20 l. of THF at −70° was added 1.20 l. of a 1.6 *M* solution

of *n*-butyllithium with stirring. After addition was complete the solution of **5** was warmed to 0° and **2a** (169 g, 1.70 mol) was added dropwise over a period of 90 min. The reaction mixture was stirred overnight at room temperature and poured into a mixture of 3 *N* HCl and $CHCl_3$. The layers were separated and the organic layer was extracted with 3 *N* HCl. The combined extracts were made basic to pH 10 with saturated KOH solution and reextracted with $CHCl_3$. The latter extracts were washed well with water, dried, and evaporated in vacuo to yield an oil which was crystallized from ether to give 81.0 g (50%) of colorless crystals of **4a** exhibiting the same physical and spectral properties as **4a** obtained by method A.

1′-Benzylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (4b). Method A. A solution of **1** was prepared as illustrated for the synthesis of **3a** utilizing 50.0 g (0.195 mol) of 2-(2-bromophenyl)-4,4-dimethyloxazoline, 5.0 g (0.21 g-atom) of Mg, and 37.8 g (0.20 mol) of 1-benzyl-4-piperidone (**2b**). After a similar work-up there was obtained an oil which was triturated with ice-cold toluene. The resulting colorless solid was crystallized from benzene to give 22.5 g (35%) of **3b** as colorless crystals: mp 97–100°; ir 3150 (OH), 1660 cm^{-1} (C=N); NMR δ 7.2–7.9 (m, 9, ArH), 3.62 (s, 2, NCH_2Ar), 3.42 (s, 2, OCH_2), 1.5–3.2 (m, 9, CH_2, OH), 1.38 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.94; H, 7.85; N, 7.49.

A solution of **3b** (48.0 g, 0.132 mol) in 1.20 l. of 3 *N* HCl was refluxed and worked up in a manner similar to that illustrated for the preparation of **4a** to give an oil which was crystallized from cyclohexane to give 29.5 g (76%) of **4b** as a colorless solid: mp 103–104° (lit.[2h] mp 105–106°); ir 1755 cm^{-1} (C=O); NMR δ 7.1–7.8 (m, 4, ArH), 3.62 (s, 2, NCH_2Ar), 1.4–3.2 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.40; H, 6.58; N, 4.96.

Method B. A solution of **5** was prepared as for the synthesis of **4a.** To this was added **2b** (282 g, 1.49 mol) at 0°. A similar work-up yielded an oil which was crystallized from cyclohexane to give 91.0 g (42%) of **4b** as a colorless solid which exhibited identical physical and spectral properties with those obtained from method A.

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (6a). To a solution of **4a** (8.0 g, 37 mmol) in 80 ml of THF cooled to 0° was added dropwise 74 ml of 1 *M* diborane (THF) with stirring. After addition was complete the mixture was kept at room temperature for 30 min and then refluxed overnight. The solution was then cooled to 0° and 29 ml of 6 *N* HCl was added dropwise. The mixture was then refluxed for 5 hr and the solvents were evaporated in vacuo to give an oil which was layered between ether and water. The pH of the aqueous layer was adjusted to 10 with saturated KOH solution. The layers were separated and the aqueous layer was extracted with ether. The combined extracts were washed with water, dried, and evaporated in vacuo to give an oil which was converted to the hydrochloride in the usual manner to obtain 5.3 g (60%) of colorless crystals: mp 281–282°; NMR (DMSO) δ 7.2–7.5 (m, 4, ArH), 5.06 (s, 2, OCH_2), 4.46 (s, 3, NCH_3), 3.1–3.5 (m, 4, NCH_2), 2.2–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{17}NO \cdot HCl$: C, 65.05; H, 7.56; N, 5.84. Found: C, 65.06; H, 7.62; N, 5.60.

1′-Benzylspiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (6b). A solution of **4b** (58.6 g, 0.20 mol) in 600 ml of THF was treated with 400 ml of 1 *M* diborane (THF) as for the preparation of **6a.** A similar work-up gave an oil which was converted to the hydrochloride in the usual manner to obtain 52.0 g (93%) of colorless crystals: mp 252–253°; nmr δ 7.1–7.9 (m, 9, ArH), 5.05 (s, 2, NCH_2Ar), 4.25 (s, 2, OCH_2), 1.6–3.6 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{21}NO \cdot HCl$: C, 72.21; H, 7.02; N, 4.43. Found: C, 72.30; H, 7.28; N, 4.41.

Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (7). To a suspension of 1.0 g of 10% Pd/C in 250 ml of EtOH was added 5.0 g (17 mmol) of lactone **4b.** The mixture was hydrogenated at atmospheric pressure for 20 hr. Filtration and evaporation of the filtrate gave an oil which triturated with ether to yield analytically pure material, 2.2 g (63%): mp 124–127° (lit.[5] mp 130.5–131.5°); ir 3290 (NH), 1755 cm^{-1} (C=O); NMR δ 7.2–8.1 (m, 4, ArH), 2.9–3.3 (m, 4, CH_2N), 1.4–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.28; H, 6.52; N, 6.88.

Spiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (8). A suspension of 2.6 g of 10% Pd/C and 13.0 g (41 mmol) of **6b** in 200 ml of EtOH was hydrogenated as in the preparation of **7** to give an oil which was crystallized from CH_3CN to obtain 5.9 g (64%) of colorless crystals, mp 200–202°.

Anal. Calcd for $C_{12}H_{15}NO \cdot HCl \cdot H_2O$: C, 59.31; H, 7.47; N, 5.76. Found: C, 59.66; H, 7.62; N, 5.86.

Alkylations of Phthalan 8. A. A mixture of 8 (4.50 g, 20 mmol), 2-bromomethyl-5-methoxy-2,3-dihydrobenzofuran (2.84 g, 24 mmol), and 7.2 g of Na_2CO_3 in 20 ml of 2-butanone was refluxed for 24 hr. The mixture was filtered and the solvent was evaporated in vacuo to give an oil which was triturated with ether–petroleum ether to obtain a solid which was crystallized from cyclohexane to give 2.0 g (24%) of **9c** as a tan solid, mp 97–99°.

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 74.78; H, 7.05; N, 3.86.

B. A mixture of 4.50 g (20 mmol) of **8,** 4.80 g (24 mmol) of γ-chloro-4-fluorobutyrophenone, and 7.2 g of Na_2CO_3 in 50 ml of 2-butanone was treated and processed as in example A to obtain an oil which was converted to the hydrochloride in the usual manner to yield 2.5 g (27%) of **9d** as a colorless solid when crystallized from CH_3CN–MeOH, mp 209–212°.

Anal. Calcd for $C_{22}H_{24}FNO_2 \cdot HCl$: C, 67.92; H, 6.48; N, 3.60. Found: C, 67.58; H, 6.45; N, 3.59.

3,4-Dihydro-2-methylindeno[2,1-*c*]pyridin-9(1*H*)-one (10a). A suspension of 16.0 g (74 mmol) of lactone **4a** in 320 g of PPA was stirred at 210° for 90 min. The reaction mixture was cooled to room temperature and poured onto excess ice. The pH of the mixture was adjusted to 9 with concentrated NH_4OH. This was then extracted with ether, washed, dried, charcoaled, and evaporated in vacuo to yield 5.0 g of a yellow oil. Chromatography on 480 g of neutral alumina (activity 3) by elution with ether gave 2.6 g (18%) of yellow-green solid after crystallization from cyclohexane: mp 74–77°; ir 1700 cm^{-1} (C=O); uv λ_{max} 234 nm (ε 38,380), 242 (44,320), 315 (1400), 325 (1210), 365 (670); NMR δ 6.8–7.5 (m, 4, ArH), 3.17 (m, 2, $C{=}CCH_2N$), 2.5–2.8 (m, 4, CH_2), 2.47 (s, 3, NCH_3).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.46; H, 6.58; N, 7.04. Found: C, 78.32; H, 6.50; N, 6.89.

General Procedure for Reaction of 4a with Grignard Reagents. A 10–20% solution of **4a** was added dropwise at room temperature to a 1–3 *M* solution of the appropriate Grignard reagent (20% excess). After addition was complete the milky suspension was refluxed for 6 hr. The mixture was cooled to room temperature and layered between $CHCl_3$ and water. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed well with water, dried, and evaporated in vacuo to obtain an oil which was crystallized from a suitable solvent (listed in Table II). The free bases were converted to the hydrochlorides in the usual manner (excluding **11f,g**). Compounds **11e, 11h,** and **11i** formed stable hydrochlorides and pertinent data are listed in Table II. Compounds **11j–p** dehydrated under these conditions to yield correspondingly **12q–v,y** whose physical properties are listed in Table III.

Reaction of 4a,b with Organolithium Reagents. A. To 400 ml of a 0.09 *M* benzyllithium solution in 1:2:10 hexane–THF–toluene[17] was added dropwise 6.5 g (30 mmol) of **4a** in 60 ml of toluene. This mixture was stirred overnight at room temperature and was then layered between $CHCl_3$ and water. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed well with water, dried, and evaporated in vacuo to yield an oil which crystallized from EtOAc to give 6.1 g (68%) of **11m** as a colorless solid which converted in the usual manner to the hydrochloride to yield 6.3 g (68%) of **12t** as colorless crystals: mp 289–291°; uv λ_{max} 224 nm (ε 9610), 230 (11,270), 237 (10,860), 245 (7650), 256 sh (4500), 304 sh (22,620), 314 (27,480), 326 (29,370), 342 (17,230); NMR δ 7.0–7.9 (m, 9, ArH), 6.24 (s, 1, C=CH), 3.2–3.8 (m, 4, NCH_2), 2.97 (s, 3, NCH_3), 1.7–2.7 (m, 4, CH_2).

Anal. Calcd for $C_{20}H_{21}NO \cdot HCl$: C, 73.23; H, 6.76; N, 4.27. Found: C, 73.37; H, 6.94; N, 4.40.

B. *n*-Butyllithium (1.6 *M*, 10.3 ml) was added dropwise at room temperature to diphenylmethane (16 mmol) in 10 ml of THF. After addition was complete a solution of **4a** (3.0 g, 15 mmol) in 25 ml of THF was added dropwise with stirring to the blood-red solution. The reaction mixture was stirred for 2 hr at room temperature, at which time the color had faded to pale yellow. The usual work-up yielded an oil which was triturated with ether to obtain 3.5 g (66%) of **11n** as analytically pure crystals, mp 168–170°. Formation of the hydrochloride gave 3.5 g (65%) of **12u** as colorless crystals: mp >315°; uv λ_{max} 220 nm (ε 12,950), 232 (13,970), 237 (13,810), 318–324 (21,230), 328 (21,430), 341 (14,880).

Anal. Calcd for $C_{26}H_{25}NO \cdot HCl$: C, 77.48; H, 6.50; N, 3.48. Found: C, 77.63; H, 6.69; N, 3.66.

C. A solution of 2-thienyllithium was prepared according to the literature procedure[18] utilizing 1.4 g (17 mmol) of thiophene in 5 ml of ether and 10.3 ml of 1.6 *M* *n*-butyllithium. To this solution

was added dropwise a solution of **4a** (3.0 g, 14 mmol) in 25 ml of THF. This was allowed to stand at room temperature overnight. The usual work-up gave an oil which crystallized from EtOAc to yield 1.7 g (41%) of **11h** as a colorless solid: mp 194–196°; NMR δ 6.8–7.6 (m, 7, ArH), 2.8–3.6 (m, 4, NCH_2), 2.32 (s, 3, NCH_3), 1.5–2.9 (m, 5, CH_2, OH).

Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.83; H, 6.36; N, 4.65. Found: C, 67.95; H, 6.59; N, 4.32.

D. A solution of 3-methyl-5-isoxazolyllithium was prepared according to the literature procedure[19] utilizing 7.8 g (81 mmol) of 3,5-dimethylisoxazole in 60 ml of THF and 52 ml (83 mmol) of 1.6 *M* *n*-butyllithium. A solution of **4a** (9.0 g, 42 mmol) in 75 ml of THF was added dropwise at −50°. After addition was complete the reaction mixture was allowed to warm to room temperature and stand overnight. The usual work-up gave an oil which was converted to the hydrochloride in the usual manner to yield 5.4 g (38%) of **12w** as colorless crystals (CH_3CN–MeOH): mp >315°; uv λ_{max} 236 nm (ε 8850), 245 (8330), 284 (9600), 297 (14,740), 308 (19,780), 322 (25,580), 337 (22,700); NMR (D_2O) δ 7.0–7.9 (m, 4, ArH), 6.43 (s, 1, C=CH), 5.59 (s, 1, ArC=CH), 3.42 (s, 3, NCH_3), 2.64 (s, 3, CCH_3), 2.2–4.1 (m, 6, CH_2), 1.3–1.8 (m, 2, CH_2).

Anal. Calcd for $C_{18}H_{20}N_2O_2 \cdot HCl$: C, 65.07; H, 6.32; N, 8.43. Found: C, 65.03; H, 6.47; N, 8.51.

E. A solution of 4-picolyllithium was prepared utilizing 1.6 g (16 mmol) of diisopropylamine, 10 ml (16 mmol) of 1.6 *M* *n*-butyllithium, and 1.5 g (16 mmol) of 4-picoline in 5 ml of THF. A solution of **4a** (3.0 g, 14 mmol) in 25 ml of THF was added dropwise at 0°. This was allowed to stand at room temperature overnight and then worked up in the usual manner to give an oil which was converted to the hydrochloride to yield 2.1 g. This material was hygroscopic and was therefore reconverted to the free base to give 1.8 g (45%) of **12x** as colorless crystals (cyclohexane): mp 154–156°; uv λ_{max} 235 nm (ε 13,500), 244 (10,430), 286 (9270), 300 (14,950), 324 (32,400), 337 (33,600), 353 (18,660); NMR δ 7.0–7.8 (m, 8, ArH), 5.80 (s, 1, C=CH), 2.46 (s, 3, NCH_3), 1.4–3.2 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.25; H, 6.74; N, 9.45.

3-Phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (13e). Phthalanol **11e** (8.0 g, 27 mmol) was dissolved in 80 ml of 97% HCOOH. The solution was refluxed for 2 hr and then the excess solvent was evaporated in vacuo and the residue was layered between $CHCl_3$ and water. The aqueous layer was adjusted to pH 10 with saturated KOH and the layers were separated. The aqueous layer was reextracted with $CHCl_3$ and the combined extracts were washed well with water, dried, and evaporated in vacuo to give an oil which crystallized from cyclohexane to yield 7.0 g (92%) of colorless solid, mp 120–123°. This was converted to the hydrochloride in the usual manner to obtain colorless crystals: mp 257–258° (CH_3CN–MeOH); NMR (DMSO) δ 6.9–7.5 (m, 9, ArH), 6.28 (s, 1, CH), 3.1–3.7 (m, 4, NCH_2), 2.84 (s, 3, NCH_3), 1.9–2.6 (m, 4, CH_2).

Anal. Calcd for $C_{19}H_{21}NO \cdot HCl$: C, 72.21; H, 7.02; N, 4.43. Found: C, 71.92; H, 6.99; N, 4.33.

3-Methoxy-4′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),-4′-piperidine] (14e). Phthalanol **11e** (8.0 g, 27 mmol) was dissolved in 80 ml of 95% H_2SO_4. The yellow solution was kept at room temperature for 3 hr and then poured in a stream into 160 ml of MeOH. This was then layered between $CHCl_3$ and water. The usual work-up for free base gave a colorless solid which crystallized from EtOAc–cyclohexane to yield 4.5 g (54%) of colorless crystals: mp 172–174°; NMR δ 7.0–7.9 (m, 9, ArH), 3.22 (s, 3, OCH_3), 2.38 (s, 3, NCH_3), 1.6–3.0 (m, 8, CH_2).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.78; H, 7.70; N, 4.39.

1-Benzyl-3-[2-(4,5-dihydro-5,5-dimethyl-2-oxazolyl)phenyl]-3-piperidinol (16b). A solution of **1** was prepared as illustrated for the synthesis of **3a** utilizing 150 g (0.59 mol) of 2-(2-bromophenyl)-4,4-dimethyloxazoline and 15.0 g (0.63 g-atom) of Mg. To this was added at room temperature 122 g (0.65 mol) of 1-benzyl-3-piperidone (**15b**). The usual work-up gave after crystallization from CH_3CN 100 g (47%) of colorless solid: mp 118–120°; ir 3100 (OH), 1675 cm^{-1} (C=N); NMR δ 7.0–7.9 (m, 9, ArH), 3.56 (q, 2, OCH_2), 3.47 (s, 2, $NCH_2C_6H_5$), 3.14 (s, 1, OH), 2.3–2.9 (m, 4, NCH_2), 1.6–2.0 (m, 4, CH_2), 1.43 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.51; H, 7.81; N, 7.78.

1′-Benzylspiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (17b). A solution of 200 g (0.548 mol) of **16b** in 2 l. of 3 *N* HCl was hydrolyzed as indicated for the preparation of **4a** utilizing method A. A similar work-up gave an oil which was converted to the hydrochloride in ether to yield 135 g (75%) of analytically pure crystals: mp 248–250°; ir 1765 cm^{-1} (C=O); NMR (DMSO) δ 7.2–8.1 (m, 9, ArH), 4.45 (s, 2, $NCH_2C_6H_5$), 2.9–3.9 (m, 4, CH_2), 1.6–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{19}H_{19}NO_2 \cdot HCl$: C, 69.15; H, 6.11; N, 4.24. Found: C, 69.34; H, 6.22; N, 4.31.

Spiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (18). A suspension of **17b** (130 g, 0.395 mol) and 26 g of 10% Pd/C in 1 l. of EtOH was hydrogenated on a Parr apparatus at 3 atm for 3 hr. The mixture was filtered and the filter cake was washed with 1 l. of water. The filtrate was evaporated in vacuo to obtain a solid which was crystallized from CH_3CN–MeOH to yield 87.0 g (92%) of colorless crystals: mp >315°; ir 1755 cm^{-1} (C=O); NMR (D_2O) δ 7.8–8.3 (m, 4, ArH), 3.4–4.5 (m, 4, NCH_2), 1.8–3.0 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2 \cdot HCl$: C, 60.05; H, 5.88; N, 5.84. Found: C, 59.68; H, 6.07; N, 5.73.

1′-Methylspiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (19a). The lactone **18** (65 g, 0.32 mol) was dissolved in ice-cold HCOOH (36 g, 0.78 mol). A 37% formalin solution (12 g, 0.40 mol) was added in a thin stream and the mixture was stirred at 80° for 4 hr. The excess reagents were stripped in vacuo to give an oil which was converted to the hydrochloride in the usual manner to yield 65 g (80%) of colorless crystals: mp 298–300°; ir 1750 cm^{-1} (C=O); NMR (DMSO) δ 7.5–8.2 (m, 4, ArH), 3.91 (q, 2, NCH_2), 3.3–3.6 (m, 2, NCH_2), 3.87 (s, 3, NCH_3), 1.6–2.6 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{15}NO_2 \cdot HCl$: C, 61.71; H, 6.38; N, 5.54. Found: C, 61.60; H, 6.53; N, 5.53.

3-Benzylidenespiro[isobenzofuran-1(3*H*),3′-piperidine] Hydrochloride (20a). A solution of **19a** (10.5 g, 4.84 mmol) in 50 ml of toluene was added to a benzyllithium solution prepared as illustrated for the preparation of **12t** utilizing 50 ml of 1.2 *M* *sec*-butyllithium. After addition was complete, the mixture was stirred at 60° for 15 hr. A similar work-up as for **21a** yielded an oil which was converted with attendant dehydration to the hydrochloride in the usual manner to obtain a gum which was triturated with EtOAc to yield a solid which was crystallized from CH_3CN–MeOH to give 2.0 g (17%) of colorless crystals: mp 290–292° dec; NMR (TFA) δ 6.8–8.0 (m, 9, ArH), 5.8 (s, 1, C=CH), 3.5–4.2 (m, 4, NCH_2), 3.10 (s, 3, NCH_3), 1.9–2.9 (m, 4, CH_2).

Anal. Calcd for $C_{20}H_{21}NO \cdot HCl$: C, 73.46; H, 6.78; N, 4.28. Found: C, 73.29; H, 6.59; N, 4.14.

3-[*o*-(α-Hydroxy-α-phenylbenzyl)phenyl]-1-methyl-3-piperidinol (21a). A solution of 17.0 g (78.2 mmol) of **19a** in 170 ml of THF was added dropwise at room temperature to 37.4 ml of 2.5 *M* C_6H_5MgCl with stirring. After addition was complete the reaction mixture was refluxed for 15 hr. This was then layered between $CHCl_3$ and water, dried, and evaporated in vacuo to give an oil. This was triturated with EtOAc and crystallized from EtOAc–MeOH to yield 2.0 g (7%) of **21a** as colorless crystals: mp 148–150°; NMR δ 6.5–7.5 (m, 14, ArH), 4.5 (s, broad, 2, OH), 2.3–2.9 (m, 4, NCH_2), 2.17 (s, 3, NCH_3), 1.3–2.0 (m, 4, CH_2).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.37; H, 7.30; N, 3.73.

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Registry No.—**2a,** 1445-73-4; **2b,** 3612-20-2; **3a,** 54595-98-1; **3b,** 54595-99-2; **4a** HCl, 54596-00-8; **4b** HCl, 54596-01-9; **4c** HCl, 54596-02-0; **4d** HCl, 54596-03-1; **4e** HCl, 54596-04-2; **4f** HCl, 54596-05-3; **4g** HCl, 54596-06-4; **4h** HCl, 54596-07-5; **6a** HCl, 54596-08-6; **6b** HCl, 54596-09-7; **7,** 37663-46-0; **8** HCl, 37663-44-8; **9c,** 54596-10-0; **9d** HCl, 54596-11-1; **10a,** 54596-12-2; **13e** HCl, 54596-13-3; **14e,** 54596-14-4; **16b,** 54596-15-5; **17b** HCl, 54596-16-6; **18** HCl, 54596-17-7; **19a** HCl, 54596-18-8; **21a,** 54596-20-2; 2-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide, 54596-21-3; 2-amino-2-methyl-1-propanol, 124-68-5; 2-bromobenzoyl chloride, 7154-66-7; 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline hydrochloride, 51849-83-3; 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline, 32664-13-4.

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(7) (a) W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.*, **66**, 1444 (1944). (b) Although yields are better via this method, enolization is again the predominant side reaction, as only starting materials are isolated besides the product. (c) The generality of this method was established at this point by the reaction of **5** with 1-dimethylamino-3-pentanone to yield 3-ethyl-3-dimethylaminoethylphthalide, bp 123–125° (0.3 mm) (56%). The reaction failed utilizing 3-dimethylamino-1-phenyl-1-propanone owing to complete enolization of the substrate under these conditions. However, this type of derivative is readily available via 3-arylphthalide alkylations.[2g]
(8) It was ascertained that use of *N*-phenylbenzamide rather than *N*-methylbenzamide in this reaction consistently gave better results, e.g., 50% as compared to 23% with **2a**.
(9) It was reported in ref 5 that quenching with saturated NH_4Cl will give the intermediate hydroxyamides in good yield.
(10) (a) The fact of obtaining phthalides on work-up perforce indicates ortholithiation. However, utilization of 3-methoxy-*N*-phenylbenzamide presents ambiguity owing to the presence of two nonequivalent ortho positions. In fact the product isolated was proven unequivocally to be the 7-OCH_3 isomer by NMR absorption which indicated a single downfield aromatic proton exhibiting ortho coupling.
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(12) The stereochemistry of the dehydration products deserves consideration. Products **12t,w–y** were shown to exist in the *trans*-stilbene configuration by uv absorption, e.g., **12t**, λ_{max} 314 nm (ϵ27,480), 326 (29,370), 342 (17,230). (For complete spectrum see Experimental Section.) The alkyl derivatives **12q,v** were assigned the trans configuration by analogy.
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Synthesis and Cyclization of 2-(3-Indolylmethyl)-3-hydroxy-4-piperidineacetic Acid Derivatives

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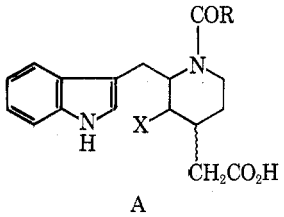
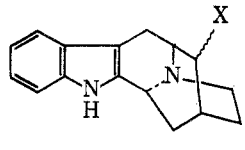
Modifications of a previously reported method for synthesis of 2-(3-indolylmethyl)-4-piperidineacetic acid derivatives by alkylation of the pyrrolidine enamine of 1-acyl-4-carbalkoxymethyl-3-piperidones are reported. The synthesis of the piperidones has been facilitated by using a selenium dioxide oxidation of ethyl 1-benzoylpiperidine-$\Delta^{4,\alpha}$-acetate. A method for inversion of the stereochemistry of the alkylated piperidones is reported. Although the trans isomer is the predominant product of the enamine alkylation, use of an easily removable *N*-acyl group (carbobenzyloxy) permits epimerization at C-2 and reacylation gives predominantly the cis isomer. A method for cyclization involving the side chain carboxyl group and C-2 of the indole ring is described. It proceeds from the alkylated piperidone *c*-**10**, by reduction and cyclization to the lactone **11** followed by partial reduction (diisobutylaluminum hydride) and acid-catalyzed cyclization to **16**. Structural characterization of **16** and and its derivatives is discussed. Since **16** contains the basic carbon skeleton of the sarpagine and vobasine alkaloid groups it is a potential intermediate in the synthesis of deethyl analogs of these groups of alkaloids.

In a previous paper[1] a method for the preparation of several derivatives of 2-(3-indolylmethyl)-4-piperidineacetic acid (A) was described. This molecule possesses all the atoms present in the skeletal framework (B) of the sarpagine and vobasine types[2] of indole alkaloids. The method, however, led primarily to the trans series of compounds, whereas the cis derivatives are required for cyclization to the alkaloidal skeleton. We have now developed a modified synthesis which makes the cis series available. The cyclization of one of these compounds is also reported in this paper.

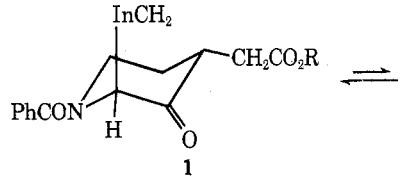


A

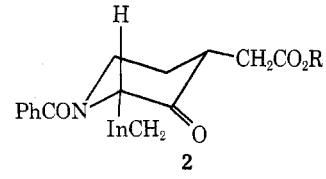


B

The underlying cause of the predominant formation of the trans ketone **1** over **2** in the earlier synthetic method is the $A^{1,3}$ strain[3] which exists between the *N*-benzoyl and C-2 substituents in the diequatorial cis conformation. The trans ketone **1** is more stable, despite the axial indolylmethyl substituent. The strategy adopted to circumvent



1



2

this problem was to introduce an *N*-acyl substituent which could be removed at some stage. The N-deacylated derivative would be expected to exist primarily in the diequatorial cis form at equilibrium. The original synthesis was therefore modified to incorporate a carbobenzyloxy group as the *N*-acyl substituent.