Novel Tetracyclic Spiropiperidines. II. Synthesis of 2-Aryl-2,3-dihydrospiro[benzofuran-3,4'-piperidines] (1,2)

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A series of 2-aryl-2,3-dihydropsiro[benzofuran-3,4'-piperidines] has been synthesized as potential psychotropic agents *via* an efficient intramolecular fluorine displacement reaction. Treatment of a key intermediate, 4-cyano-4-(2-fluorophenyl)-1-methylpiperidine (**2**), with a large excess of phenylmagnesium bromide in refluxing tetrahydrofuran led to some 2-arylspiro[3*H*-indole-3,4'-piperidine] derivatives, **10** and **11**, whose structures are elucidated on the basis of chemical and spectral evidence.

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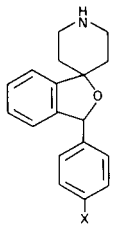
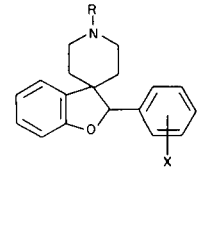
The 3-aryl-1,3-dihydrospiro[isobenzofuran-1-(3*H*),4'-piperidine] system (I) has served as a rich source for a variety of CNS and pharmacodynamic agents. Marked antidepressant (3), neuroleptic (4), hypotensive (5) and diuretic activity (6) have been demonstrated in animal models by various analogues bearing different *N*-substituents, and two congeners of this chemical class, HP 505 and HRP 197, are of continued clinical interest as psychoactive agents. As part of a program aimed at discovering novel tetracyclic spiropiperidines of therapeutic potential, we have undertaken the study of a series of isomeric 2-aryl-2,3-dihydrospiro[benzofuran-3,4'-piperidines] (II). The



I R = H; HP 505
R = CH_3; HRP 197



II

present report details the synthesis of these compounds by an efficient intramolecular fluorine displacement reaction, as well as the characterization of some 3*H*-indole derivatives resulting from an unexpected cyclization.

The starting phenylacetonitrile **1** was prepared by nucleophilic displacement of the corresponding chloride with sodium cyanide in dimethylsulfoxide. As shown in Scheme 1, condensation of **1** with 2,2'-dichloro-*N*-methyldiethylamine in the presence of dimsyl sodium (7), as previously described by Ong, *et al.* (8), gave the piperidine derivative **2** in 90% yield. Conversion of this sterically hindered nitrile to the benzoylpiperidines **3a-d** was best carried out at room temperature (20°), with a large excess of the appropriately substituted phenylmagnesium bromide over a period of several days. The ketones so obtained were of high purity, unlike the grossly contaminated products isolated from reaction of **2** with the same Grignard reagents at 65° (refluxing tetrahydrofuran).

Ketones **3a-d** were readily reduced to the corresponding alcohols with lithium aluminum hydride; the use of sodium borohydride, surprisingly, led to incomplete reduction. Ring closure of **4a-d** to the target compounds **5a-d** was based upon an intramolecular fluorine displacement reaction (9,10), and the nucleophilic alkoxide was generated with sodium hydride in dimethylformamide. As expected, the resultant 2,3-dihydrospiro[benzofuran-3,4'-piperidines] were somewhat labile toward treatment with strong alkali, yet stable to acids even at elevated temperature. The tertiary amines **5a-d** were readily demethylated by a modified von Braun procedure to give secondary amines **7a-d** *via* the intermediary cyanamides, **6a-d**. In order to explore the analgesic and neuroleptic potential of this series, *N*-cyclopropylmethyl analogues (**8a-c**) and *N*-butyrophenone derivatives (**9a-c**) were prepared by direct alkylation of **7a-c**.

In an earlier attempt to synthesize **3a**, compound **2** was treated with slightly more than two equivalents of phenylmagnesium bromide in tetrahydrofuran for 1 day at reflux. The product mixture after a conventional work-up with aqueous ammonium chloride was found to be quite complex. Gc-ms analyses showed that in addition to some unreacted **2** (21%) and the desired ketone **3a** (29%), there were two other products present, **10** (25%) and **11**, (15%), neither of which retained the nuclear fluorine substituent (Scheme 2). Compound **11**, the least volatile compound and the last one to elute from the gc column (7.4 minutes), was analyzed by gc-ms in the chemical ionization mode using methane as the carrier gas. The molecular ion at m/e 353 (MH^+) was the base peak, suggesting a molecular formula of $C_{25}H_{24}N_2$, which was consistent with results of elemental analyses on a pure sample of **11** obtained after extensive column chromatography. Minor fragments occurring at m/e 310 (2.2%) and m/e 296 (2.4%) may be readily explained by fragmentation of the piperidine ring system.

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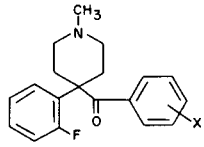
Table 1

4-Benzoyl-4-(2-fluorophenyl)-1-methylpiperidines

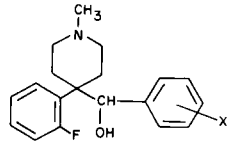


Compound No.	X	M.p. °C	Yield % (a)	Recrystallization Solvent	Molecular Formula	Analyses % Calcd./Found		
3a	H	202-203	80	ethanol-ether	$C_{19}H_{20}FNO \cdot C_2H_2O_4$ (b)	C, 65.10;	H, 5.72;	N, 3.62
						C, 65.19;	H, 5.77;	N, 3.64
3b	4-Cl	120-124	84	benzene-hexane	$C_{19}H_{19}ClFNO$	C, 68.78;	H, 5.77;	N, 4.22
						C, 68.87;	H, 5.80;	N, 4.22
3c	3-F	118-120	78	hexane	$C_{19}H_{19}F_2NO$	C, 72.36;	H, 6.07;	N, 4.44
						C, 72.58;	H, 6.11;	N, 4.29
3d	4-F	201-203	64	methanol-ether	$C_{19}H_{19}F_2NO \cdot C_2H_2O_4$ (b)	C, 62.21;	H, 5.22;	N, 3.45
						C, 62.07;	H, 5.25;	N, 3.50

(a) Isolated yields; no efforts were made to optimize these yields. (b) Acid oxalate salt.

Table 2

4-(α-Hydroxybenzyl)-4-(2-fluorophenyl)-1-methylpiperidines



Compound No.	X	M.p. °C	Yield % (a)	Recrystallization Solvent	Molecular Formula	Analyses % Calcd./Found		
4a	H	139-140	83	benzene-hexane	$C_{19}H_{22}FNO$	C, 76.22;	H, 7.40;	N, 4.68
						C, 76.72;	H, 7.41;	N, 4.60
4b	4-Cl	163-165	64	ether-hexane	$C_{19}H_{21}ClFNO$	C, 68.36;	H, 6.34;	N, 4.29
						C, 68.45;	H, 6.52;	N, 4.21
4c	3-F	154-155	86	acetone-hexane	$C_{19}H_{21}F_2NO$	C, 71.90;	H, 6.67;	N, 4.41
						C, 72.14;	H, 6.73;	N, 4.20
4d	4-F	235-236	77	methanol-ether	$C_{19}H_{21}F_2NO \cdot HBr$	C, 57.29;	H, 5.57;	N, 3.51
						C, 57.46;	H, 5.62;	N, 3.60

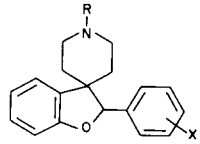
(a) Isolated yields; no efforts were made to optimize these yields.

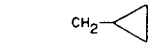
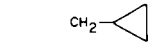
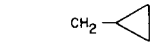
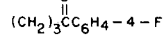
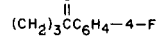
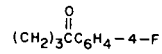
The proton magnetic resonance spectrum of **11** showed the presence of thirteen aromatic protons (δ 7-8), an increase of nine over starting material **2**, suggesting the possible incorporation of a biphenyl moiety. Other features of this spectrum included signals for four piperidine ring protons adjacent to a basic nitrogen (δ 2.2-2.8), three *N*-methyl protons (δ 2.32), two piperidine ring protons adjacent to the spiro center (δ 1.4-2.1), as well as two additional piperidine ring protons (also adjacent to the spiro center) shifted, surprisingly, to a much higher field (δ 0.5-1.1). Inspection of Dreiding models revealed that a diamagnetic shift of this proportion (0.5 ppm) could have been the result of a deshielding anisotropic effect exerted by a closely situated, out-of-plane aromatic ring: presumably, the monosubstituted phenyl group of a 2-[(1,1′-biphenyl)-2-yl] substituent as illustrated in Table 4.

Further structural evidence for **11** was provided by its infrared spectrum, which showed the presence of a cyclic, conjugated C=N (1488 cm^{-1}), and by ^{13}C nuclear magnetic resonance spectrum which displayed all the carbon nuclei required for the structure of 2-[(1,1′-biphenyl)-2-yl]-1′-methylspiro[3*H*-indole-3,4′-piperidine] (Table 4). With respect to the more crucial aromatic-type carbons, an excellent agreement seems to exist between the observed chemical shifts and the calculated values obtained by applying the general additivity relationships described by Stothers (11,12). The chemical shift of the imino carbon (C-2), specifically, was estimated by taking the chemical shift value of the imino carbon in *N*-benzilidene aniline and adding the proper parameter for a cyclohexyl ring deduced from the study of a series of cyclohexyl aromatic compounds. The multiplicities indicated in Table 4 were

Table 3

2-Aryl-2,3-dihydrospiro[benzofuran-3,4'-piperidines]



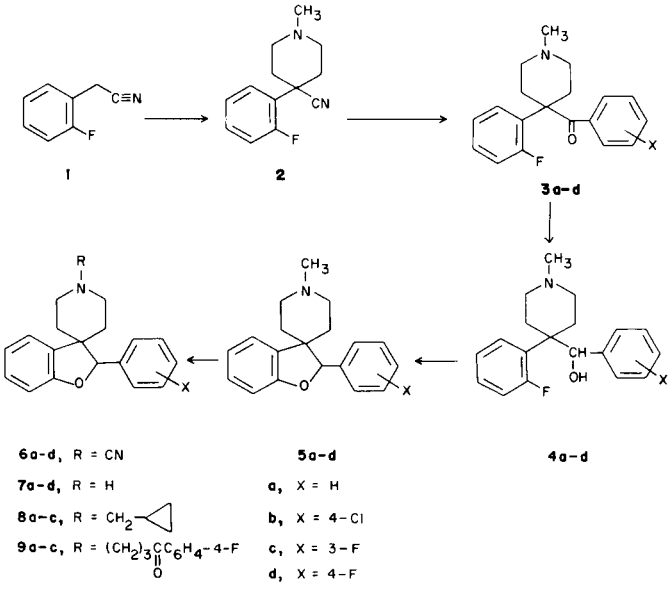
Compound No.	X	R	M.p. °C	Yield (a) %	Recrystallization Solvent	Molecular Formula	Analyses % Calcd./Found		
5a	H	CH_3	182-183	88	ethanol-ether	$C_{19}H_{21}NO \cdot C_2H_2O_4$ (b)	C, 68.27;	H, 6.27;	N, 3.79
							C, 68.13	H, 6.26;	N, 3.67
5b	4-Cl	CH_3	103-105	95	hexane	$C_{19}H_{20}ClNO$	C, 72.77;	H, 6.42;	N, 4.46
							C, 72.70;	H, 6.44;	N, 4.41
5c	3-F	CH_3	271-273	86	methanol-ether	$C_{19}H_{20}FNO \cdot HBr$	C, 60.32;	H, 5.60;	N, 3.70
							C, 60.43;	H, 5.62;	N, 3.61
5d	4-F	CH_3	253-256	80	methanol-ether	$C_{19}H_{20}FNO \cdot HBr$	C, 60.32;	H, 5.60;	N, 3.70
							C, 60.42;	H, 5.62;	N, 3.69
6a	H	CN	128-130	57	acetone-hexane	$C_{19}H_{18}N_2O$	C, 78.58;	H, 6.24;	N, 9.64
							C, 78.53;	H, 6.32;	N, 9.62
6b	4-Cl	CN	141-143	88	acetone-hexane	$C_{19}H_{17}ClN_2O$	C, 70.26;	H, 5.27;	N, 8.61
							C, 70.50;	H, 5.41;	N, 8.80
6c	3-F	CN	140-142	85	acetone-hexane	$C_{19}H_{17}FN_2O$	C, 74.00;	H, 5.59;	N, 9.08
							C, 74.28;	H, 5.67;	N, 9.32
6d	4-F	CN	159-161	88	acetone-hexane	$C_{19}H_{17}FN_2O$	C, 74.00;	H, 5.59;	N, 9.08
							C, 74.00;	H, 5.58;	N, 8.87
7a	H	H	203-205	65	methanol-ether	$C_{18}H_{19}NO \cdot HBr$	C, 62.34;	H, 5.75;	Br, 22.75
							C, 62.70;	H, 5.89;	Br, 22.83
7b	4-Cl	H	278-280	90	methanol-ether	$C_{18}H_{18}ClNO \cdot$ *HCl*	C, 64.28;	H, 5.69;	N, 4.16
							C, 64.31;	H, 5.75;	N, 4.38
7c	3-F	H	236-238	86	methanol-ether	$C_{18}H_{18}FNO \cdot HCl$	C, 67.59;	H, 5.99;	N, 4.38
							C, 67.09;	H, 6.08;	N, 4.21
7d	4-F	H	237-239	90	methanol-ether	$C_{18}H_{18}FNO \cdot$ *HBr*	C, 59.34;	H, 5.26;	N, 3.85
							C, 59.54;	H, 5.35;	N, 3.78
8a	H		201-203	59	methanol-ether	$C_{22}H_{25}NO \cdot C_2H_2O_4$ (b)	C, 70.39;	H, 6.65;	N, 3.42
							C, 70.35;	H, 6.62;	N, 3.31
8b	4-Cl		94-96	59	ether-hexane	$C_{22}H_{24}ClNO$	C, 74.66;	H, 6.86;	N, 3.96
							C, 74.72;	H, 6.87;	N, 3.94
8c	3-F		267-268	72	methanol-ether	$C_{22}H_{24}FNO \cdot HBr$	C, 63.16;	H, 6.07	N, 3.35
							C, 63.30;	H, 6.06;	N, 3.34
9a	H		196-198	61	methanol-ether	$C_{28}H_{28}FNO_2 \cdot C_2H_2O_4$ (b)	C, 69.36;	H, 5.82;	N, 2.67
							C, 69.15;	H, 5.83	N, 2.68
9b	4-Cl		241-243	60	methanol-ether	$C_{28}H_{27}ClFNO_2 \cdot HBr$	C, 61.72	H, 5.18	N, 2.57
							C, 61.73;	H, 5.22;	N, 2.51
9c	3-F		208-209	50	methanol-ether	$C_{28}H_{27}F_2NO_2 \cdot HBr$	C, 63.64;	H, 5.34;	N, 2.65
							C, 63.65;	H, 5.43;	N, 2.64

(a) Isolated yields, no efforts were made to optimize these yields. (b) Acid oxalate salt.

established by continuous wave off-resonance decoupling experiments. It is also worth noting that data presented in Table 4 definitely ruled out the possibility of a 2-[(1,1'-biphenyl)-4-yl] substituent, since the presence of the latter would have reduced the total number of aromatic carbon signals by two, due to its added element of symmetry. Additional structure proof for **11** was provided by the observation that this compound was readily reducible to a spiro[indoline-3,4'-piperidine] derivative, **12**, which was isolable as a dihydrobromide salt. The most characteristic feature in the ^1H nmr spectrum of **12** (taken in the form of free base) were a sharp singlet at δ 5.12, attributed to the methine proton at C-2, and a broad (deuterium exchangeable) singlet at δ 4.25 arising from the indoline NH (13).

Due to its instability and solubility, compound **10** could not be obtained in sufficient purity to allow rigorous structural determination. Data from gc-ms studies (m/e 277; MH^+), coupled with mechanistic considerations, nevertheless suggest a 2-phenylspiro[3*H*-indole-3,4'-piperidine] structure, similar to that assigned to compound **11**. In view of the many published examples of nuclear fluorine displacements by carbanions (2) and alkoxides (9,10), it is quite conceivable that a similar nucleophilic attack by an

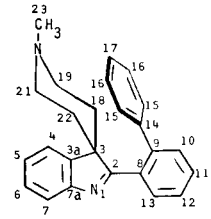
Scheme 1



anion (or negatively charged complex) generated from an imine had led to the formation of **10**. We would further speculate that the introduction of a second phenyl group, as shown, might have been facilitated by the formation of a *quasi* cyclic complex between **10** and the excess Grignard reagent (Scheme 3); without excluding other possible mechanisms, this could be followed by a hydride ion loss to give the biphenyl derivative **11**.

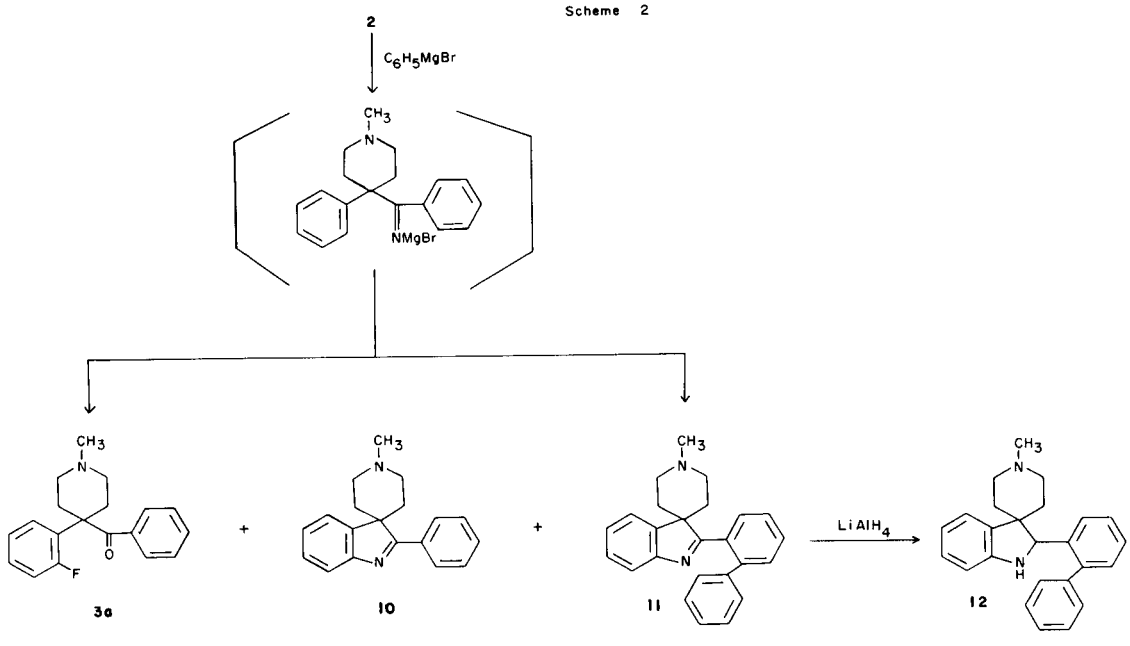
Table 4

^{13}C Chemical Shifts of Compound **11**

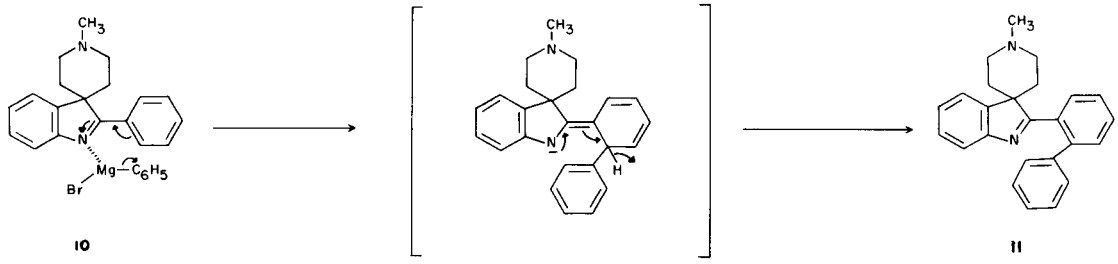


Carbon	Chemical Shift, δ, ppm Observed (calculated)	Multiplicity (Jr)
2	187.8 (~182)	s
3	57.6	s
3a	140.8 (140.2)	s
4, 10, 12, 17	129.1, 127.7, 127.0, 126.8 (127.0, 127.6, 127.5, 127.3)	d, d, d, d
5	124.3 (125.6)	d
6	125.0 (126.0)	d
7	121.3 (120.6)	d
7a	154.1 (150.4)	s
8	134.0 (135.1)	s
9	143.4 (142.1)	s
11	130.4 (131.5)	d
13	129.8 (129.4)	d
14	141.4 (141.6)	s
15	128.0 (127.4)	d
16	130.1 (128.9)	d
18, 22	30.5	t
19, 21	51.1	t
23	46.3	q

Scheme 2



Scheme 3



10 11

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 or a Pye Unicam SP3-200 spectrophotometer. ^1H nuclear magnetic resonance spectra were taken at 60 MHz on either a JEOL C-60HL or a JEOL FX-60 spectrometer, and chemical shifts are given relative to internal tetramethylsilane. ^{13}C Nuclear magnetic resonance spectra were recorded at 15.03 MHz using a JEOL FX-60 fourier transform spectrometer with a spectral width of 3.4 KHz, a pulse width of 3 μs, a pulse repetition rate of 2.0 seconds, and a data size of 8 K. All chemical shifts are reported relative to internal tetramethylsilane. Mass spectra were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 gas chromatograph and equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Thin-layer chromatograms were run on a silica gel PF-254 plates (E. Merck, AG) and GC analyses were performed on a Hewlett-Packard 5880A chromatograph using a 2 mm ID × 2 m glass column packed with 3% OV-101 on 80/100 Supelcoport.

2-Fluorophenylacetonitrile (**1**).

A solution of 2-fluorobenzoyl chloride (14.5 g., 0.1 mole) in 150 ml. of dimethylsulfoxide was added, with good stirring, to a suspension of sodium cyanide (6 g., 0.12 mole) in 100 ml. of the same solvent. After stirring at room temperature for 2 hours, the mixture was poured onto 500 g. of ice-water and the organic materials were extracted with ether (3 × 250 ml.). The combined ether extract was washed with water (4 × 400 ml.), dried (magnesium sulfate) and concentrated under reduced pressure to give an oily residue. Vacuum distillation afforded, as the main product, a pale yellowish oil which boiled at 65-67° (0.4 mm) [lit. (14) b.p. 112° (18 mm)].

4-Cyano-4-(2-fluorophenyl)-1-methylpiperidine (**2**).

A solution of 2-fluorophenylacetonitrile (14.9 g., 0.11 mole) in 250 ml. of anhydrous dimethylformamide was added over 5 minutes to 9.6 g. of sodium hydride with good stirring. Gas evolution was immediate and after stirring at room temperature for 30 minutes, there was added a solution of 2,2'-dichloro-*N*-methyldiethylamine in 100 ml. of the same solvent at a rate that the temperature remained below 50°. The mixture was gradually heated to 90° and stirred at this temperature for 16 hours. The dark bluish reaction mixture was quenched with 1500 g. of ice-water, the organic materials were extracted with ether (4 × 500 ml.) and the combined ether solution was shaken with a large excess of 2*N* hydrochloric acid. The acidic layer was separated, rendered basic with cautious addition of concentrated ammonia to liberate an oily amine. The oily product slowly crystallized on standing and was filtered and air-dried. Recrystallization from acetone-hexane with the aid of Norite gave 20 g. (91%) of colorless crystals, m.p. 69-71°; ir (chloroform): 2240 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 2.5 (s, 3, NCH_3); 2.18-3.30 (m, 8, piperidine CH_2); 7.20-8.05 (m, 4, aromatic H).

Anal. Calcd. for $C_{13}H_{15}FN_2$: C, 71.50; H, 6.92; N, 12.83; F, 8.70. Found: C, 71.76; H, 7.03; N, 12.98; F, 8.56.

4-Benzoyl-4-(2-fluorophenyl)-1-methylpiperidine Oxalate (**3a**).

A solution of **2** (7.5 g., 34 mmoles) in 30 ml. of anhydrous ether was added to 60 ml. of 2.0*M* phenylmagnesium bromide in tetrahydrofuran. The clear solution was stirred at room temperature for 96 hours and decomposed with aqueous ammonium chloride. The organic phase was separated, washed with water, brine, and dried over magnesium sulfate. Evaporation of the solvent left a thick oil which was converted to a crystalline oxalate in ether; ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (DMSO-d_6): δ 2.93 (s, 3, $\dot{N}CH_3$), 2.48-2.90 (m, 4, CH_2), 3.22-3.80 (m, 4, $\dot{N}CH_2$), 7.25-8.30 (m, 9, aromatic H).

Properties of **3a**, and of **3b-d** prepared in a similar manner, are given in Table 1.

4-(2-Fluorophenyl)-4-(α-hydroxybenzyl)-1-methylpiperidine (**4a**).

A solution of **3a** (2.5 g. of the free base, 8.4 mmoles) in 20 ml. of anhydrous tetrahydrofuran was added dropwise over 30 minutes to a refluxing slurry of 300 mg. of lithium aluminum hydride in the same solvent. Stirring was maintained at reflux for four additional hours, cooled and decomposed in the usual manner with water and dilute sodium hydroxide. The granular aluminum oxide was filtered off and the filtrate was washed with water and dried over potassium carbonate. Removal of solvents under reduced pressure left a viscous oil which crystallized on standing to give colorless prisms; ir (chloroform): 3580 cm^{-1} (OH); nmr (deuteriochloroform): δ 2.18 (s, 3, NCH_3), 1.80-3.05 (m, 8, piperidine CH_2), 5.02 (s, 1, CH-O), 7.10-7.80 (m, 9, aromatic H).

Properties of **4a**, and of **4b-d** prepared in a similar manner, are given in Table 2.

2,3-Dihydro-1'-methyl-2-phenylspiro[benzofuran-3,4'-piperidine] Oxalate (**5a**).

A solution of **4a** (7.5 g., 25 mmoles) in 100 ml. of dimethylformamide was added to a stirred mixture of 1.0 g. of sodium hydride in 150 ml. of the same solvent. Stirring was maintained at 100-110° with the exclusion of moisture for 2 hours. The cooled mixture was poured onto 500 g. of ice-water; the organic product was extracted with methylene chloride (3 × 300 ml.) and the combined organic solution was dried over magnesium sulfate. Removal of solvent under reduced pressure gave an oily product which resisted all attempts at crystallization. The oily residue was thus dissolved in ether and treated with a large excess of ethereal oxalic acid. The crude salt was filtered off and recrystallized from ethanol-ether to give 6.2 g. (88%) of white granules; ir (potassium bromide): 3400 cm^{-1} (broad, NH); nmr (DMSO-d_6): δ 1.50-3.95 (m, 8, piperidine CH_2), 2.82 (s, 3, $\dot{N}CH_2$), 5.70 (s, 1, CH-O), 7.0-7.8 (m, 9, aromatic H).

Properties of **5a**, and of **5b-d** prepared in a similar manner, are given in Table 3.

1-Cyano-2,3-dihydro-2-phenylspiro[benzofuran-3,4'-piperidine] (**6a**).

A mixture of **5a** (0.85 g. of the free base, 3 mmoles), 0.42 g. of cyanogen bromide and 1 g. of potassium carbonate in 20 ml. of anhydrous chloroform was stirred at reflux for 4 hours. Water (20 ml.) was added; the chloroform solution was separated, washed with dilute

alkali and dried over magnesium sulfate. Removal of solvent *in vacuo* left a viscous oil which crystallized on standing; ir (chloroform): 2310 cm^{-1} (NC≡N); nmr (deuteriochloroform): δ 1.25-2.25 (m, 4, CH_2), 2.70-3.90 (m, 4, NCH_2), 5.60 (s, 1, CH-O), 7.1-7.9 (m, 9, aromatic H).

2,3-Dihydro-2-phenylspiro[benzofuran-3,4'-piperidine] Hydrobromide (**7a**).

A mixture of **6a** (1.16 g., 4 mmoles) in 40 ml. of 3*N* hydrochloric acid was stirred at reflux for 16 hours. The cooled mixture was extracted once with ether to remove neutral materials; the aqueous solution was basified with potassium carbonate to liberate the amine. The oily product was extracted into ether (3 × 100 ml.), washed with water and dried over magnesium sulfate. The anhydrous ether solution was treated with a large excess of ethereal hydrogen bromide to give, after two recrystallizations, 0.9 g. (65%) of pure **7a**; ir (potassium bromide): 3450 cm^{-1} (NH); nmr (DMSO-d_6): δ 1.10-3.85 (m, 8, CH_2), 6.00 (s, 1, CH-O), 7.18-8.10 (m, 9, aromatic H).

Properties of **7a**, and of **7b-d** prepared in a similar manner, are given in Table 3.

1-Cyclopropylmethyl-2,3-dihydro-2-phenylspiro[benzofuran-3,4'-piperidine] Oxalate (**8a**).

To the free base of **7a** (1.0 g., 3.8 mmoles) in 15 ml. of anhydrous dimethylformamide was added 0.46 g. (5.03 mmoles) of chloromethylcyclopropane, 1.06 g. of sodium bicarbonate and a few crystals of potassium iodide. The mixture was stirred at 80° for 16 hours. To the cooled mixture was added 35 g. of ice-water and the solution was extracted with three 30 ml. portions of ether. The combined ether solution was washed with water, brine and dried over magnesium sulfate to give 0.89 g. of a heavy oil. The crude product was chromatographed over a 2.5 × 15 cm column of silica gel packed in ether, elution with 10% methanol-ether gave 0.75 g. of a pale yellowish oil which was converted to 0.91 g. (59%) of a crystalline oxalate in ether.

Properties of **8a**, and of **8b,c** prepared in a similar manner, are give in Table 3.

1'-[3-(4-Fluorobenzoyl)propyl]-2,3-dihydro-2-phenylspiro[benzofuran-3,4'-piperidine] Oxalate (**9a**).

To the free base of **7a** (1.2 g., 4.4 mmoles) in 20 ml. of anhydrous dimethylformamide was added 1.0 g. of sodium bicarbonate, followed by 1.0 g. of potassium iodide and 1.4 g. of γ-chloro-*p*-fluorobutyrophenone ethylene glycol ketal. The mixture was stirred at 80° for 16 hours and filtered to remove the inorganic salts. The filtrate was concentrated *in vacuo* to an oil residue, which was warmed on a steam bath for 30 minutes with 60 ml. of an ethanolic solution of hydrochloric acid (prepared by mixing 30 ml. of 95% ethanol with 30 ml. of 3*N* hydrochloric acid). The acidic solution was basified with 40% sodium hydroxide and the liberated amine was extracted into ether (3 × 150 ml.). Purification of the crude amine was carried out by passing through a filtering column of alumina (Fisher adsorption), elution with ether afforded a colorless oil which could be converted to a crystalline oxalate in ether; ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.0-3.7 (m, 14, piperidine and aliphatic CH_2), 5.79 (s, 1, CH-O), 6.9-7.81 (m, 11, aromatic H), 8.05-8.65 (m, 2, aromatic H *ortho* to C=O).

Properties of **9a** and of **9b,c** prepared in a similar manner, are given in Table 3.

2-[(1,1'-Biphenyl)-2-yl]-2'-methylspiro[3*H*-indole-3,4'-piperidine] Dihydrobromide (**11**).

A solution of **2** (8.8 g., 40 mmoles) in 50 ml. of anhydrous tetrahydrofuran was added dropwise to a solution of phenylmagnesium bromide (28 ml., 1.9*M*) in the same solvent. The mixture was refluxed under nitrogen for 24 hours and decomposed with an excess of saturated ammonium chloride solution. The organic materials were extracted with ether and dried over potassium carbonate before gc-ms analysis.

A crude separation of **2, 10** and **11** from the remaining products could be effected by column chromatography over silica gel packed in dichloromethane. Elution with 10% methanol-dichloromethane gave fractions which contained a mixture of **2, 10** and **11** (R_f = 0.8-0.7); these were pooled and concentrated *in vacuo* to give a heavy oily residue. Trituration with hexane, followed by standing at 0° for several days, deposited 1.33 g. (9.5%) of **11** of almost analytical purity; further recrystallization from benzene-hexane gave yellowish rhombic crystals, m.p. 168-169°; ir (chloroform): 1488 cm^{-1} (cyclic, conjugated C=N); nmr (deuteriochloroform): δ 0.5-1.1 (m, 2, piperidine CH_2), 1.4-2.1 (m, 2, piperidine CH_2), 2.32 (s, 3, NCH_3), 2.2-2.8 (m, 4, piperidine CH_2), 7.0-8.0 (m, 13, aromatic H), ms: m/e 353 $(MH)^+$.

Anal. Calcd. for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 84.98; H, 6.93; N, 8.13.

2-[(1,1'-Biphenyl)-2-yl]-1'-methylspiro[indoline-3,4'-piperidine] Dihydrobromide (**12**).

A solution of **11** (250 mg., 0.7 mmole) in 10 ml. of tetrahydrofuran was added dropwise to a refluxing slurry of lithium aluminum hydride in 10 ml. of tetrahydrofuran. After 3 hours at reflux, the mixture was decomposed with water in the usual manner to give a crude oil which was converted to a crystalline hydrobromide with ethereal hydrogen bromide. Recrystallization from ethanol-ether gave 220 mg. (61%) of off-white crystals, m.p. 267-270°; ir (potassium bromide): 3450 cm^{-1} (NH); nmr (DMSO-d_6): 1.00-3.52 (m, 11, NCH_3 and piperidine CH_2), 5.01 (d, 1, CH-O), 6.75-8.05 (m, 13, aromatic H); ms: m/e 355 $(MH)^+$.

Anal. Calcd. for $C_{25}H_{28}Br_2N_2$: C, 58.16; H, 5.46; Br, 30.95; N, 5.62. Found: C, 58.22; H, 5.61; Br, 30.83; N, 5.35.

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