Synthesis of 2,3-Dihydrospiro[benzofuran-2,4′-piperidines] and 2,3-Dihydrospiro[benzofuran-2,3′-pyrrolidines]

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The synthesis of 2,3-dihydrospiro[benzofuran-2,4′-piperidines] **3** and 2,3-dihydrospiro[benzofuran-2,3′]-pyrrolidine] **6** is described. The synthesis was achieved by a Grignard reaction of a 2-fluorobenzylhalide with an appropriate cycloazaalkyl ketone to yield the tertiary alcohols **1** and **4**. Subsequent intramolecular displacement of the aromatic fluoride by the derived alkoxides provided the novel system.

Nitration of 1′-acetyl-2,3-dihydrospiro[benzofuran-2,4′-piperidine] **7** resulted in a 5-nitro derivative.

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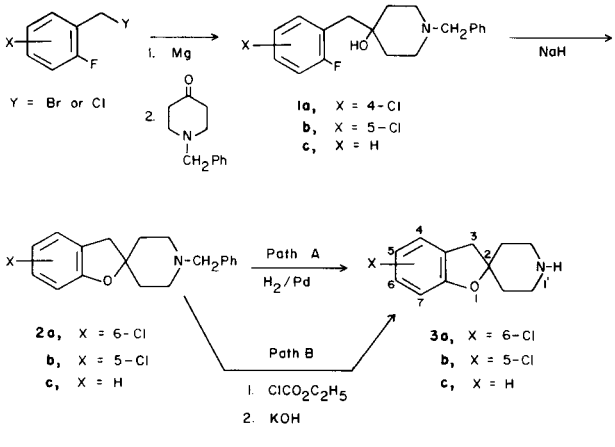
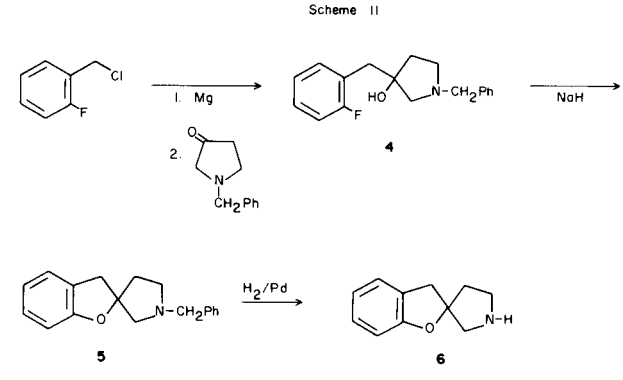
As part of a program to develop unique analgesic and CNS active drugs, our laboratory was interested in synthesizing some novel 2,3-dihydrospiro[benzofuran-2,4′-piperidines] **3** and 2,3-dihydrospiro[benzofuran-2,3′-pyrrolidines] **6**. Our prior experiences in synthesizing aromatic-cycloheteroalkyl ethers by intermolecular aromatic fluoride displacement (1), suggested a facile method to construct the novel ring system by using the same concept, but doing the displacement intramolecularly. Thus, the appropriately substituted 2-fluorobenzyl halide was condensed via a Grignard reaction with 1-benzyl-4-piperidone to give the tertiary piperidinol **1** (2). Reaction of the alcohol with sodium hydride in benzene-dimethylformamide at reflux temperatures readily provided the spriobenzofuran **2**. Debenzylation, either catalytically (path A) or by the use of ethyl chloroformate (3) followed by basic hydrolysis (path B) gave the 1′-unsubstituted structure **3** (Scheme I).

Scheme I



Similarly, use of 1-benzyl-3-pyrrolidinone in the Grignard reaction produced the tertiary pyrrolidinol **4**, which upon cyclizaton and debenzylation yielded compounds **5** and **6**, respectively (Scheme II).

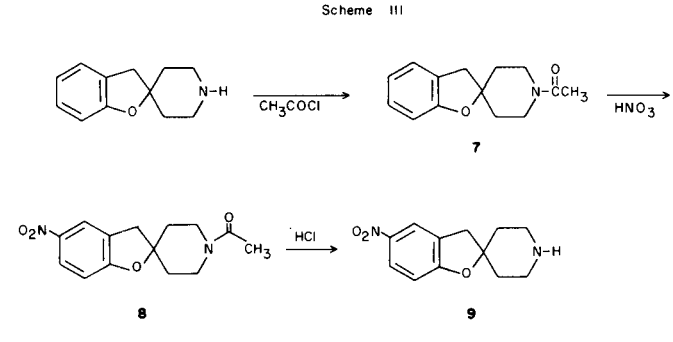
Scheme II



Nitration of the acetylated derivative **7** was accomplished in acetic acid using nitric acid as the nitrating agent. The product **8**, isolated in 63% yield, showed the expected H^1-nmr pattern in the aromatic region for the 5-nitro derivative (4). The nmr showed a one proton doublet (J = 7.5 H) corresponding to H-7, and a two proton multiplet corresponding to H-4 and H-6.

Subsequent acid hydrolysis of **8** yielded the deacylated derivative **9** (Scheme III).

Scheme III



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Jeol C-60HL instrument.

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Chemical shifts are reported as δ units with tetramethylsilane as an internal standard.

Compounds whose synthesis are not described in the text were purchased from commercial sources.

1-Benzyl-4-(4-chloro-2-fluorobenzyl)-4-piperidinol Hydrochloride (**1a**).

To a stirring suspension of 8.5 g. (0.35 mole) of magnesium shavings in 50 ml. of anhydrous ether, under nitrogen, was added a crystal of iodine followed by 3 ml. of 4-chloro-2-fluorobenzyl bromide. The reaction was initiated with a high intensity heat gun, then 60.0 g. (0.27 mole) of 4-chloro-2-fluorobenzyl bromide dissolved in 150 ml. of ether was added dropwise at a rate maintaining reflux. After complete addition, the reaction was stirred and was refluxed for 20 hours. An additional 300 ml. of ether was added, and 47.5 g. (0.25 mole) of 1-benzyl-4-piperidinone in 250 ml. of ether was added dropwise with vigorous stirring. The resulting suspension was stirred at ambient temperature for 2 hours, was filtered and the filter cake was washed well with ether. The filter cake was hydrolyzed by stirring in an ice-ammonium chloride solution (150.0 g. in 1 l. of water). The aqueous solution was extracted with ether and the ether extract was dried over sodium sulfate. The ether was evaporated to give a brown oil, and the oil was distilled at 175-180° (0.18 mm) to give 11.6 g. (13.5%) of orange oil. A hydrochloride salt was prepared by dissolving the oil in ether and adding a solution of ether-hydrogen chloride. The resultant salt was recrystallized four times from ethanol-ether to give the analytically pure hydrochloride, m.p. 211-213°; ir (chloroform): 3060, 2450, 2350, 1600, cm^{-1}; nmr (deuterochloroform): 2.76 (11H, broad m), 4.35 (2H, unresolved d), 7.58 (8H, m), 12.7 (1H, broad s).

Anal. Calcd. for $C_{19}H_{21}ClFNO\cdot HCl$: C, 61.63; H, 5.99; Cl, 19.15; N, 3.78. Found: C, 61.62; H, 6.06; Cl, 19.18; N, 3.81.

1-Benzyl-4-(5-chloro-2-fluorobenzyl)-4-piperidinol Hydrochloride (**1b**).

The compound was prepared as for **1a** using 18.6 g. (0.77 mole) of magnesium, 138.8 g. (0.62 mole) of 5-chloro-2-fluorobenzyl bromide. The product, a brown oil, was distilled at 210° (0.15 mm) to yield 28.3 g. (15.5%) of an orange oil. The compound was characterized as its hydrochloride salt, m.p. 217-219° (from ethanol-ether); ir (potassium bromide): 3350, 2550, 1480, 1000 cm^{-1}; nmr (deuterochloroform + DMSO-d_6): δ 2.00 (4H, broad m), 2.79 (2H, s), 3.17 (4H, m), 4.15 (2H, s), 4.69 (1H, s), 7.33 (8H, m), 11.50 (1H, broad s).

Anal. Calcd. for $C_{19}H_{21}ClFNO\cdot HCl$: C, 61.63; H, 5.99; Cl, 19.15; N, 3.78. Found: C, 61.92; H, 6.01; Cl, 19.03; N, 3.83.

1-Benzyl-4-(2-fluorobenzyl)-4-piperidinol Hydrochloride (**1c**).

The compound was prepared as for **1a** using 2.7 g. (0.11 mole) of magnesium, 14.5 g. (0.1 mole) of 2-fluorobenzyl chloride and 18.9 g. (0.1 mole) of 1-benzyl-4-piperidinone. The resultant yellow oil, 23.7 g. (79%), formed a hydrochloride salt, m.p. 210-211° (from 2-propanol); ir (potassium bromide): 3480, 2700, 2580, 760, 705 cm^{-1}; nmr (DMSO-d_6): δ 1.33 (4H, broad m), 2.60 (6H, m), 4.30 (2H, s), 7.32 (9H, m), 10.35 (1H, broad s).

Anal. Calcd. for $C_{19}H_{22}FNO\cdot HCl$: C, 67.94; H, 6.92; F, 5.66; N, 4.17. Found: C, 67.93; H, 6.94; F, 5.74; N, 4.09.

1'-Benzyl-6-chloro-2,3-dihydrospiro[benzofuran-2,4'-piperidine] Hydrochloride (**2a**).

To a stirring suspension of 1.5 g. (0.031 mole) of sodium hydride (50% oil dispersion) in 100 ml. of benzene, under nitrogen was added dropwise a solution of 8.3 g. (0.024 mole) of 1-benzyl-4-(4-chloro-2-fluoro)-4-piperidinol in 75 ml. of benzene. The reaction was brought to reflux, then 35 ml. of dimethylformamide was added. The reaction was refluxed for 15 minutes, cooled to room temperature, and 100 ml. of water was added dropwise. The reaction was poured into 1 l. of ice water, and the aqueous mixture was extracted with ether. The ether extract was washed with saturated sodium chloride solution, and was dried over sodium sulfate. The ether was evaporated under reduced pressure, and the resultant oil was extracted with boiling hexane. The hexane was evaporated to give 7.1 g. (95%) of a yellow oil which solidified on standing. A hydrochloride salt was prepared by dissolving a sample of the oil in ether and adding a solution of ether-hydrogen chloride. The resultant salt was recrystallized three times from ethanol-ether to yield analytically pure hydrochloride, m.p. 257-259°; ir (chloroform): 2950, 2450, 2350, 1600, 910 cm^{-1}; nmr (deuterochloroform): δ 2.77 (10H, broad m), 4.30 (2H, s), 7.25 (8H, m), 11.80 (1H, broad s).

Anal. Calcd. for $C_{19}H_{20}ClNO\cdot HCl$: C, 65.15; H, 6.04; Cl, 20.24; N, 4.00. Found: C, 65.01; H, 6.07; Cl, 20.11; N, 4.05.

1'-Benzyl-5-chloro-2,3-dihydrospiro[benzofuran-2,4'-piperidine] Hydrochloride (**2b**).

To a stirring suspension of 4.4 g. (0.09 mole) of sodium hydride (50% oil dispersion) in 250 ml. of benzene, under nitrogen, was added dropwise a solution of 21.5 g. (0.065 mole) of 1-benzyl-4-(5-chloro-2-fluoro)-4-piperidinol dissolved in 150 ml. of benzene. The reaction was brought to reflux, then 125 ml. of dimethylformamide was added. The reaction was refluxed for 4 hours, was cooled to ambient temperature, and 100 ml. of water was added dropwise. The reaction was poured into 1 l. of ice water, and the aqueous mixture was extracted with ether. The ether extract was washed with saturated sodium chloride solution, and was dried over sodium sulfate. The ether was evaporated under reduced pressure, and the resultant oil was extracted with boiling hexane. The hexane was evaporated to give 16.5 g. (81%) of yellow oil which solidified on standing. A hydrochloride salt was prepared by dissolving a sample of the oil in ether and addind a solution of ether-hydrogen chloride. The resultant salt was recrystallized three times from ethanol-ether to yield the analytically pure hydrochloride, m.p. 255-258°; ir (chloroform): 2950, 2460, 2370, 1470, 980, 940 cm^{-1}; nmr (deuterochloroform): δ 2.72 (10H, broad m), 4.23 (2H, s), 6.74 (1H, broad d, J = 7.5 Hz), 7.45 (7H, m).

Anal. Calcd. for $C_{19}H_{20}ClNO\cdot HCl$: C, 65.15; H, 6.04; Cl, 20.24; N, 4.00. Found: C, 65.21; H, 6.11; Cl, 20.06; N, 3.98.

1'-Benzyl-2,3-dihydrospiro[benzofuran-2,4'-piperidine] Hydrochloride (**2c**).

To a stirring suspension of 1.4 g., (0.057 mole) of 98% sodium hydride in 50 ml. of dimethylformamide and 10 ml. of benzene, under nitrogen, was added a solution of 1-benzyl-4-(2-fluorobenzyl)-4-piperidinol (6.9 g., 0.023 mole) in 25 ml. of dimethylformamide and 10 ml. of benzene. The reaction was heated at 110-120° with an air condenser (to allow evaporation of benzene) for five hours, then it was allowed to cool to room temperature. The reaction was poured into ice water, and the aqueous suspension was extracted with ether. The ether extract was washed with water, then with saturated sodium chloride solution and was dried over magnesium sulfate. The ether was evaporated to give 2.5 g. (40%) of an oil that solidified to a light yellow solid, m.p. 69-71°. A hydrochloride salt was prepared by dissolving the free base in ether and adding a solution of ether-hydrogen chloride. The resultant white solid was recrystallized from 2-propanol to yield the analytically pure hydrochloride, m.p. 246-247°; ir (chloroform): 2970, 2470, 2360, 1600, 1230, 990, 950 cm^{-1}; nmr (deuterochloroform): δ 2.67 (10H, broad m), 4.16 (2H, unresolved d), 7.15 (9H, m), 11.70 (1H, broad s).

Anal. Calcd. for $C_{19}H_{21}NO\cdot HCl$: C, 72.24; H, 7.03; N, 4.44. Found: C, 71.95; H, 7.06; N, 4.34.

6-Chloro-2,3-dihydrospiro[benzofuran-2,4'-piperidine] Hydrochloride (**3a**).

A solution of 6.1 g. (0.019 mole) of 1'-benzyl-6-chloro-2,3-dihydrospiro[benzofuran-2,4'-piperidine], 2.5 g. (0.022 mole) of ethyl chloroformate and 150 ml. of benzene was stirred at reflux for 18 hours. The reaction was cooled to room temperature, was washed with water, saturated sodium bicarbonate solution, saturated sodium chloride solution, was dried over sodium sulfate, and the solvent was evaporated to give 7.0 g. of a brown oil. The oil was refluxed for 18 hours in 50 ml. of 50% potassium hydroxide solution and 100 ml. of ethanol, then was cooled to ambient temperature and the ethanol was removed under reduced pressure. The remaining aqueous suspension was extracted with ether, the ether extract was washed with 3*N* hydrochloric acid, the acidic wash

was made basic with 6*N* sodium hydroxide solution, the basic solution was extracted with ether and the ether extracts were dried over sodium sulfate. Subsequent evaporation of the solvent yielded 3.2 g. (75.7%) of white solid. The hydrochloride salt was prepared by dissolving 0.5 g. of the piperidine in ether and adding a solution of ether-hydrogen chloride. The precipitate was collected and was recrystallized twice from ethanol to give the analytically pure hydrochloride, m.p. 281-283°; ir (chloroform): 2960, 2750, 2710, 1590, 990, 920 cm^{-1}; nmr (deuterochloroform + DMSO-d_6): δ 2.25 (4H, m), 2.63 (2H, s), 5.06 (4H, m), 7.21 (3H, m), 8.40 (2H, broad s).

Anal. Calcd. for $C_{12}H_{14}ClNO\cdot HCl$: C, 55.40; H, 5.81; Cl, 27.26; N, 5.38. Found: C, 55.21; H, 5.86; Cl, 27.07; N, 5.38.

5-Chloro-2,3-dihydrospiro[benzofuran-2,4′-piperidine] Hydrochloride (**3b**).

A solution of 16.0 g. (0.065 mole) of 1′-benzyl-5-chloro-2,3-dihydrospiro[benzofuran-2,4′-piperidine], 6.9 g. (0.09 mole) of ethyl chloroformate and 500 ml. of benzene was stirred at reflux for 24 hours. The reaction was cooled to room temperature, was washed with water, 3*N* hydrochloric acid, saturated sodium bicarbonate solution, saturated sodium chloride solution, was dried over sodium sulfate and the solvent was evaporated to give 17.0 g. of brown oil. The oil was refluxed for 18 hours in 150 ml. of 50% potassium hydroxide solution and 300 ml. of ethanol, then was cooled to ambient temperature and the ethanol was removed under reduced pressure. The remaining aqueous suspension was extracted with ether, the ether extract was washed with 3*N* hydrochloric acid, the acidic wash was made basic with 6*N* sodium hydroxide solution, the basic solution was extracted with ether, and the ether extracts were dried over sodium sulfate. Subsequent evaporation of the solvent yielded 8.9 g. (61.5%) of off-white solid. The hydrochloride salt was prepared by dissolving 0.5 g. of the piperidine in ether and adding a solution of ether-hydrogen chloride. The precipitate was collected and was recrystallized from ethanol (twice) and ethanol-ether to give the analytically pure hydrochloride, m.p. 217-218; ir (chloroform): 2970, 2700, 2620, 1590, 1000, 980 cm^{-1}; nmr (deuterochloroform): δ 2.15 (4H, broad s), 3.03 (2H, s), 3.45 (4H, m), 6.53 (1H, broad d, J = 6 Hz), 7.03 (2H, m), 8.70 (2H, broad s).

Anal. Calcd. for $C_{12}H_{14}ClNO\cdot HCl$: C, 55.40; H, 5.81; Cl, 27.26; N, 5.38. Found: C, 55.53; H, 5.84; Cl, 27.11; N, 5.40.

2,3-Dihydrospiro[benzofuran-2,4′-piperidine] (**3c**).

A solution of 5.3 g. (0.019 mole) of 1′-benzyl-2,3 dihydrospiro[benzofuran-2,4′-piperidine] in 250 ml. of 2-propanol was hydrogenated over 1 g. of 10% palladium on charcoal catalyst at 50 psi and 65-70°. After the uptake of the theoretical amount of hydrogen, the solution was cooled to ambient temperature, was filtered, and the solvent was evaporated to give a colorless oil which solidified on standing. The solid was dissolved in benzene-ether, was filtered through Celite, and the solvent was evaporated to give a white solid. The solid was triturated with ether and was collected to yield 2.1 g. (58%) of the piperidine as a white solid, m.p. 56-58.5°; ir (chloroform): 2950, 1600, 1250, 990, 645 cm^{-1}; nmr (deuterochloroform): δ 1.85 (5H, m), 3.02 (6H, m), 7.3 (4H, m).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.14; H, 8.00; N, 7.40. Found: C, 76.05; H, 8.08; N, 7.27.

1-Benzyl-3-(2-fluorobenzyl)-3-pyrrolidinol (**4**).

The compound was prepared as for **1a** using 3.4 g. (0.14 mole) of magnesium, 20.6 g. (0.14 mole) of 2-fluorobenzyl chloride and 25.0 g. (0.14 mole) of *N*-benzyl-3-pyrrolidinone. The product was purified by distillation, and yielded 12.2 g. (30%) of yellow, viscous oil which distilled at 135-140° (0.1 mm.) The compound solidified upon standing, m.p. 75-77° (from ethanol-water); ir (chloroform): 3450, 2800, 1580 cm^{-1}; nmr (deuterochloroform): δ 2.40 (7H, m), 3.10 (2H, s), 3.78 (2H, s), 7.46 (9H, m).

Anal. Calcd. for $C_{18}H_{20}FNO$: C, 75.76; H, 7.06; N, 4.91; F, 6.66. Found: C, 75.82; H, 7.20; N, 4.87; F, 6.57.

1′-Benzyl-2,3-dihydrospiro[benzofuran-2,3′-pyrrolidine] (**5**).

To a stirring suspension of 4.7 g. (0.2 mole) of 98% sodium hydride in 125 ml. of benzene and 125 ml. of dimethylformamide at 90° was added dropwise, 38.1 g. (0.13 mole) of 1-benzyl-3-(2-fluorobenzyl)-3-pyrrolidinol dissolved in 500 ml. of benzene-dimethylformamide (50% v/v). The reaction was stirred at 90° for five days, was cooled to ambient temperature, and was poured into 1 l. of ice water. The aqueous mixture was extracted with ether, the ether extract was dried over sodium sulfate, and the ether was evaporated to leave a brown oil. Distillation of the oil gave 24 g. (70%) of a light yellow oil which distilled at 170-175° (0.1 mm.) The oil crystallized, and recrystallization from isopropanol gave the analytically pure pyrrolidine, m.p. 43-45°; ir (chloroform): 2840, 1610, 1500, 1470, 890 cm^{-1}; nmr (deuterochloroform): δ 2.60 (6H, m), 3.35 (2H, s), 3.85 (2H, s), 7.39 (9H, m).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.59; H, 7.39; N, 5.16.

2,3-Dihydrospiro[benzofuran-2,3′-pyrrolidine] Hydrochloride (**6**).

A solution of 21.4 g. (0.08 mole) of 1′-benzyl-2,3-dihydrospiro[benzofuran-2,3′-pyrrolidine], in 200 ml. of 2-propanol was hydrogenated over 2.0 g. of 10% palladium on charcoal catalyst at 47 psi, and 50° until the uptake of hydrogen was complete. The reaction was filtered and the solvent was removed under reduced pressure giving 13.2 g. (75%) of yellow oil. A small amount of the debenzylated material (3.0 g.) was removed, dissolved in ether and hydrogen chloride gas was bubbled into the solution. The precipitate was collected and was recrystallized twice from ethanol-ether to give the analytically pure pyrrolidine hydrochloride, m.p. 174-178°, ir (potassium bromide): 2900, 2750, 1600, 1000, 965 cm^{-1}; nmr (deuterochloroform + DMSO-d_6: δ 2.49 (2H, m), 3.70 (6H, m), 7.25 (4H, m).

Anal. Calcd. for $C_{11}H_{13}NO\cdot HCl$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.17; H, 6.72; Cl, 16.60; N, 6.58.

1′-Acetyl-2,3-dihydrospiro[benzofuran-2,4′-piperidine] (**7**).

To a stirring suspension of 14 g. of sodium bicarbonate and 6.0 g. (0.03 mole) of 2,3-dihydrospiro[benzofuran-2,4′-piperidine] in 75 ml. of chloroform was added dropwise 3 ml. (0.042 mole) of acetyl chloride in 10 ml. of chloroform. The reaction was stirred overnight at ambient temperature, was filtered, was washed with water, dilute acid, dilute base, and saturated sodium chloride solution. The chloroform was dried over sodium sulfate, and was evaporated to give 6.9 g. of yellow oil which solidified on standing. The solid was recrystallized twice from hexane to yeild 4.0 g. (62%) of white crystals of the piperidine, m.p. 94-97°; ir (chloroform): 3000, 1630, 1480, 1000, 970 cm^{-1}; nmr (deuterochloroform): δ 1.85 (7H, m), 3.11 (2H, s), 3.57 (3H, m), 4.40 (1H, m), 7.35 (4H, m).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.86; H, 7.47; N, 6.08.

1′-Acetyl-2,3-dihydro-5-nitrospiro[benzofuran-2,4′-piperidine] (**8**).

To a stirring solution of 4.7 g. (0.02 mole) of 1′-acetyl-2,3-dihydrospiro[benzofuran-2,4′-piperidine] in 65 ml. of glacial acetic acid was added dropwise 3.8 g. of nitric acid (sp. gr. 1.42) in 30 ml. of glacial acetic acid. The reaction was brought to 100° over a period of two hours at which time it was cooled and was poured into 500 ml. of water and was extracted with chloroform. The chloroform extract was washed with saturated sodium bicarbonate solution, saturated sodium chloride solution and was dried over sodium sulfate. The solvent was evaporated and the residue was triturated with ether. The resultant orange precipitate was collected and was recrystallized from ethanol-ether and then from ethanol to give 3.5 g. (63.5%) of the nitrobenzofuran m.p. 149-150°; ir (chloroform): 1630, 1520, 1340, 1000, 965 cm^{-1}; nmr (deuterochloroform): δ 1.94 (4H, m), 2.25 (3H, s), 3.26 (2H, s), 2.70 (3H, m), 4.45 (1H, broad m) 7.17 (1H, d, J = 7.5 Hz), 8.47 (2H, m).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.83; H, 5.82; N, 10.14.

2,3-Dihydro-5-nitrospiro[benzofuran-2,4'-piperidine] Hydrochloride (**9**).

A solution of 3.4 g. (0.012 mole) of 1'-acetyl-2,3-dihydro-5-nitrospiro[benzofuran-2,4'-piperidine] in 150 ml. of 6*N* hydrochloric acid was refluxed for 4.5 hours, then stirred at ambient temperature for 16 hours. The reaction mixture was extracted with ether, was made basic with 6N sodium hydroxide solution, then was extracted with ether. The ether extract was dried over sodium sulfate, and the solvent was evaporated to give a yellow oil. The oil was dissolved in ether, and a solution of ether-hydrogen chloride was added. The precipitate was collected and was recrystallized twice from ethanol to give 1.4 g. (45%) of the piperidine hydrochloride m.p. 265-266°; ir (potassium bromide): 3000, 2800, 1600, 1510, 1340, 985 cm^{-1}; nmr (DMSO-d_6): δ 1.72 (4H, m), 3.33 (6H, m), 7.32 (1H, d, J = 7.5 Hz), 8.47 (2H, m).

Anal. Calcd. for $C_{12}H_{14}N_2O_3 \cdot HCl$: C, 53.24; H, 5.59; N, 10.35. Found: C, 53.36; H, 5.77; N, 10.28.

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