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Received March 30, 1987

As part of an on-going research project, we required an efficient method for the preparation of compounds containing the 1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine ring nucleus. The parent compound **1** has not been described in the literature, and there is only one reference to the *N*-methyl analog **2** [1]. A series of structurally related compounds, the 2-substituted-4-hydroxy-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridines, has been described [2].

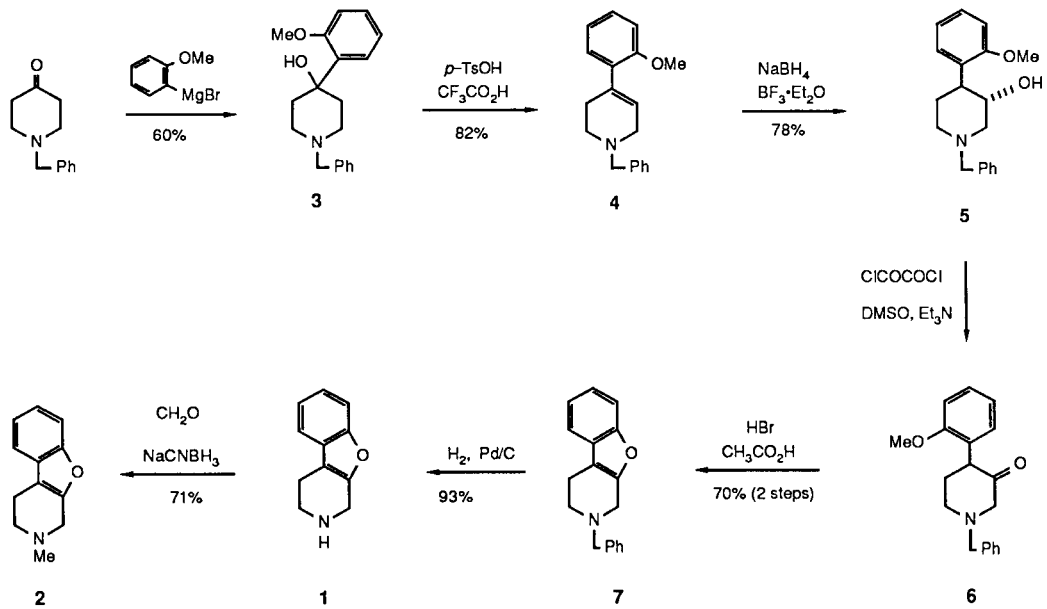
J. Heterocyclic Chem., **24**, 1317 (1987).

Our synthesis of compounds **1** and **2** is described in Scheme I. 1-Benzyl-4-piperidone was treated with (2-methoxyphenyl)magnesium bromide to produce alcohol **3**. Dehydration of **3** with trifluoroacetic acid and *p*-toluenesulfonic acid yielded alkene **4**. Regioselective hydroboration of **4** was achieved with diborane, generated *in situ* from sodium borohydride and boron trifluoride in diglyme [3]. The use of commercial diborane reagents led to the quantitative recovery of unreacted alkene **4**. The highly crystalline alcohol **5** was readily converted to ketone **6** by a Swern oxidation [4]. Treatment of **6** with hydrobromic acid in glacial acetic acid effected the hydrolysis of the methyl ether and formation of the furan ring, yielding 2-benzyl-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine (**7**) in 70% yield. Removal of the benzyl group proceeded smoothly under catalytic hydrogenation conditions to yield the target compound **1**.

This five step sequence was easily carried out on a 50 g scale. The high crystallinity of alcohols **3** and **5**, which allowed their purification by recrystallization, and the lack of by-products in the reactions leading to **4**, **6**, **7** and **1** makes this procedure particularly attractive for the preparation of large amounts of 1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine (**1**). In addition, the availability of a large number of substituted 2-methoxyphenyl Grignard reagents should make the synthetic method reported here suitable to the preparation of other 5, 6, 7 or 8-substituted 1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridines.

The *N*-methyl derivative **2** was prepared by reductive alkylation of **1** with formaldehyde and sodium cyanoborohydride under acidic conditions. This compound contains as part of its structure the elements of the recently described neurotoxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [5]. Thus, until its biological activity has

Scheme I



been explored in detail, we suggest that compound **2** be handled with extreme caution.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained on a Nicolet MX-1 FT spectrometer. The main bands are described by their frequency (cm^{-1}) and their relative intensity (weak, medium, strong). The proton nmr spectra were obtained on a IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz). The peaks are described in ppm downfield from tetramethylsilane (internal standard). The carbon nmr spectra were obtained with a Varian XL 300 nmr spectrometer (300 MHz). The spectra recorded on the Varian spectrometer are indicated by an asterisk. The Mass Spectra were recorded on a Finnigan 4500 Mass Spectrometer or a VG Analytical 7070E/HF Mass Spectrometer; the latter instrument was used for exact mass determinations. The main peaks are given, followed by their relative intensities in parenthesis.

1-Benzyl-4-hydroxy-4-(2-methoxyphenyl)piperidine (**3**).

Magnesium chips (13.0 g, 0.534 mole) were placed in a dry 3-liter 3-neck round bottom flask equipped with a reflux condenser, an addition funnel and a dry nitrogen inlet. The flask was charged with 1250 ml anhydrous tetrahydrofuran under a nitrogen atmosphere. A solution of 2-bromoanisole (75.0 g, 0.401 mole) and 1,2-dibromoethane (25.0 g, 0.133 mole) in 100 ml tetrahydrofuran was placed in the addition funnel. About 2 ml of this solution was added to the flask all at once while magnetically stirring its contents. An iodine crystal was also added to initiate the reaction. Once the reaction began, the rest of the solution was added dropwise, controlling the rate of addition as to maintain a gentle reflux of the solvent. When all the magnesium was consumed, a solution of 1-benzyl-4-piperidone [6] (76.0 g, 0.401 mole) in 150 ml tetrahydrofuran was added dropwise. Following addition, the solution was refluxed for 20 minutes, then stirred at room temperature for two hours. The flask was placed in an ice bath and 10% hydrochloric acid was added dropwise until the *p*H of the mixture was 1-2. At this point, the hydrochloride salt of **3** precipitated. The solvent was decanted, and the salt was recrystallized from ethanol (150 ml)/ethyl acetate (750 ml). A first crop of 50.6 g (0.151 mole, 38%) was obtained, mp = 213-214° dec, followed by a second crop of 30.0 g (0.090 mole, 22%), mp = 208-210° dec, which were combined for the next step, combined yield, 60%, nmr (deuteriochloroform): 2.20 (2H, broad d, J = 17 Hz), 2.60-3.15 (2H, m), 3.20-3.50 (4H, m), 3.90 (3H, s), 4.20 (2H, d, J = 7 Hz), 6.90-7.05 (2H, m), 7.20-7.35 (2H, m), 7.35-7.55 (3H, m), 7.60-7.80 (2H, m); ir (potassium bromide): 758 (s), 1244 (s), 1456 (s), 1599 (w), 2900 (m), 3250 (s); ms: 297 (M, 24), 279 (20), 206 (47), 91 (100).

Anal. Calcd. for $C_{19}H_{23}NO_2 \cdot HCl \cdot (0.5\ H_2O)$: C, 66.56; H, 7.34; N, 4.08; Cl, 10.34. Found: C, 66.33; H, 7.04; N, 4.04; Cl, 10.44.

1-Benzyl-1,2,3,6-tetrahydro-4-(2-methoxyphenyl)pyridine (**4**).

Compound **3**·HCl (79.5 g, 0.238 mole) was dissolved in 1200 ml toluene, treated with trifluoroacetic acid (40.0 g, 0.349 mole) and *p*-toluenesulfonic acid (9.0 g, 0.052 mole) and heated at reflux using a Dean-Stark trap until no more water separated (about five hours). After cooling to room temperature, an equal volume of 10% sodium bicarbonate solution was added. The organic layer was dried and filtered through a short length of silica gel, using ethyl acetate, to remove origin material. After evaporation of the solvent, a light yellow oil remained which was characterized spectroscopically as **4** (54.7 g, 0.196 mole, 82%); nmr* (deuteriochloroform): 2.551-2.573 (2H, m), 2.675-2.713 (2H, m), 3.168-3.197 (2H, broad s), 3.661 (2H, s), 3.798 (3H, s), 5.762-5.784 (1H, broad s), 6.839-6.927 (2H, m), 7.155-7.412 (7H, m); ir (liquid film): 754 (s), 1252 (s), 1491 (s), 2798 (m), 2900 (m), 3027 (w); ms: 279 (M, 100); 91 (62).

trans-1-Benzyl-4-(2-methoxyphenyl)-3-piperidinol (**5**).

Sodium borohydride (11.90 g, 0.313 mole) was added at once to a solution of **4** (54.7 g, 0.196 mole) in 200 ml anhydrous diglyme (predried over calcium hydride, then distilled from lithium aluminum hydride *in vacuo*). The flask was placed in an ice bath for five minutes; the bath was then removed, and a solution of boron trifluoride etherate (55.57 g, 0.391 mole) in 50 ml diglyme was added dropwise under a nitrogen atmosphere [3]. Following this addition, stirring was continued at 25° for two hours. Water (17 ml) was then added to the reaction mixture very slowly, followed by 6*N* sodium hydroxide (51 ml). The flask was placed in a water bath at 50° and 30% hydrogen peroxide (46.5 ml, 0.405 mole) was added over a period of one hour. Stirring was continued at 50° for another 45 minutes. Concentrated hydrochloric acid (46.5 ml) was added, and the solvents were evaporated *in vacuo*. Water (200 ml) was added to the residue, and the evaporation was repeated. The residue was partitioned between dichloromethane and 2% ammonium hydroxide solution. The organic layer was dried (magnesium sulfate) and evaporated to give a clear oil containing a white solid. Recrystallization from ethyl acetate yielded **5** as a white solid, mp, 118-122° (45.2 g, 0.152 mole, 78% yield); nmr* (deuteriochloroform): 1.791-2.180 (5H, m), 2.910-3.045 (2H, m), 3.184-3.256 (1H, dd, J = 10.4, 4.0 Hz), 3.615 (2H, s), 3.827 (3H, s), 3.785-3.949 (1H, m), 6.892 (1H, d, J = 8.5 Hz), 6.974 (1H, t, J = 7.5 Hz), 7.188-7.416 (7H, m); ir (potassium bromide): 709 (m), 751 (m), 1242 (s), 1495 (s), 1601 (w), 2824 (w), 2940 (m); ms: 297 (M, 7), 279 (4), 268 (4), 206 (7), 91 (100).

Anal. Calcd. for $C_{19}H_{23}NO_2$ (0.25 H_2O): C, 75.59; H, 7.84; N, 4.64. Found: C, 75.68; H, 7.58; N, 4.59.

1-Benzyl-4-(2-methoxyphenyl)-3-piperidone (**6**).

Oxalyl chloride (37.75 g, 0.30 mole) was dissolved in 400 ml dry dichloromethane under a nitrogen atmosphere. The solution was cooled to -60° (chloroform/Dry Ice bath). Dimethylsulfoxide (46.8 g, 0.60 mole) was added dropwise [4]. After ten minutes, a solution of alcohol **5** (44.5 g, 0.149 mole) in 200 ml dichloromethane was added dropwise. Stirring was continued for 30 minutes, and triethylamine (150 ml) was added over a period of 15 minutes. The flask was kept at -60° for another ten minutes; the cold bath was removed, and the reaction was allowed to warm up to room temperature. The reaction was worked-up by repeated extractions between dichloromethane and water. The combined organic extracts were successively washed with 2% hydrochloric acid, 10% sodium bicarbonate solution and brine, then dried over magnesium sulfate. The solvent was evaporated *in vacuo*, leaving a thick oil. The homogeneity of this material was assessed by tlc (silica gel, 1% ammonium hydroxide in ethyl acetate, R_f = 0.72), and it was carried on to the next step without purification; nmr (deuteriochloroform): 2.04-2.43 (2H, m), 2.54-2.67 (1H, m), 2.96 (1H, d, J = 14.1 Hz), 3.09 (1H, br d, J = 12 Hz), 3.41 (1H, dd, J = 14.2, 1.7 Hz), 3.67 (2H, d, J = 1.4 Hz), 3.78 (3H, s), 3.74-3.94 (1H, m), 6.87-6.99 (2H, m), 7.12 (1H, dd, J = 7.5, 1.7 Hz), 7.18-7.45 (6H, m); ir (liquid film): 1673 (s), 1723 (s), 2941 (m); ms: 295 (M, 12), 267 (44), 91 (100).

2-Benzyl-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine (**7**).

The crude ketoamine **6** obtained in the previous step was dissolved in 150 ml glacial acetic acid. To this solution, 300 ml of 48% hydrobromic acid was added, and the mixture was refluxed under nitrogen for four hours. After cooling to room temperature, the reaction mixture was poured over 1700 ml of ice-cold ethyl acetate containing 250 ml of concentrated ammonium hydroxide. The organic phase was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. Analysis (tlc) of the crude reaction product indicated the presence of a single component (R_f = 0.67, silica, 1% ammonium hydroxide in ethyl acetate), plus a small amount of origin material. Following purification by flash-chromatography (silica; ethyl acetate:hexane, 2:1), the title compound was obtained as a light colored oil which easily crystallized when triturated with about 50 ml of ether, mp 82-84° (26.1 g, 70% from **5**); nmr* (deuteriochloroform): 2.706-2.763 (2H, m), 2.856-2.916 (2H, m), 3.673 (2H, t, J = 1.8 Hz), 3.788 (2H, s), 7.187-7.455 (9H, m); ir (potassium bromide): 754 (s), 1454 (m), 1652 (w), 2910 (w); ms: 263 (M, 49), 144 (100), 115 (26), 91 (51).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.50; N, 5.32. Found: C, 81.84; H, 6.63; N, 5.22.

1,2,3,4-Tetrahydrobenzofuro[2,3-*c*]pyridine (**1**).

Compound **7** (5.26 g, 20 mmoles) was dissolved in 98.5 ml methanol, treated with 1.5 ml glacial acetic acid and 1 g of 20% palladium on carbon. The mixture was hydrogenated in a Parr shaker (T = 24°, P = 3 atmospheres of hydrogen) until the theoretical amount of hydrogen was taken up (about 20 hours). The catalyst was filtered and the filtrate was evaporated *in vacuo*, leaving a semi-solid residue which was partitioned between toluene (250 ml) and 2% ammonium hydroxide (150 ml). The organic layer was washed with brine and dried over magnesium sulfate. The resulting solution was diluted with an equal volume of ether, and a solution of hydrogen chloride in ether was added dropwise until no more precipitation occured. The salt formed was filtered and dried. An off-white solid was obtained, mp 275° dec, (3.90 g, 93%), which was characterized as the hydrochloride salt of **1**; tlc, R_f = 0.14, silica, 1% ammonium hydroxide in ethyl acetate; nmr* (dimethylsulfoxide-d_6): 2.912-2.949 (2H, m), 3.426-3.466 (2H, m), 4.365 (2H, s), 7.263-7.359 (2H, m), 7.543-7.600 (2H, m); ir (potassium bromide): 753 (s), 1434 (s), 1578 (w), 2443 (m), 2750 (s), 2910 (s); ms: 173 (M, 42), 172 (M-1, 48), 144 (100), 115 (24).

Anal. Calcd. for $C_{11}H_{11}NO\cdot HCl$: C, 63.01; H, 5.76; N, 6.68; Cl, 16.91. Found: C, 62.99; H, 5.92; N, 6.38; Cl, 16.47.

2-Methyl-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine (**2**).

A solution of 1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine hydrochloride (**1**·HCl) (0.63 g, 3 mmoles) in 50 ml methanol, containing a couple of methyl orange crystals, was treated at once with 0.75 ml (10 mmoles) of a 35% aqueous formaldehyde solution, followed by sodium cyanoborohydride (0.63 g, 10 mmoles). During the next ten minutes, enough 10% hydrochloric acid was added, dropwise, to maintain a red color in the solution. After this time, the color no longer remained, and the solution was stirred for another 45 minutes. The solvent was evaporated *in vacuo*, and the residue was partitioned between ethyl acetate (50 ml) and 1% ammonium hydroxide (50 ml).

The organic layer was washed with brine and dried over magnesium sulfate. Following filtration of the drying agent, the organic solution was treated with an excess of hydrogen chloride ethereal solution. The solvent was evaporated *in vacuo* and the residue was recrystallized from methanol/ethyl acetate to yield the hydrochloride salt of **2**, mp 305° dec, (0.49 g, 71%); nmr (dimethylsulfoxide-d_6): 2.96 (3H, s), 3.03 (2H, broad s), 3.54 (2H, broad s), 4.50 (2H, broad s), 7.28-7.38 (2H, m), 7.58-7.64 (2H, m); ^{13}C-nmr (dimethylsulfoxide-d_6): 17.48, 41.69, 48.85, 50.36, 110.70, 111.34, 119.49, 123.24, 124.74, 126.33, 144.92, 154.31; ir (potassium bromide): 762 (s), 1453 (s), 1648 (w), 2523 (s), 3066 (w); ms: 187 (M, 36), 186 (M-1, 21), 144 (100), 115 (27); Calcd. for exact mass for $C_{12}H_{13}NO$: 187.0997. Found: 187.10052.

Anal. Calcd. for $C_{12}H_{13}NO\cdot HCl$: C, 64.43; H, 5.85; N, 6.26; Cl, 15.85. Found: C, 64.09; H, 6.18; N, 5.88; Cl, 16.01.

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