Pyrrolo[2,1-c][1,4]benzoxazepines. 2. Synthesis of 5-Phenyl Derivatives

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A series of 5-phenylpyrrolo[2,1-c][1,4]benzoxazepines with basic substituents at the 11-position has been synthesized utilizing a nucleophilic aromatic fluoride displacement-cyclization. Piperidinyl derivatives were prepared by Vilsmeier formylation of the key 1-[(2-fluorophenyl)phenylmethyl]pyrrole (4) followed by addition of a piperidinyl Grignard reagent and cyclization of the resulting carbinol. A (dimethylamino)methyl derivative was prepared via an analogous cyclization of α -(dimethylamino)methyl-1-[(2-fluorophenyl)phenylmethyl]-1H-pyrrole-2-methanol (10), obtained by the Hoeben-Hoesch acylation of 4 with chloroacetonitrile, addition of dimethylamine to the resulting α -chloroketone 8, and reduction of the α -(dimethylamino)ketone 9 with sodium borohydride to give 10.

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We have previously reported a synthesis of some pyrrolo[2,1-c][1,4]benzoxazepines I with antinociceptive and central nervous system (CNS) depressive activity [1]. In a continuing effort to develop pyrrole-containing heterocycles with CNS activity, we have expanded upon our previous results and report here the synthesis of a series of 5phenylpyrrolo[2,1-c][1,4]benzoxazepines with basic substituents at the 11-position (II).

The synthesis of these compounds is illustrated in Schemes 1, 2 and 3. The key 1-[(2-fluorophenyl)phenylmethyl]pyrrole (4) was synthesized from the condensation of the known α-(2-fluorophenyl)benzenemethanamine (3) [2] with 2,5-dimethoxytetrahydrofuran according to the procedure of Clauson-Kaas and Tyle [3] (Scheme 1). Vilsmeier formylation of this pyrrole (Scheme 2) gave the 2-aldehyde 5 in a ratio of almost 4:1 with the 3-isomer. Aldehyde 5 reacted cleanly with the Grignard reagent derived from an N-substituted 4-chloropiperidine to give the substituted methanols 6a and 6b as single diastereo-

mers in each case ('H nmr, see Experimental section). As in the previous synthesis of the parent pyrrolobenzoxaze-pine [1], treatment of the alcohols **6a** and **6b** with sodium hydride effected the ring closure to **7a** and **7b** via a nucleophilic aromatic fluoride displacement.

Alternatively, pyrrole 4 could be reacted with chloroacetonitrile in a Hoeben-Hoesch acylation [4] using zinc chloride as a catalyst to give 1-{[(2-fluorophenyl)phenylmethyl]pyrrol-2-yl}-2-chloroethanone (8) as the product. Condensation of this α-chloroketone with dimethylamine in methanol gave the α-aminoketone 9 in good yield. Ketone 9 was then reduced with sodium borohydride to give an inseparable mixture of diastereomeric alcohols 10 which was cyclized under these conditions described above for 6a and 6b to give 7c, also as a mixture of diastereomers. This mixture could be separated by preparative hplc, giving a major and a minor diastereomer, 7c' and 7c'', respectively.

The major diastereomer of the (dimethylamino)methyl compound 7c' was monodealkylated according to Scheme 3. Treatment of 7c' with ethyl chloroformate gave the ethyl carbamate 11 which was then hydrolyzed with ethanolic sodium hydroxide solution to give 11-(methylamino)methyl-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]benzoxazepine (12).

Scheme I

Preliminary biological testing has shown these compounds to have antinociceptive activity and to be active in animal models of genetic hypertension. These compounds are currently undergoing more extensive evaluation in our laboratories.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 and nuclear magnetic resonance spectra were taken on a Gemini 200 instrument, except the compounds noted were taken on a JEOL C60HL instrument. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectral data were determined by direct insertion at 70 eV with a Finnigan 4500 GC-MS equipped with a INCOS data system. The preparative hplc purifications were performed on a Waters Prep LC/System 500A using silica gel cartridges. Flash chromatographic separations were performed using E. Merck 230-400 mesh silica gel as the solid phase. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Il.

Although this compound is known in the literature [2], its preparation has not been described in detail. To a solution of the known oxime 2 [5] (50.0 g, 0.232 mole) in 500 ml of 200° ethanol, in a high pressure reaction vessel, was added a slurry of a Raney Ni alloy (5 g, Grace 4200). The mixture was saturated with ammonia gas, pressurized to 500 psi with hydrogen gas and then shaken for 6 hours at 90°. The reaction was then cooled, the catalyst was filtered and the solvent removed to give 93% of an oil (97% gc purity, OV-101, 200°) which was used without further purification; 'H nmr (deuteriochloroform, 60 MHz): δ 1.82 (br s, 2H, N H_2 , exchanges with deuterium oxide), 5.50 (s, 1H, Ar₂CH), 6.80-7.70 (m, 9H, aromatic); ms: m/z 201 (M*).

1-[(2-Fluorophenyl)phenylmethyl]pyrrole (4).

To 100 ml of chilled acetic acid was added 13.09 g (0.065 mole) of compound 3. This was followed by the addition of 8.6 g (0.065 mole) of 2,5-dimethoxytetrahydrofuran. The mixture was heated at reflux for 1.5 hours after which the solvent was evaporated and the residue was taken up in diethyl ether. The organics were washed sequentially with saturated sodium bicarbonate solution, water and saturated sodium chloride solution and then dried over magnesium sulfate. Purification by distillation (bp 117°/0.15 mm Hg) gave 11.33 g (70%) of a slightly yellow solid which was recrystallized from acetonitrile to give analytically pure 4, mp 81-82.5°; 'H nmr (deuteriochloroform): δ 6.20 (m, 2H, H-3,4 pyr-

role), 6.61 (m, 2H, H-2,5 pyrrole), 6.78 (s, 1H, Ar₃CH), 6.81 (m, 1H, aromatic), 7.10 (m, 4H, aromatic), 7.30 (m, 4H, aromatic); ms: m/z 251 (M⁺).

Anal. Calcd. for C₁₇H₁₄FN: C, 81.25; H, 5.62; N, 5.57. Found: C, 81.02; H, 5.51; N, 5.71.

1-[(2-Fluorophenyl)phenylmethyl]pyrrole-2-carboxaldehyde (5).

To cooled N.N-dimethylformamide (2.92 g, 0.04 mole) was added phosphorus oxychloride (6.13 g, 0.04 mole). This mixture was stirred for 20 minutes then brought to room temperature. The reaction mixture was diluted with 35 ml of 1,2-dichloroethane and to this was added compound 4 (10.0 g, 0.04 mole) dissolved in 80 ml of 1,2-dichloroethane. The reaction mixture was then heated at reflux for 3.5 hours, cooled and to this was added a solution of sodium acetate trihydrate in 75 ml of water. Reflux was continued for 1 hour after which the layers were separated and the aqueous phase was extracted with ethyl ether. The combined organics were washed with water and saturated sodium chloride solution and then dried over magnesium sulfate. Concentration of the solvents gave an oil, the components of which were purified via flash chromatography (eluent: dichloromethane) to give 7.33 g (66%) of 5, and 17% of the corresponding 3-carboxaldehyde. Recrystallization of the 2-isomer from ethyl ether/petroleum ether (1:3) gave analytically pure 5, mp 80-83.5°; ir (chloroform): ν cm⁻¹, 1665 (C = 0); ¹H nmr (DMSO): δ 6.32 (m, 1H, H-4 pyrrole), 6.70 (m, 1H, aromatic), 6.78 (m, 1H, H-3 pyrrole), 7.10 (m. 2H, aromatic), 7.20 (m. 1H, H-5 pyrrole), 7.22 (m. 2H, aromatic), 7.40 (m, 4H, aromatic), 7.83 (s, 1H, Ar₃CH), 9.52 (s, 1H, CHO); ms: m/z 279 (M*).

Anal. Calcd. for C₁₈H₁₄FNO: C, 77.40; H, 5.05; N, 5.02. Found: C, 77.51; H, 5.06; N, 4.88.

 α -(1-Methyl-4-piperidinyl)-1-[(2-fluorophenyl)phenylmethyl]-1 H-pyrrole-2-methanol (**6a**).

To the Grignard reagent generated from the reaction of magnesium turnings (0.53 g, 0.022 g-atom) and 4-chloro-1-methyl piperidine (2.79 g, 0.021 mole) in 25 ml of a 10% ethyl ether/tetrahydrofuran solution was added compound 5 (2.92 g, 0.011 mole) in 30 ml of 10% ethyl ether/tetrahydrofuran. The reaction was refluxed for 1 hour after which time the solvent was reduced by 1/2 and then treated with an iced ammonium chloride solution. The aqueous was extracted with ethyl ether and the combined organics were washed sequentially with water and saturated sodium chloride and then dried with anhydrous magnesium sulfate. Concentration of the solvent and trituration of the residue with ethyl ether/petroleum ether gave 3.76 g (90%) of a yellow solid. Recrystallization from hexane/ethanol gave pure 6a as slightly yellow crystals, mp 121.5-124°; 'H nmr (deuteriochloroform): δ 1.02 (m, 1H, aliphatic), 1.37 (m, 2H, aliphatic), 1.65 (m, 2H, aliphatic), 1.87 (m, 1H, aliphatic), 2.12 (m, 2H, 1 aliphatic, OH exchanges with deuterium oxide), 2.20 (s, 3H, NCH₃), 2.66 (m, 1H, aliphatic), 2.86 (m, 1H, aliphatic), 4.27 (d, 1H, CHOH), 6.07 (m, 1H, H-4 pyrrole), 6.15 (m, 1H, H-3 pyrrole), 6.38 (m, 1H, H-5 pyrrole), 6.75 (m, 1H, aromatic), 6.97 (m, 1H, aromatic), 7.03 (s, 1H, Ar₃CH), 7.10 (m, 4H, aromatic), 7.30 (m, 3H, aromatic); ms: m/z 378 (M⁺).

Anal. Calcd. for $C_{24}H_{27}FN_2O$; C, 76.16; H, 7.19; N, 7.40. Found: C, 75.91; H, 7.02; N, 7.48.

 α -(1-Benzyl-4-piperidinyl)-1-[(2-fluorophenyl)phenylmethyl]-1H-pyrrole-2-methanol (**6b**).

This compound was prepared in 35% yield from 1-benzyl-4-chloropiperidine, magnesium turnings and compound 5 in a manner analogous to that described for compound 6a. After preparative hplc purification (hexane,ethyl acetate,diethylamine; 80:20:1), the oxalate salt was formed and this was recrystallized from isopropyl ether/ethanol to give 6b oxalate as a white solid, mp 130° dec; 'H nmr (deuteriochloroform, free base): δ 1.05 (m, 1H, aliphatic), 1.25 (m, 2H, aliphatic), 1.75 (m, 4H, 3 aliphatic, OH exchanges with deuterium oxide), 2.05 (m, 1H, aliphatic), 2.72 (m, 1H, aliphatic), 2.92 (m, 1H, aliphatic), 3.43 (s, 2H, CH₂C₆H₅), 4.28 (d, 1H, CHOH), 6.08 (m, 1H, H-4 pyrrole), 6.18 (m, 1H, H-3 pyrrole), 6.38 (m, 1H, H-5 pyrrole), 6.73 (m, 1H, aromatic), 7.05 (m, 5H, 4 aromatic, Ar₃CH), 7.30 (m, 9H, aromatic).

Anal. Calcd. for C₃₀H₃₁FN₂O·C₂H₂O₄: C, 70.57; H, 6.11; N, 5.14. Found: C, 70.69; H, 6.39; N, 4.75.

11-(1-Methyl-4-piperidinyl)-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]-benzoxazepine (7a).

To a suspension of sodium hydride (obtained from 0.764 g of 50% suspension in oil, washed with hexane) in 20 ml of benzene, was added a solution of compound **6a** (4.8 g, 0.013 mole) in 50 ml of 20% dimethylformamide/benzene. After stirring for 3 hours at 80°, the reaction was quenched into water and the aqueous phase was extracted with ethyl ether. The organic phase was washed with water, saturated sodium chloride, dried with magnesium sulfate and the solvent was concentrated *in vacuo* to give 80% of a white solid. This was recrystallized from ethyl ether/petroleum ether to give pure **7a**, mp 183-186°; 'H nmr (deuteriochloroform): δ 1.07 (m, 1H, aliphatic), 1.38 (m, 1H, aliphatic), 1.77 (m, 1H, aliphatic), 2.05 (m, 4H, aliphatic), 2.23 (s, 3H, NC H_3), 2.60 (m, 1H, aliphatic), 2.76 (m, 1H, aliphatic), 4.58 (d, 1H, H-11), 6.20 (m, 3H, H-1, 2, and 3), 6.90 (m, 4H, H-5 and aromatic), 7.23 (m, 5H, aromatic); ms: m/z 358 (M*).

Anal. Calcd. for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.52; H, 7.30; N, 7.82.

11-(1-Benzyl-4-piperidinyl)-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]-benzoxazepine (**7b**).

Compound 7b was prepared in a manner analogous to that described for compound 7a. The compound was purified as its oxalate salt in 67% yield after recrystallization from ethyl acetate/methanol, mp 176-180°; ¹H nmr (DMSO): δ 1.13 (m, 1H, aliphatic), 1.42 (m, 1H, aliphatic), 1.78 (m, 1H, aliphatic), 2.20 (m, 2H, aliphatic), 2.77 (m, 2H, aliphatic), 3.00 (m, 1H, aliphatic), 3.18 (m, 1H, aliphatic), 4.04 (s, 2H, NCH₂C₆H₅), 4.50 (d, 1H, H-11), 6.10 (m, 1H, H-2), 6.27 (m, 1H, H-1), 6.60 (br s, 2H, CO₂H, exchanges with deuterium oxide), 6.65 (s, 1H, H-5), 6.73 (d, 1H, aromatic), 6.88 (d, 1H, aromatic), 7.02 (dd, 1H, aromatic), 7.20 (m, 1H, H-3), 7.33 (m, 9H, aromatic); ms: m/z 434 (M*).

Anal. Calcd. for $C_{30}H_{30}N_2O \cdot C_2H_2O_4$: C, 73.26; H, 6.15; N, 5.34. Found: C, 73.09; H, 6.17; N, 5.33.

1-{[(2-Fluorophenyl)phenylmethyl]pyrrol-2-yl}-2-chloroethanone (8).

A cooled mixture of chloroacetonitrile (11.3 g, 0.15 mole) and zinc chloride (10.2 g, 0.075 mole) in 100 ml of diethyl ether was saturated with gaseous hydrogen chloride. A solution of compound 4 was then added and this was stirred for 6 hours. The resulting solid was collected, added to water and heated at 95° for 2 hours. The aqueous phase was then cooled and extracted with ethyl ether. The organics were washed with water, saturated sodium chloride and dried with anhydrous magnesium sulfate.

The solvent was evaporated to give 83% of **8** as an oil, a portion of which was crystallized from methanol giving a white solid, mp 86-91°. This was used without further purification; ir (chloroform): ν 1660 cm⁻¹ (C=0); ¹H nmr (deuteriochloroform, 60 MHz): δ 4.47 (s, 2H, COCH₂Cl), 6.17-6.35 (m, 1H, H-4 pyrrole), 6.53-6.90 (m, 2H, H-3 and 5 pyrrole), 6.90-7.55 (m, 9H, aromatic), 8.09 (s, 1H, Ar₃CH); ms: m/z 327 (M⁺).

1-{[(2-Fluorophenyl)phenylmethyl]pyrrol-2-yl}-2-dimethylaminoethanone (9).

To a solution of methanol saturated with dimethylamine was added a solution of compound 8 (20.4 g, 0.06 mole) in 500 ml of methanol. This was heated at 85° for 2 hours. The mixture was cooled, the solvent concentrated and the residue was treated with water and extracted with ethyl ether. The organics were sequentially washed with water and saturated sodium chloride and then dried with anhydrous magnesium sulfate. The solvent was concentrated to give 89% of compound 9 as an oil. A portion of this was made into its hydrochloride salt and recrystallized from ethanol/isopropyl ether to give a white solid, mp 219-221°; ir (potassium bromide): ν 1655 cm⁻¹ (C=0); ¹H nmr (DMSO): δ 2.88 (s, 6H, $N(CH_3)_2$, 4.82 (s, 2H, $COCH_2N$), 6.47 (m, 1H, H-4 pyrrole), 6.77 (m, 1H, aromatic), 7.03 (m, 1H, H-3 pyrrole), 7.20 (m, 2H, H-5 pyrrole, 1 aromatic), 7.32 (m, 2H, aromatic), 7.50 (m, 5H, aromatic), 7.98 (s, 1H, Ar₃CH), 10.05 (br s, 1H, HCl, exchanges with deuterium oxide); ms: m/z 336 (M*).

Anal. Caled. for $C_{21}H_{21}FN_2O \cdot HCl$: C, 67.64; H, 5.95; N, 7.51. Found: C, 67.70; H, 6.07; N, 7.48.

 α -(Dimethylamino)methyl-1-[(2-fluorophenyl)phenylmethyl]-1H-pyrrole-2-methanol (10).

To a suspension of sodium borohydride (3.53 g, 0.09 mole) in 150 ml of 2-propanol was added a solution of compound 9 (13.8 g, 0.04 mole) in 200 ml of 2-propanol. The mixture was heated at reflux for 6 hours, then cooled, added to water and extracted with dichloromethane. The organics were washed with a saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Concentration of the solvent gave an oil which was purified via preparative hplc (hexane, ethyl acetate, diethylamine; 80:20:2) to give 83% of compound 10 as an inseparable mixture of diasteromers, mp 75.5-78°. A portion of this was made into an oxalate salt and recrystallized from ethanol/isopropyl ether to give light yellow crystals, mp 141-143.5°; ¹H nmr (DMSO): δ 2.63, 2.68 (2 x s, 6H, N(C H_3)₂), 3.15 (m, 2H, C H_2 N), 4.45 (m, 1H, CHOH), 6.05 (m, 1H, H-4 pyrrole), 6.18 (m, 1H, H-3 pyrrole), 6.38 (m, 1H, H-5 pyrrole), 6.74 (m, 1H, aromatic), 6.95 (br s, 3H, OH, 2CO₂H), 7.05 (m, 1H, aromatic), 7.13 (m, 2H, 1 aromatic, Ar₃CH), 7.22 (m, 1H, aromatic), 7.40 (m, 5H, aromatic); ms: m/z 338 (M+).

Anal. Calcd. for $C_{21}H_{23}FN_2O \cdot C_2H_2O_4$: C, 64.48; H, 5.88; N, 6.54. Found: C, 64.37; H, 6.00; N, 6.49.

11-(Dimethylamino)methyl-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]-benzoxazepine (7c).

Compound 7c was prepared in a manner analogous to that described for compound 7a. Separation of the diastereomers was accomplished by preparative hplc (hexane, ethyl acetate, diethylamine; 80:20:2) to give 75% of a major diastereomer 7c', mp 82-87°, and 18% of a minor diastereomer 7c', mp 119-122.5°. The major diastereomer 7c' was dissolved in ether and treated with an ethereal solution of hydrogen chloride to give a solid

which was recrystallized from ethanol/isopropyl ether to give 7c' hydrochloride, mp 205-205.5°; ¹H nmr (DMSO): δ 2.70 (br s, 6H, N(C H_3)₂), 3.72 (m, 2H, C H_2 N), 5.20 (m, 1H, H-11), 6.10 (m, 1H, H-2), 6.20 (m, 1H, H-1), 6.70 (s, 1H, H-5), 6.78 (m, 2H, aromatic), 7.10 (m, 2H, H-3, 1 aromatic), 7.30 (m, 6H, aromatic), 10.10 (br s, 1H, HCl, exchanges with deuterium oxide); ms: m/z 318 (M⁺).

Anal. Calcd. for $C_{21}H_{22}N_2O \cdot HCl$: C, 71.08; H, 6.53; N, 7.89. Found: C, 70.86; H, 6.61; N, 7.80.

The minor diastereomer 7c'' was treated as was 7c' to give a light tan solid, mp 217.5-219.5°; 'H nmr (DMSO): δ 2.88 (s, 6H, N(C H_3)₂), 3.45 (dd, 1H, C H_2 N), 3.88 (d, 1H, C H_2 N), 5.52 (d, 1H, H-11), 6.18 (m, 2H, H-1, H-2), 6.66 (s, 1H, H-5), 6.68 (m, 2H, aromatic), 7.00 (m, 1H, H-3), 7.25 (m, 4H, aromatic), 7.45 (m, 2H, aromatic), 7.82 (d, 1H, aromatic), 10.65 (br s, 1H, HCl, exchanges with deuterium oxide); ms: m/z 318 (M*).

Anal. Calcd. for $C_{21}H_{22}N_2O \cdot HCl$: C, 71.08; H, 6.53; N, 7.89. Found: C, 70.90; H, 6.63; N, 7.59.

11-(N-Ethoxycarbonyl-N-methylaminomethyl)-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]benzoxazepine (11).

A mixture of 7c' (9.92 g, 0.031 mole), ethyl chloroformate (6.73 g, 0.062 mole) and milled potassium carbonate (4.28 g, 0.031 mole) in 150 ml of benzene was heated at 65° for 6 hours. The mixture was then poured into water and extracted with ethyl ether. The combined organics were successively washed with a dilute hydrochloric acid solution, water and a saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was removed to give compound 11 as an oil that was used without further purification; 'H nmr (deuteriochloroform, 60 MHz): δ 0.65-1.45 (m, 3H, OCH₂CH₃), 2.90 (br s, 3H, NCH₃), 3.90-4.30 (m, 4H, OCH₂CH₃, CH₂N), 4.92-5.20 (m, 1H, H-11), 6.05-6.32 (m, 3H, H-1, 2, and 3), 6.70-7.45 (m, 10H, H-5, aromatic); ms: m/z 376 (M*).

11-(Methylamino)methyl-5-phenyl-5H,11H-pyrrolo[2,1-c][1,4]-benzoxazepine (12).

A solution of compound 11 (10.4 g, 0.028 mole) in 100 ml of ethanol was treated with 75 ml of a 20% solution of sodium hydroxide in water. This mixture was refluxed for 48 hours after which the phases were separated and the aqueous was extracted with ethyl acetate. The combined organics were then washed with a saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The amine was purified via flash chromatography (50% ethyl acetate/chloroform then 5% methanol/ethyl acetate) to give 3.45 g (41%) of compound 12, mp 82-86°. The hydrochloride was formed in ethyl ether using ethereal hydrogen chloride to give a solid which was recrystallized from methanol/ethyl ether to give pure 12 hydrochloride, mp 235-236.5°; 'H nmr (DMSO): δ 2.58 (s, 3H, NCH₃), 3.55 (m, 2H, CH₂N), 5.19 (m, 1H, H-11), 6.10 (m, 1H, H-2), 6.20 (m, 1H, H-1), 6.72 (s, 1H, H-5), 6.78 (m, 2H, aromatic), 7.15 (m, 2H, H-3, 1 aromatic), 7.33 (m, 6H, aromatic), 8.97 (br s, 2H, NHCH₃, HCl, exchanges with deuterium oxide); ms: m/z 304 (M+).

Anal. Calcd. for $C_{20}H_{20}N_2O$ ·HCl: C, 70.48; H, 6.21; N, 8.22. Found: C, 70.27; H, 6.18; N, 8.14.

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