A Practical Synthesis of 1,3,4,14b-Tetrahydro-2-methyl-10*H*-pyrazino-[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (1:1) Maleate

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A practical synthesis of the anti-depressant, 1,3,4,14b-tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo-[2,1-*c*][1,4]benzodiazepine (1:1) maleate (Aptazapine **10**) is reported in seven steps and approximately 20% overall yield. The key step of the synthesis was the formation of the tricyclic intermediate methyl 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-11-carboxylate (**7**) *via* a "Pictet-Spengler" type condensation of *o*-aminobenzylpyrrole (**6**) and methyl glyoxylate or the methoxy hemiacetal thereof.

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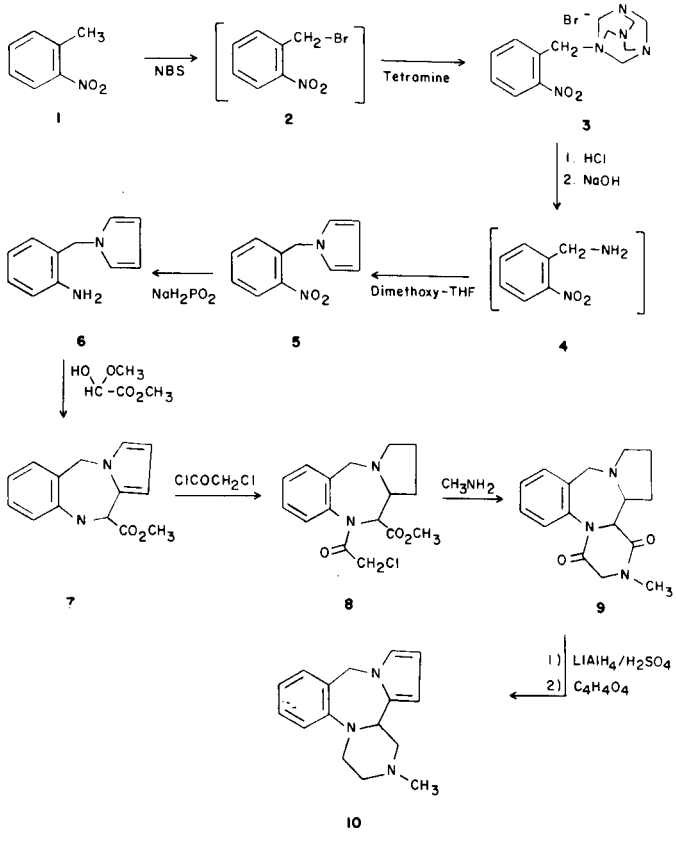
Introduction.

Recent interest in the biological activity of aptazapine (CGS 7525A) (**10**) as a potential antidepressant drug, structurally related to mianserin, necessitated the preparation of additional quantities of this material for clinical trials. Previously, **10** had been prepared by an eleven-step synthesis in an overall yield of 4% [1]. Several attendant difficulties associated with certain intermediates in this initial synthesis made it unsuitable for scale-up and prompted our investigation of a more facile preparation. We now wish to report an improved synthesis of **10** *via* Scheme 1 which is suitable for scale-up and offers many advantages over the previous synthesis.

Results and Discussion.

o-Nitrobenzylpyrrole (**5**) was prepared in a two step operation according to a modification of the original sequence [1]. Thus, bromination of *o*-nitrotoluene with *N*-bromosuccinimide (NBS) followed by *in situ* displacement of the resulting benzylbromide (**2**) with hexamethylene tetramine afforded the amine salt **3** in 63% yield. Aqueous acid hydrolysis of **3** followed by treatment with sodium hydroxide afforded the free base of the *o*-nitrobenzylamine (**4**) which was reacted immediately with 2,5-dimethoxytetrahydrofuran to yield *o*-nitrobenzylpyrrole (**5**), isolated as a crude tar in 85% yield. The crude **5** was reduced almost quantitatively by using either hydrogen in the presence of platinum oxide, or a more convenient modification of the procedure of Johnstone *et al.* [2] which involves addition of an aqueous solution of sodium hypophosphite to a tetrahydrofuran (THF) solution of **5** in the presence of 5% palladium-on-carbon. This latter procedure afforded comparable yields to that of hydrogenation. The cyclization of *o*-aminobenzylpyrrole (**6**) to the aminoester **7** *via* a "Pictet-Spengler" type condensation provided the key step in the new synthesis of aptazapine. This was readily carried out by addition of methyl glyoxylate or its more readily available methoxy hemiacetal to a methanolic solution of *o*-aminobenzylpyrrole (**6**), followed by filtration of the crystalline aminoester **7** in greater than 75% isolated yield.



Treatment of aminoester **7** with chloroacetyl chloride followed by an aqueous solution of methylamine afforded the diketopiperazine **9** in 77% yield *via* the chloro ester (**8**), a sample of which was isolated for identification purposes. Reduction of **9** *via* either diborane, or simply lithium aluminum hydride/sulfuric acid, (2:1), afforded the free base which on treatment with maleic acid produced the aptazapine salt (**10**) in 83% yield from the diketopiperazine **9** (overall yield >25%).

EXPERIMENTAL

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; nmr spectra on a Perkin-Elmer R-600 using TMS as an internal standard. The following abbreviations are used: (br) broad, (w) weak, (ex) exchangeable with deuterium oxide, (s) singlet, (t) triplet, (q) quartet, (m) multiplet.

Preparation of the Methoxy Hemiacetal of Methyl Glyoxylate.

A solution of glyoxylic acid monohydrate (100 g, 0.92 mole) in 650 ml of methanol was refluxed for 24 hours. The reaction mixture was cooled and the methanol removed *in vacuo* to yield 127.5 g of a pale yellow oil which by nmr was >90% porduct containing 10% residual methanol. For most purposes this product could be used as such for the next step, however, it was also possible to distill the hemiacetal if desired (bp 135-138°), lit [3] bp 47-48° at 13 mm and 71° at 50 mm; nmr (deuteriochloroform): 4.9 (s, 1H, CH), 4.6 (s, 1H, OH), 3.8 (s, 3H, OCH_3), 3.45 (s, 3H, CH_3); ir (neat): 3425 (b, OH), 2950 (w, C-H), 1745 (S, C=O), 1440, 1275, 1225, 1090 cm^{-1}.

Preparation of 2-Nitrobenzyl Hexamethylene Tetramine Salt (**3**).

A mixture of *N*-bromosuccinimide (305 g, 1.7 moles), *o*-nitrotoluene (227 g, 1.6 moles) and benzoylperoxide (6.5 g, 0.02 moles) in carbon tetrachloride (2.8 l) was refluxed for 5 hours. The reaction mixture was cooled, filtered and the carbon tetrachloride layer washed with water (2 l). The aqueous layer was back extracted with fresh carbon tetrachloride and the organic layers combined. To the carbon tetrachloride layer was added hexamethylene tetramine (174 g, 1.2 moles) and the reaction mixture was refluxed for an additional 3 hours. The reaction mixture was cooled and the product filtered and washed with carbon tetrachloride (0.4 l), chloroform (0.4 l) and dried under vacuum to yield compound **3** (400 g, 68%). An analytical sample could be obtained by recrystallizing from ethanol, mp 140-150° dec; nmr (DMSO): 8.4-7.6 (m, 4H, aromatic), 5.36 (s, 6H, methylenes), 4.62 (s, 8H, methylenes).

Anal. Calcd. $C_{13}H_{18}BrN_5O_2$: C, 43.83; H, 5.09; N, 19.66. Found: C, 43.70; H, 4.88; N, 20.04.

Preparation of 2-Nitrobenzylpyrrole (**5**).

A mixture of compound **3** (549 g, 1.5 moles) and hydrochloric acid 36% (676 g), in methanol (1 l) was refluxed, during which time 1 l of distillate was removed. Water (1 l) was added and the distillation was continued until a temperature of 96° was obtained. The reaction mixture was cooled and the *p*H adjusted to 2.7-3.2 with sodium hydroxide solution (50%). The aqueous layer was extracted with chloroform (three times) and separated. Toluene was then added to the aqueous layer and the *p*H adjusted to 9.2-9.5. The layers were separated and the aqueous layer extracted twice with additional toluene. To the combined toluene layers was added water (1 l) and the *p*H was adjusted to 2.7-3.0, followed by the addition of 2,5-dimethoxytetrahydrofuran (200 g, 1.5 moles). The reaction mixture was stirred while maintaining a *p*H between 1-2 until the reaction mixture was complete. The *p*H was adjusted to 6-6.5 and the reaction was filtered, separated, and the toluene layer washed with saturated salt solution, water, and concentrated to yield the product as a crude tar (85%). This was used as is for the next step.

Preparation of *o*-Aminobenzylpyrrole (**6**).

A slurry consisting of *o*-nitrobenzylpyrrole (**5**) (300 g, 1.25 moles), potassium carbonate (123 g, 0.89 mole), 5% palladium-on-carbon (5 g) in water (225 ml) and tetrahydrofuran (300 ml) was heated to 60°. To this reaction mixture was added, dropwise over two hours with vigorous stirring, a solution of sodium hypophosphite (504.2 g, 4.75 moles) in 1,025 ml of water. Upon completion of the addition, the reaction mixture was refluxed an additional two hours, cooled, and toluene (300 ml) was added. The reaction mixture was filtered, separated, and the aqueous layer extracted with toluene (250 ml). The combined organic layers were washed with water, dried and concentrated *in vacuo* to yield crude product which solidified on standing in the cold. The dark crude product was purified by vacuum distillation to yield a white/pale yellow solid upon cooling, bp 94-99° (at 180-200 microns), mp 42-43°; nmr (deuteriochloroform): 7.3-6.5 (m, 4H, Ar), 6.63 (t, J = 2 Hz, 2H, pyrrole), 6.19 (t, J = 2 Hz, 2H, pyrrole), 4.9 (s, 2H, CH_2), 3.4 (s, 2H, NH_2); ir (neat): 3450-3300, 1620, 1495, 1261, 1080, 775 cm^{-1}.

Anal. Calcd. ($C_{11}H_{12}N_2$): C, 76.71; H, 7.03; N, 16.27. Found: C, 76.89; H, 7.21; N, 16.22.

Preparation of Methyl-10,11-dihydro-5*H*-pyrrole[2,1-*c*][1,4]benzodiazepin-11-carboxylate (**7**).

To a cool (0°) solution of *o*-aminobenzylpyrrole (**6**) (10 g, 0.06 mole) in methanol (50 ml) was added dropwise to a solution of the methoxy hemiacetal of methyl glyoxylate (10 g) in methanol (10 ml). the reaction mixture was stirred between 0 and -5° for 23 hours, filtered, and the filtrate washed with 50-70 ml of precooled methanol. The product was carefully dried under vacuum at room temperature to yield 10 g of compound **7** (70%), first crop (mp 105-107°); nmr (deuteriochloroform): 7.2-6.5 (m, 5H, pyrrole + Ar), 6.0 (m, 2H, pyrrole), 5.46 (s, 1H, CH), 5.1 (q, J = 15 Hz, 2H, CH_2), 4.55 (s, 1H, NH), 3.8 (s, 3H, CH_3); ir (neat): 3350, 2900, 1721 (C=O), 1600, 1575, 1450, 1230, 750, 698 cm^{-1}.

Anal. Calcd. ($C_{14}H_{14}N_2O_2$): C, 69.40; H, 5.83; N, 11.56. Found: C, 69.59; H, 5.98; N, 11.67.

Preparation of 13,14b-Dihydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo-[2,1-*c*][1,4]benzodiazepin-1,4-dione (**9**).

To a slurry consisting of aminoester **7** (242 g, 0.95 mole) and sodium bicarbonate (92.4 g, 1.1 moles) in methylene chloride (1,200 ml) was added dropwise to chloroacetyl chloride (15 ml). The addition was stopped and the reaction mixture was stirred for 20 minutes. Over a period of 0.5 hour additional chloroacetyl chloride (85 ml) was added and the reaction mixture was stirred at 18° for an additional 0.5 hour. The reaction was quenched by careful addition of water (700 ml), stirring for 0.5 hour and separation of the layers. The organic layer was washed with water (500 ml), separated, and 40% aqueous methylamine (15 ml) was added to the methylene chloride layer. The combined mixture was concentrated *in vacuo* (55°), the solid residue was dissolved in ethanol (1 l), and 40% aqueous methylamine (255 ml, 230 g) was added. The reaction mixture was stirred at 35-40° for 4 hours, concentrated to 900 ml, cooled to 18° and allowed to stir overnight. The solids were filtered, washed with cold 95% ethanol (300 ml) and dried in a vacuum oven at 55° to yield diketopiperazine **9** (210 g 80%), mp 176-178°; nmr (deuteriochloroform): 7.35 (s, 4H, Ar), 6.69 (m, 1H, pyrrole), 6.3-6.0 (m, 2H, pyrrole), 5.34 (s, 1H, CH), 5.05 (q, J = 15 Hz, 2H, CH_2Ar), 4.05 (q, J = 18 Hz, 2H, CH_2), 3.06 (s, 3H, CH_3); ir (nujol): 2060-2847, 1675 (C=O), 1495, 1460, 1440, 1410, 1325, 1285, 1248, 710 cm^{-1}.

Anal. Calcd. ($C_{16}H_{15}N_3O_2$): C, 68.31; H, 5.38; N, 14.94. Found: C, 68.12; H, 5.43; N, 15.09.

Preparation of 1,3,4,14b-Tetrahydro-2-methyl-10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (1:1) Maleate (**10**).

To a cold (0°) solution of lithium aluminum hydride (34.4 g, 0.91 mole) in tetrahydrofuran (725 ml) was carefully added dropwise over 1.5 hours concentrated sulfuric acid (23.4 ml). Upon completion of the addition, the reaaction mixture was stirred for approximately 0.5 hours followed by slow dropwise addition of a solution of the diketopiperazine **9** (20.24 g, 0.072 mole) in tetrahydrofuran (200 ml). The reaction mixture was stirred for one hour, cooled to -15° and then carefully quenched by slow dropwise addition of 2*N* sodium hydroxide (272 ml). The inorganic salts were then filtered and washed with tetrahydrofuran (225 ml), and the combined filtrate and wash were concentrated *in vacuo* to a residue. The residue was dissolved in ethanol (400 ml) and decolorized by heating to 65° for 15 minutes with carbon (5 g). The solution was filtered and a cold ethanolic solution of maleic acid (8 g, 0.069 mole) in ethanol (100 ml) was added dropwise to the ethanolic filtrate. the reaction mixture was cooled and the product was filtered, washed with cold ethanol (130 ml) and dried in a vacuum oven to yield **10** (20.5 g, 77%) from the first crop (m.p. 181-183°C); nmr of free base (deuteriochloroform): 7.3.6.7 (m, 4H, Ar), 6.46 (t, J = 2 Hz, 1H, pyrrole), 5.85 (m, 2H, pyrrole), 5.4 (d, J = 13 Hz,

1H, CH_2Ar), 4.4 (d, J = 13 Hz, 1H, CH_2Ar), 4.2 (m, 1H, CH), 3.4-2.0 (m, 6H, CH_2), 225 (s, 3H, CH_3); ir 2950, 2825, 1595, 1490, 1450, 1300, 1250, 1140, 750 cm^{-1}.

Anal. Calcd. ($C_{16}H_{19}N_3 \cdot C_4H_4O_4$): C, 65.03; H, 6.28; N, 11.38. Found: C, 65.11; H, 6.45; N, 11.19.

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