The Synthesis of 1,3-Dihydro-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidinyl]-2*H*-benzimidazol-2-one (1:1) Maleate (CGS 9343 B, Potent Calmodulin Inhibitor)

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A practical synthesis of the title compound **7b** is described in seven steps in approximately 10% overall yield. The key step in the synthesis is the formation of the unusual tricyclic ring system **4** *via* acid catalyzed cyclization.

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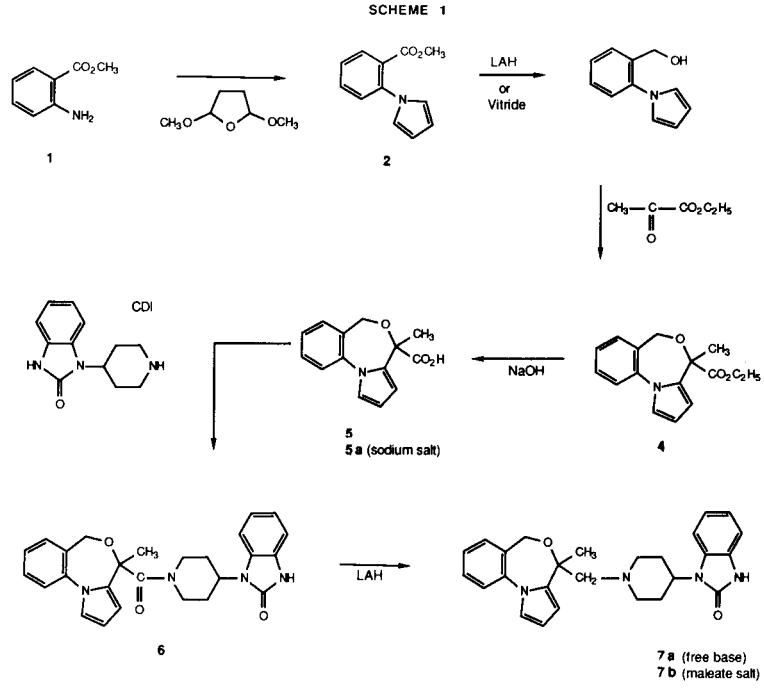
Introduction.

1,3-Dihydro-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4-1]-benzoxazepin-4-yl)methyl]-4-piperidinyl]-2*H*-benzimidazol-2-one 1:1 maleate (**7b**) (CGS 9343B) has been identified as a potent calmodulin inhibitor *in vitro* with demonstrated *in vivo* antidiarrheal activity [1]. We now wish to report on the synthesis of CGS 9343B (Scheme 1).

Results and Discussion.

2-(1*H*-Pyrrol-1-yl)benzenemethanol (**3**) was prepared in two steps. Thus, when methyl 2-aminobenzoate (**1**) was condensed with 2,5-dimethoxytetrahydrofuran in glacial acetic acid at 70°, the major product formed was methyl 2(1*H*-pyrrol-1-yl)benzoate (**2**) [2]. After removal of the acetic acid, the crude ester **2** was reduced with vitride in toluene to afford the desired 2-(1*H*-pyrrol-1-yl)benzenemethanol (**3**) in 84% yield after distillation. Alternatively, this reduction could be carried out with lithium aluminum hydride [3]. The condensation of **3** with ethyl pyruvate to the 4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine-4-carboxylic acid ethyl ester **4** provided the key step in the synthesis. This reaction was originally carried out in acetic acid. The desired cyclization reaction **3** to **4** was investigated using different solvents (toluene, methylene chloride, tetrahydrofuran, ethanol, water) and catalysts (hydrochloric acid, hydrobromic acid, sulfuric acid, *p*-toluenesulfonic acid, ion exchange resins, trifluoroacetic acid, pyruvic acid) in varying amounts and different tempera-

SCHEME 1



tures. A satisfactory cyclization was finally achieved by carrying out the reaction neat using a catalytic amount of hydrobromic acid which afforded a 90% conversion of **3** to **4** when monitored by gc and hplc. Although the tricyclic benzoxazepine ester **4** could be isolated and crystallized, losses incurred in its crystallization led us to isolate it as the sodium salt of the carboxylic acid **5a** obtained after hydrolysis of **4** with sodium hydroxide. Several attempts were made to convert ester **4** directly to amide **6**. Heating **4** with 4-(2-keto-1-benzimidazolinyl)piperidine in toluene, xylene or 1-methyl-2-pyrrolidone was unsuccessful, as were all attempts to catalyze the amide formation using trimethylaluminum. Thus, hydrolysis of the crude cyclic ester **4** led to the isolation of the sodium salt **5a** which, upon acidification, afforded the crystalline tricyclic acid **5**. Activation of **5** with *N,N*-carbonyldiimidazole followed by treatment with 4-(2-keto-1-benzimidazolinyl)piperidine afforded amide **6**, which was readily reduced with lithium aluminum hydride to yield the desired product **7a**. Treatment of **7a** in ethanol with maleic acid afforded CGS 9343B **7b**. The overall yield for this seven step sequence was ~10%.

EXPERIMENTAL

The physical data were obtained as follows: melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Pekin-Elmer model 281 B, Perkin-Elmer model 137 or Perkin Elmer model 521 spectrophotometer. Samples were run neat or in Nujol. Optical rotations were recorded with a Perkin-Elmer model 141 or Perkin-Elmer model 241 polarimeter. Mass spectra were obtained with an AEI, MS 902 spectrometer by direct insertion. Proton nmr spectra were determined on a Varian EM-390, Varian A-60, Varian XL-100, or Perkin-Elmer R-600 spectrometer using tetramethylsilane as internal standard. The following abbreviations are used: nmr, ex, exchangeable with deuterium oxide; s, singlet; t, triplet; q, quartet; m, multiplet; ir; s, strong; m, medium; w, weak.

2-(1*H*-Pyrrol-1-yl)benzemethanol (**3**).

A solution of methyl 2-aminobenzoate (**1**) (13.3 g, 0.09 mole), and 2,5-dimethoxytetrahydrofuran (17.3 g, 0.13 mole) in glacial acetic acid (25 ml) was heated at reflux (~95°) for 2 hours. The acetic acid was removed by vacuum distillation and the residue was further azeotroped with xylene by vacuum distillation to assure the complete removal of acetic acid. The remaining crude methyl 2-(1*H*-pyrrol-1-yl)benzoate (**2**) was dissolved in toluene (~100 ml) and warmed to 45°. To the solution of **2** was added vitride (33 g, 0.114 mole) at such a rate that a reaction temperature of 45-55° was maintained. When the addition was complete, the reaction was maintained at 45° for an additional 1 hour, cooled to 0-5° and quenched by the careful addition of aqueous 4*N* hydrochloric acid. The aqueous layer was separated and the toluene layer was washed consecutively with water (100 ml), saturated sodium bicarbonate solution (160 ml) and saturated sodium chloride solution (160 ml). The toluene layer was treated with carbon (5 g), filtered, dried over magnesium sulfate and concentrated to yield crude **3** which was isolated as a pale orange oil. Distillation of the crude oil (bp 120° 0.2 mm Hg) afforded pure **3** (12.9 g, 84%); nmr (deuteriochloroform): 2.70 (s, 1H), 4.40 (s, 2H), 6.26 (t, 2H), 6.76 (t, 2H), 7.2-7.5 (m, 4H); ir (neat): 3340 (s), 1605 (m) 1500 (s) 1328 (s) 1070 (s) 1038 (s) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.48; H, 6.33; N, 7.83.

Sodium 4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine-4-carboxylate (**5a**).

A mixture of 2-(1*H*-pyrrol-1-yl)benzenemethanol (**3**) (28.0 g, 0.162 mole) and ethyl pyruvate (24.4 g, 0.21 mole) was cooled to below 20° and 48% hydrobromic acid (5.5 ml) was slowly added at a rate such that the temperature of the reaction mixture remained below 45°. When the addition was complete, the reaction mixture was heated at 45° for 6 hours. The reaction mixture was cooled to 30°, diluted with methylene chloride (70 ml) and quenched with a solution of sodium carbonate. The methylene chloride layer was washed consecutively with water, a solution of sodium bisulfite (65 ml) and water (65 ml). The methylene chloride extracts were decolorized with carbon (3 g, ½ hour), dried over magnesium sulfate and concentrated under reduced pressure to yield ethyl 4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine-4-carboxylate (**4**) which was obtained in greater than 90% yield (hplc). A sample of **4** was isolated and purified for identification purposes, mp 103-105° (recrystallized from methyl *t*-butyl ether); nmr (deuteriochloroform): 0.85 (t, 3H), 1.31 (s, 3H), 3.78 (q, 2H), 4.58 (q, 2H), 6.40 (m, 2H), 7.05 (t, 1H), 7.38 (m, 4H); ir (Nujol): 1727 (s), 1607 (m) 1500 (s) 1240 (s) 1111 (s) 1028 (s) cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.91; H, 6.54; N, 5.35.

In most cases, the ester **4** was never isolated but used "without further purification" in the next step. Thus, the crude ester **4** was dissolved in ethanol (200 ml) and treated with a solution of sodium hydroxide (prepared from 50% sodium hydroxide (24 g) and water (12 ml), and heated at reflux temperature (80°) for 1 hour. Upon cooling, the sodium salt precipitated out and was isolated by filtration, washed with cold ethanol (40 ml) and dried under vacuum (60°) to yield the desired product as the sodium salt **5a** (10.0 g, 40%); nmr (deuterium oxide): 2.3 (s, 3H), 5.1 (q, 2H), 7.05 (m, 2H), 7.76 (t, 1H), 8.00 (m, 4H); ir (Nujol): 1620 (s) 1495 (s) cm^{-1}.

4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine-4-carboxylic Acid (**5**).

To a mixture of the sodium salt **5a** (g, 0.03 mole) in water (120 ml) and methylene chloride (64 ml) was added a solution of 4*N* hydrochloric acid until *p*H 2 was obtained. The layers were separated and the aqueous layer was extracted with fresh methylene chloride (65 ml), the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield crude **5** which was crystallized from heptane (80 ml); the crystals were separated by filtration and dried under vacuum to afford pure **5** (5.5 g, 75%), mp 178-179°; nmr (deuteriochloroform): 1.79 (s, 3H), 4.54 (s, 2H), 6.41 (m, 2H), 7.02 (m, 1H), 7.32 (m, 4H); ir (Nujol): 1711 (s) 1500 (m) 1110 (m) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.85; H, 5.33; N, 5.67.

1,3-Dihydro-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)-carbonyl]-4-piperidinyl]-2*H*-benzimidazol-2-one (**6**).

To a solution of *N,N*-carbonyldiimidazole (7.3 g, 0.04 mole) in tetrahydrofuran (25 ml), a solution of the carboxylic acid **5** (10 g, 0.04 mole) in tetrahydrofuran (60 ml) was added slowly. The reaction mixture was stirred at 25° for 1 hour and 4-[2-keto-1-benzimidazolinyl)piperidine (8.93 g, 0.04 mole) was added. The reaction mixture was stirred 1 hour at room temperature, then heated to 45° over 3 hours and maintained at 45° for 24-48 hours. The reaction was cooled to 25°, diluted with chloroform (125 ml) and quenched with a 10% solution of hydrochloric acid. The aqueous layer was re-extracted with chloroform and the combined chloroform layers were washed consecutively with a 10% solution of sodium carbonate (100 ml). The chloroform layer was concentrated under vacuum to yield a foam which crystallized when heated (60°) in ethanol (80 ml) and allowed to cool to -5 to 0°. The crystalline product **6** was isolated by filtration, washed with cold ethanol (30 ml) and dried under vacuum (100°) to afford **6** (11.4 g, 65%), mp 182-183°; nmr (deuteriochloroform): 1.8 (s, 3H), 1.5-3.0 (m, 6H), 4.2-5.0 (m, 5H), 6.4 (m, 2H), 7.1

(s, 4H), 7.80 (m, 1H), 7.5 (m, 4H); ir (Nujol): 3130 (m), 1680, 1652, 1635 (s), 1495 (s) cm^{-1}.

Anal. Calcd. for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.33; H, 5.85; N, 12.58.

1,3-Dihydro-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl]2*H*-benzimidazol-2-one (**7**).

To a cooled (5°) mixture of lithium aluminum hydride (1.0 g, 0.026 mole) in tetrahydrofuran (85 ml) was added a solution of the amide **6** (5.7 g, 0.013 mole) in tetrahydrofuran (85 ml) over ½ hour. The reaction mixture was stirred at 10° to ½ hour, then warmed to 45° over 1 hour and maintained at this temperature for 4 hours. The reaction mixture was cooled to 0° and carefully quenched by consecutively adding water (1 ml), 15% sodium hydroxide solution (1 ml) followed by water (3 ml). When the quench was completed, the reaction mixture was heated to 20-25° for ¼ hour, then 65° for 1 hour and was then cooled to 25°. A solution of 15% sodium hydroxide (12 ml) was added and the mixture stirred for ½ hour and then allowed to separate on standing for 1 hour. The tetrahydrofuran layer was decanted and concentrated under vacuum to yield a white foam which was dissolved in methylene chloride (115 ml) and washed consecutively with water (85 ml), and saturated salt solution (115 ml). The methylene chloride layer was concentrated under vacuum to yield a white foam which was crystallized by dissolving in 60% ethanol at 60° for 1 hour followed by cooling to 20-25°. The product was isolated by filtration, washed with cold 60% ethanol and dried under vacuum at 70° to yield the amine **7a** (4.5 g, 82%) as the free base, mp 173-175°; nmr (deuteriochloroform): 1.7 (s, 3H), 1.4-3.0 (m, 10H), 4.0-4.3 (m, 1H), 4.55 (q, 2H), 6.35 (m, 2H), 7.0-7.6 (m, 9H), 10.6 (s, 1H); ir (Nujol): 3135 (w) 1702 (s), 1496 (m), 1084 (m), 755 (m), 734 (m), 711 (m) cm^{-1}.

Anal. Calcd. for $C_{26}H_{28}N_4O_2 \cdot H_2O$: C, 69.93; H, 6.77; N, 12.55. Found: C, 70.10; H, 6.77; N, 12.55.

1,3-Dihydro-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidinyl]-2*H*-benzimidazol-2-one (1:1) Maleate (**7b**).

To a solution of the amine **7a** (4 g, 0.009 mole) in ethanol (250 ml) was added a solution of maleic acid (1.1 g, 0.009 mole) in ethanol (10 ml). The reaction mixture was stirred for 22 hours at room temperature and the product was isolated by filtration, washed with ethanol (20 ml) and dried under vacuum at 60° to yield the salt **7b** (3.7 g, 73%), mp 189-190°; nmr (dimethylsulfoxide-d_6): 1.66 (s, 3H), 1.45-1.85 (m, 2H), 2.25-3.75 (m, 8H), 4.40 (m, 1H), 4.62 (q, 2H), 6.13 (s, 2H), 6.4 (t, 1H), 6.51 (m, 1H), 7.05 (m, 3H), 7.41 (m, 3H), 7.60 (m, 2H), 7.7 (d, 1H); ir (Nujol): 3132 (w), 1693 (s), 1570 (m), 1498 (s), 1070 (m), cm^{-1}.

Anal. Calcd. for $C_{26}H_{28}N_4O_2 \cdot C_4H_4O_4$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.21; H, 5.98; N, 10.22.

REFERENCES AND NOTES

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