Synthesis of Pyrrolo[2,1-*c*][1,4]benzoxazepines. 1. A Novel Heterocyclic Ring System

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The synthesis of a novel pyrrolo[2,1-*c*][1,4]benzoxazepine ring system (II) by a nucleophilic aromatic fluoride displacement-cyclization is described. Aminoalkyl derivatives were prepared by either the Mannich reaction, or Vilsmeier formylation to provide the 3-formyl derivative which was further elaborated.

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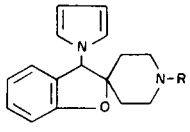
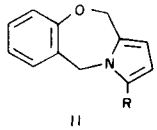
We have recently reported on the synthesis and biological activity of a pyrrole containing heterocycle I prepared *via* a nucleophilic aromatic fluoride displacement [1]. Our continuing interest in the synthesis of novel heterocyclic systems of pharmacological interest *via* this intramolecular aromatic fluorine displacement [2], and in pyrrole containing heterocycles, has led us to prepare as a novel ring system the tricyclic pyrrolo[2,1-*c*][1,4]benzoxazepine II.

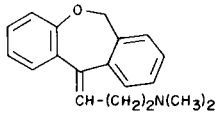


I

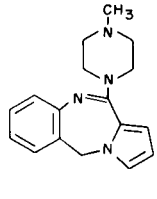


II

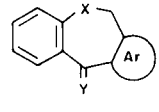
Biological activity is well known for numerous heterocyclic aromatic tricyclics, including the dibenzoxepin antidepressant [3] III and the fused pyrrolobenzodiazepine [4] IV. Accordingly, we have additionally prepared a number of aminoalkyl derivatives of the parent pyrrolobenzoxazepine system as potential pharmacologic agents. These have shown antinociceptive and CNS depressant activity in preliminary biological screening [5].



III



IV



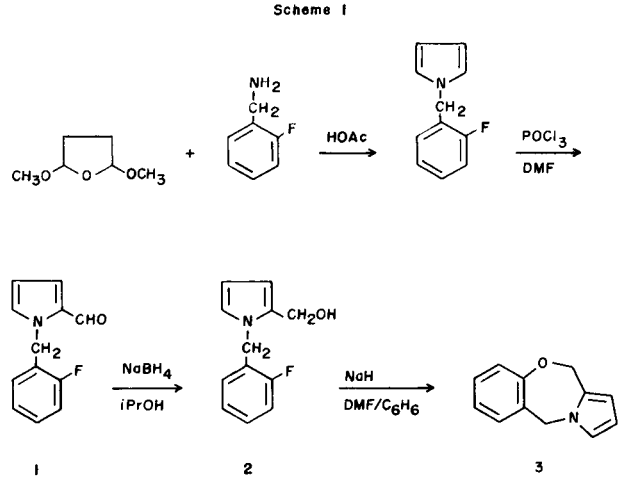
V

Synthesis of diaryl or aryl-heteroaryl[*b*,*e*]oxepins or -thiepins (V, X = O, S) is usually accomplished by electrophilic cyclization of a precursor containing an existing bond between the heteroatom X and an aromatic ring to give V (*e.g.* Y = O) [6-10]. Complete reduction would then give the parent ring system (Y = H_2). Our experience with nucleophilic displacement of aromatic fluorine suggested a method of synthesis of the tricyclic II whereby the bond between the heteroatom X and the aromatic ring could be formed in the final cyclization step.

Formylation of *N*-(*o*-fluorobenzyl)pyrrole *via* a Vilsmeier formylation with dimethylformamide and phosphorus oxychloride gave predominantly the 2-carboxaldehyde **1**. The starting *N*-(*o*-fluorobenzyl)pyrrole was prepared by condensation of *o*-fluorobenzylamine with 2,5-dimethoxytetrahydrofuran in acetic acid [1]. Reduction of the aldehyde **1** with sodium borohydride gave the alcohol **2**, which was cyclized in good yield with sodium hydride in a mixture of benzene and dimethylformamide *via* an intramolecular nucleophilic displacement of the fluorine to give the novel pyrrolobenzoxazepine **3** (Scheme I). While cyclizations of this type normally proceed smoothly with only dimethylformamide as solvent, we have found that in some instances the use of benzene or toluene with a small amount of dimethylformamide as co-solvent produces a cleaner reaction.

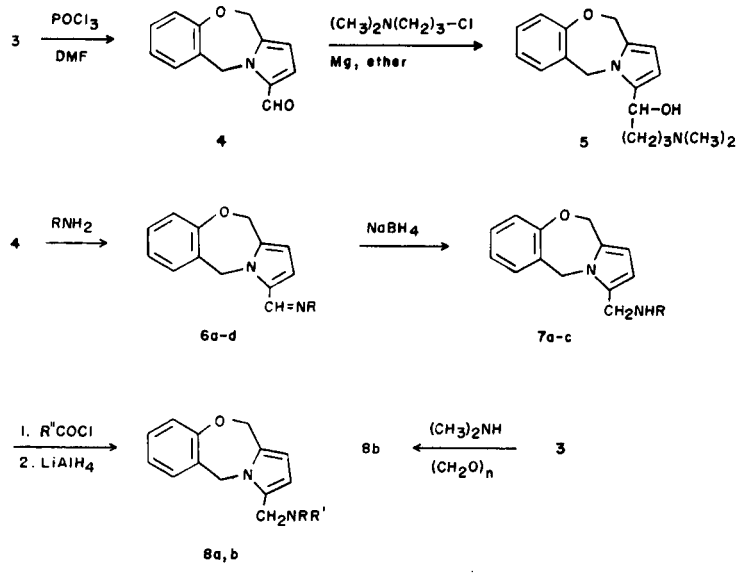
Functionalization of the pyrrole ring of **3** can be accomplished in a number of ways, including formylation to give the 3-formyl derivative **4** (Scheme II). The aldehyde was further elaborated by either a Grignard reaction on **4** to give the amino alcohol **5**, or by condensation with primary amines to give the Schiff bases **6**. Imine reduction with sodium borohydride gave the secondary amines **7**. Reaction of the secondary amines **7a** and **7c** with ethyl chloroformate gave the corresponding carbamates which were reduced with lithium aluminum hydride at room tempera-

Scheme I



1 2 3

Scheme II



ture to give the tertiary amines **8a** and **8b**. The dimethylaminomethyl **8b** was also synthesized directly by a Mannich condensation with the pyrrolobenzoxazepine **3**.

EXPERIMENTAL

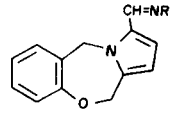
Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer. Nuclear magnetic resonance spectra were taken on a Jeol C-60HL or Varian 200XL (where indicated) instrument. Chemical shifts are reported as δ units with tetramethylsilane as an internal standard. The mass spectra were obtained from a Finnigan Model 4000 spectrophotometer with an INCOS data system at 70 eV by direct insertion. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

1-(*o*-Fluorobenzyl)pyrrole-2-carboxaldehyde (**1**).

Dimethylformamide (8 g, 0.11 mole) was cooled to 5° in a 500 ml three neck round bottom, and phosphorus oxychloride (16.9 g, 0.11 mole) added dropwise with stirring, at a rate to maintain the temperature below 20°. After the addition was complete the mixture was stirred at room temperature for 15 minutes. 1,2-Dichloroethane (25 ml) was added and the solution cooled again to 5°. A solution of 1-(*o*-fluorobenzyl)pyrrole (17.5 g, 0.1 mole) in 1,2-dichloroethane (25 ml) was added, and the mixture stirred at ice bath temperature for 15-30 minutes. After an additional 30 minutes at room temperature the reaction mixture was refluxed for 4-5 hours under a low stream of nitrogen. The mixture was then cooled to room temperature and a solution of sodium acetate trihydrate (75 g, 0.55 moles) in water (120 ml) added. The biphasic mixture was stirred vigorously at room temperature for 15 minutes, then refluxed for ½ hour. After cooling to room temperature the 1,2-dichloroethane layer was re-

Table I

(5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepine-3-ylmethylene)amines

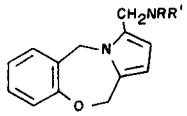


Compound	R	Mp °C	Yield % [a]	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found		
6a	-$(CH_2)_2$-C_6H_5	77-79	78	Petroleum ether	$C_{21}H_{20}N_2O$	C 79.72	H 6.37	N 8.85
						C 79.69	H 6.24	N 8.99
6b	-$(CH_2)_3$-CH-(*p*-$C_6H_4F)_2$	120 dec	92	Ethyl acetate	$C_{29}H_{26}F_2N_2O$·HCl	C 70.65	H 5.52	N 5.68
						C 70.94	H 5.78	N 5.89
6c	-CH_3	115-117	96	Petroleum ether	$C_{14}H_{14}N_2O$	C 74.31	H 6.24	N 12.38
						C 74.35	H 6.36	N 12.69
6d	-$(CH_2)_2N(C_2H_5)_2$	110 dec	70	Ethyl acetate-methanol	$C_{19}H_{25}N_3O$·2HCl	C 59.37	H 7.09	N 10.93
						C 59.94	H 7.62	N 11.20

[a] Isolated yields; no efforts were made to optimize these yields.

Table II

5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepine-3-methanamines



Compound	R	R'	Yield Mp °C	% [a]	Recrystallization Solvent	Molecular Formula	Analysis % Calcd./Found		
7a	-$(CH_2)_2$-C_6H_5	H	140 dec	96	2-Propanol-ether	$C_{21}H_{22}N_2O$·HCl	C 71.07	H 6.53	N 7.90
							C 70.71	H 6.76	N 7.84
7b	-$(CH_2)_3$CH-(p-$C_6H_4F)_2$	H	148 dec	60	Ethyl acetate	$C_{29}H_{28}F_2N_2O$·HCl	C 70.36	H 5.91	N 5.66
							C 70.20	H 6.24	N 5.71
7c	-CH_3	H	145 dec	83	Ethyl acetate-methanol	$C_{14}H_{16}N_2O$·HCl	C 63.51	H 6.47	N 10.58
							C 63.66	H 6.90	N 10.73
8a	-$(CH_2)_2$-C_6H_5	CH_3	140 dec	55	2-Propanol-ether	$C_{22}H_{24}N_2O$·$C_4H_4O_4$ [b]	C 69.62	H 6.29	N 6.25
							C 69.38	H 6.24	N 6.30
8b	-CH_3	CH_3	160 dec	40	2-Propanol	$C_{15}H_{18}N_2O$·$C_4H_4O_4$ [b]	C 63.67	H 6.19	N 7.82
							C 63.75	H 6.20	N 7.83

[a] Isolated yields; no efforts were made to optimize these yields. [b] Acid maleate salt.

moved and the aqueous portion extracted with ether. The combined extracts were washed twice with saturated sodium bicarbonate, once with saturated sodium chloride, and dried over magnesium sulfate. Removal of the solvent afforded 21.5 g (100%) of light yellow oil which solidified to a pale yellow solid. Recrystallization from ether-hexane gave nearly white crystals, mp 39-41°; ir (chloroform): 1660 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 5.65 (s, 2H, CH_2), 6.3 (2 doublets, 1H, pyrrole-4H), 7.1 (m, 6H, ArH and 3,5-pyrrole H), 9.5 (s, 1H, C*H*O); ms: m/e 203 (M^+).

Anal. Calcd. for $C_{12}H_{10}FNO$: C, 70.91; H, 4.97; N, 6.89. Found: C, 70.60; H, 5.03; N, 6.85.

[1-(*o*-Fluorobenzyl)pyrryl]methanol (**2**).

To a stirring suspension of sodium borohydride (4.4 g, 0.116 mole) in 100 ml of 2-propanol was added dropwise a solution of 1-(*o*-fluorobenzyl)pyrrolo-2-carboxaldehyde (11.7 g, 0.058 mole) in 100 ml of 2-propanol. The mixture was stirred at 80° for 20 hours. Removal of the 2-propanol gave a white semi-solid which was stirred with 500 ml water for 15 minutes, then extracted with ether. The ether layer was washed with water (2 ×), saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After filtering, the ether was evaporated to give a clear oil, 11.0 g (95%); ir (chloroform): 3550-3180, broad (OH), 3600 sharp (OH); nmr (deuteriochloroform): δ 1.4 (t, 1H, O*H*), 4.57 (d, 2H, CH_2OH), 5.28 (s, 2H, CH_2), 6.16 (m, 2H, pyrrole), 6.64-7.4 (m, 5H, 4Ar, pyrrole), 6.3-7.2 (m, 5H, Ar, α-pyrrole H).

Anal. Calcd. for $C_{12}H_{12}FNO$: C, 70.22; H, 5.90; N, 6.83; F, 9.26. Found: C, 70.01; H, 5.86; N, 6.89; F, 9.00.

5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepine (**3**).

To a suspension of sodium hydride (57% dispersion, 2.9 g, 0.07 mole) in 100 ml of dry benzene, was added dropwise, with stirring a solution of 1-(*o*-fluorobenzyl)-2-pyrrylmethanol (11.7 g, 0.0575 mole) in 50 ml of dry benzene. The mixture was stirred at reflux for one hour, then 20 ml of dry DMF was added and the resultant clear solution stirred at 80° for six hours. After cooling, the mixture was poured into 1 ℓ of ice-water, stirred for 30 minutes, then extracted with ether. The ether layer was washed with water (3 ×), then dried (saturated sodium chloride solution, anhydrous sodium sulfate). After filtering, the solvent was evaporated to give a brown oil, which solidified upon cooling, 8 g (80%), mp 80-90°. This material was sublimed at 70°/0.05 mm Hg, to yield 7 g of white crystals, mp 99-101°; nmr (deuteriochloroform): δ 5.1 (s, 4H, $2CH_2$), 5.9-6.2 (m, 2H, β-pyrrole H), 6.5-7.2 (m, 5H, Ar-*H*, α-pyrrole H).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.74; H, 6.02; N, 7.57.

5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepine-3-carboxaldehyde (**4**).

To cold dimethylformamide (11 g, 0.15 mole) was added phosphorus oxychloride (23 g, 0.15 mole) dropwise with cooling. This mixture was stirred at ambient temperature for 15 minutes, then diluted with 30 ml of 1,2-dichloroethane. To this cooled mixture was added 5*H*,11*H*-pyrrolo-[2,1-*c*][1,4]benzoxazepine (22 g, 0.12 mole) in 400 ml of 1,2-dichloroethane, dropwise, over a period of 15 minutes. The mixture was then stirred at reflux for three hours, cooled, a solution of sodium acetate trihydrate (117 g, 0.85 mole) in 200 ml of water was added, and the mixture stirred at 85° for 30 minutes. After cooling, the mixture was extracted with ether, and the ether layer was washed with saturated sodium bicarbonate solution (2 ×), water (2 ×), then dried (saturated sodium chloride solution, anhydrous sodium sulfate). After filtering the solvent was evaporated to give a brown solid, 16 g (64%), mp 85°. This material was recrystallized twice from ethyl ether to yield 10 g of the desired compound, (40%) mp 126-129°; ir (chloroform): 3020 (m), 2910 (w), 2870 (w), 2820 (m), 2750 (w), 1660 (s, C=O) cm^{-1}; nmr (deuteriochloroform): δ 5.15 (s, 2H, CH_2), 5.85 (s, 2H, CH_2), 6.15 (d, 1H, H_1), 6.6-7.3 (m, 5H, ArH(4), H_2), 9.3 (s, 1H, C*H*O).

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.32; H, 5.28; N, 6.54.

4-Dimethylamino-1-(5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-yl)-1-butanol (**5**).

To Mg turnings (2.4 g, 0.1 mole) in 50 ml of dry ether, was added a solution of dimethylaminopropyl chloride (12.2 g, 0.1 mole) in 50 ml of dry ether. (The reaction was initiated with a heat gun, and dibromoethane.) After refluxing for one hour, a solution of 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]-benzoxazepine-3-carboxaldehyde (7.0 g, 0.033 mole) in 100 ml ether was added, and the mixture refluxed for four hours. The mixture was cooled, then poured into an ice-ammonium chloride solution, stirred for 30 minutes, then extracted with chloroform. The chloroform was washed with ether (2 ×) then dried (saturated sodium chloride solution, anhydrous sodium sulfate). After filtering, the solvent was evaporated to give a yellow oil, which solidified upon trituration with petroleum ether. This solid was filtered off, and the petroelum ether solution evaporated to give an off-white solid 3.6 g (36%), mp 115°. Recrystallization from ether/methanol afforded 3.0 g, mp 124-125°; nmr (deuteriochloroform): δ 1.5-2.6 (m, 12H, $3CH_2$, $2CH_3$), 4.7-5.0 (m, 1H, CH), 5.4 (s, 2H, CH_2), 5.63 (d, 2H, CH_2), 6.15 (d, 1H, pyrrole H), 6.35 (d, 1H, pyrrole H), 6.9-7.1 (m, 4H, Ar-H); ms: m/e 300 (M^+).

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found:

C, 71.88; H, 8.18; N, 9.21.

N-(5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepin-3-ylmethylene)benzeneethanamine (**6a**).

To 50 ml dry benzene was added 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine-3-carboxaldehyde (7.0 g, 0.033 mole) and phenethylamine (6.0 g, 0.033 mole). After solution was obtained, 500 ml of cyclohexane and 50 g molecular sieves (3A) was added, and the mixture stirred at reflux (80°) for two days. After filtering, the solvent was evaporated to a yellow oil which crystallized to a white solid, 7.8 g (78%) mp 75-79°. Recrystallization from petroleum ether gave 6.0 g, mp 77-79° (60%); ir (chloroform): 1645 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 3.1 (t, 2H, CH_2), 3.9 (t, 2H, NCH_2), 5.3 (s, 2H, CH_2), 6.15 (s, 2H, CH_2), 6.35 (q, 2 doublets, 2H, pyrrole Hs), 6.7-7.6 (m, 9H, Ar), 8.2 (s, 1H, *C*H=N); ms: m/e 316 (M^+).

See Table I for elemental analysis.

4-Fluoro-δ-(4-fluorophenyl)-*N*-(5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-ylmethylene)benzenebutanamine (**6b**).

To 50 ml dry benzene was added 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine-3-carboxaldehyde (7.0 g, 0.033 mole) and 4,4-*bis*-(*p*-fluorophenyl)-butylamine (8.6 g, 0.033 mole). After solution was obtained, 500 ml cyclohexane and 25 g molecular sieves (3A) was added and the mixture stirred at reflux (80°) for four days. After filtering, the solvent was evaporated to give a yellow oil, 14 g (92%). A portion of this oil was dissolved in ether, then converted to the hydrochloride salt, 110° dec. Recrystallization from ethyl acetate yielded the pure hydrochloride, dec at 120°; ir (chloroform): 1650 (C=N) cm^{-1}; nmr (deuteriochloroform) (free base): δ 1.4-2.4 (broad m, 4H, $2CH_2$), 3.6 (triplet, 2H, N-CH_2), 3.96 (triplet, 1H, $CHAr_2$), 5.52 (s, 2H, CH_2), 6.1 (s, 2H, CH_2), 6.25 (2 doublets, 2H, pyrrole), 6.7-7.4 (m, 12H, Ar), 8.1 (s, 1H, CH=N); ms: m/e 456 (M^+) (17 eV).

See Table I for elemental analysis.

N-(5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzoxazepin-3-ylmethylene)methanamine (**6c**).

A mixture of 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine-3-carboxaldehyde (7.2 g, 0.034 mole) and 10 g 3A molecular sieves in 80 ml of dry benzene was cooled, saturated with methylamine, then heated at 80° in a sealed reaction vessel for 20 hours. The mixture was then cooled, filtered, and the solvent evaporated to give a white solid, 7.4 g (96%), mp 113-117°. Recrystallization from petroleum ether afforded 7.0 g, mp 114-117°; ir (chloroform): 1640 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 3.55 (d, 3H, CH_3), 5.47 (s, 2H, CH_2), 6.35 (s, 2H, CH_2), 6.4-6.7 (2 doublets, 2H, pyrrole Hs), 6.98-7.7 (m, 4H, Ar-H), 8.52 (d, 1H, CH=N); ms: m/e 226 (M^+).

See Table I for elemental analysis.

N,N-Diethyl-*N'*-(5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-ylmethylene-1,2-ethanediamine (**6d**).

To 50 ml dry benzene was added 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine-3-carboxaldehyde (4.5 g, 0.021 mole) and *N,N*-diethylaminoethylamine (3.4 g, 0.025 mole). After solution was obtained, the mixture was diluted with 400 ml of cyclohexane and 25 g molecular sieves (3A) was added and the mixture refluxed at 85° for 27 hours. The solvent was removed leaving a brown oil, which was stirred with 50 ml of water, then extracted with ether. The ether extract was washed with water (2 ×), then dried (saturated sodium chloride solution, anhydrous sodium sulfate). After filtering the ether was evaporated to give a brown oil, which was converted to the dihydrochloride salt. Recrystallization from ethyl acetate/methanol yielded 4.5 g (70%) of the desired compound, dec at 110°; ir (chloroform): 1660 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 1.5 (t, 6H, $2CH_3$), 3-4.3 (m, 8H, $4CH_2$), 5.3 (s, 2H, CH_2), 5.98 (s, 2H, CH_2), 6.25 (d, 1H, pyrrole), 6.5-7.4 (m, 5H, Ar and 1 pyrrole), 9.1 (broad s, 2H, 2HCl), 9.4 (s, 1H, C*H*=N).

See Table I for elemental analysis.

N-(2-Phenethyl)-(5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-methanamine (**7a**).

A solution of **6a** (2.3 g, 7.3 mmoles) in methanol (30 ml) and 2-propanol (35 ml) was added to a suspension of sodium borohydride (0.57 g, 15 mmoles) in 2-propanol (15 ml), and the resulting mixture stirred at room temperature for four hours. Evaporation of the solvent gave a white semi-solid which was stirred with water (100 ml), then extracted with ether. The ether extract was washed with water, brine, then dried over magnesium sulfate. The magnesium sulfate was removed by filtration, and the ether evaporated to give a pure clear oil, 2.2 g (96%). A small portion was converted to a hydrochloride salt which was recrystallized from 2-propanol-ether to give an analytically pure sample, mp 140° dec; nmr (deuteriochloroform) (free base): δ 1.4 (bs, 1H, NH), 2.8 (bt, 4H, N-(CH_2)$_2$-Ar), 3.75 (s, 2H, CH_2N), 5.17 (s, 2H, CH_2), 5.25 (s, 2H, CH_2), 5.9 (d, 1H, pyrrole), 6.12 (d, 1H, pyrrole), 6.6-7.4 (m, 9H, Ar); ms: m/e 319 $(MH)^+$.

See Table II for elemental analysis.

N-[4,4-bis(4-Fluorophenyl)butyl]-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-methanamine (**7b**).

A mixture of **6b** (8.0 g, 0.0175 mole) and sodium borohydride (1.52 g, 0.04 mole) in 2-propanol (250 ml) was stirred at room temperature for 20 hours. Removal of the solvent gave a white solid which was stirred with water (500 ml) for 30 minutes, then extracted with ether. The ether extract was washed successively with water (2 ×) and saturated sodium chloride, then dried over anhydrous magnesium sulfate. After filtering, the ether was removed *in vacuo* to give a yellow oil which was converted to the hydrochloride salt (6.0 g, 60%). Recrystallization from ethyl acetate (2 ×) gave an analytical sample of white crystalline product, mp 148° dec; nmr (deuteriochloroform, 200 MHz): δ 1.66 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 2.6 (t, (partially resolved), 2H, CH_2), 3.65 (t, 1H, $CHAr_2$), 4.04 (s, 2H, CH_2), 5.15 (5, 2H, ring CH_2), 5.38 (s, 2H, ring CH_2), 6.18 (s, 2H, pyrrole), 6.7-7.5 (m, 12H, Ar), 9.66 (s, 2H, NH_2); ms: m/e 459 $(MH)^+$.

See Table II for elemental analysis.

A portion was converted to the maleate salt and recrystallized from isopropanol/ether to give a white crystalline maleate, mp 168-169° dec.

Anal. Calcd. for $C_{29}H_{28}F_2N_2O{\cdot}C_4H_4O_4$: C, 68.96; H, 5.62; N, 4.87. Found: C, 69.05; H, 5.60; N, 4.94.

N-Methyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine-3-methanamine (**7c**).

A solution of **6c** (1.8 g, 8 mmoles) in methanol (20 ml) and 2-propanol (20 ml) was added to a supsension of sodium borohydride (0.6 g, 16 mmoles) in 2-propanol (20 ml), and the resulting mixture stirred at room temperature for four hours. Evaporation of the solvent gave a semi-solid which was stirred with water then extracted with ether. The ether extract was washed with water, brine, then dried over magnesium sulfate. The ether was evaporated *in vacuo* to give 1.5 g (83%) of a clear oil. Conversion of a portion of the hydrochloride salt and recrystallization from ethyl acetate/methanol provided an analytical sample, mp 145° dec; nmr (deuteriochloroform) (free base): δ 1.5 (s, 1H, NH), 2.5 (s, 3H, NCH_3), 3.85 (s, 2H, -CH_2), 5.4 (s, 2H, ring CH_2), 5.53 (s, 2H, ring CH_2), 6.18 (d, 1H, pyrrole), 6.4 (d, 1H, pyrrole), 6.9-7.65 (m, 4H, Ar); ms: m/e 228 (M^+).

See Table II for elemental analysis.

N-Methyl-*N*-(2-phenylethyl)-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-methanamine Maleate (**8a**).

To a cold solution of **7a** (2.2 g, 0.007 mole) and triethylamine (1.3 ml, 0.01 mole) in 30 ml of chloroform was added a solution of ethyl chloroformate (1.0 ml, 0.01 mole) in 5 ml of chloroform. After stirring at ambient temperature for four hours, the mixture was diluted with 50 ml of ether, washed with water (2 ×), then dried (saturated sodium chloride, anhydrous magnesium sulfate). After filtering, the solvents were evaporated to a clear oil, 2.2 g. This oil was fully characterized and determined to be the carbamate intermediate; ir (chloroform): N-C(O)-O, 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (t, 3H, CH_3), 2.33 (q, 2H, CH_2), 3.20 (q, 2H, CH_2), 4.14 (q, 2H, CH_2), 4.27 (s, 2H, CH_2), 5.22 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 6.12 (q, 2H, 2,3-pyrrolo), 6.67-7.43 (m, 9H, aromatic); ms: m/e 391 $(MH)^+$.

To a cold suspension of LAH (0.7 g, 0.0085 mole, 50% in oil) in 25 ml of THF, was added a solution of the carbamate (1.5 g, 0.0038 mole) in 15 ml of THF. After stirring at ambient temperature for four hours, the mix-

ture was quenched with 10 ml saturated ammonium chloride solution, diluted with 50 ml of ether, then filtered. The filtrate was washed with water (2 ×) then dried (saturated sodium chloride, sodium sulfate). After filtering, the solvents were evaporated to a clear oil, 0.7 g, which was dissolved in ether, the resultant solution acidified to *p*H 1 with an ether solution of maleic acid. The resultant white precipitate was collected, then recrystallized from 2-propanol/ether (1:20), resulting in white crystals, 0.5 g (55%) 140° dec; nmr (deuteriochloroform) (free base): δ 2.25 (s, 3H, CH_3), 2.65-2.97 (m, 4H, $2CH_2$), 3.58 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 6.12 (d, 1H, pyrrole), 6.35 (d, 1H, pyrrole), 6.94-7.64 (m, 9H, aromatic); ms: m/e 333 $(MH)^+$.

See Table II for elemental analysis.

N,N-Dimethyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-3-methanamine (**8b**).

a. To 30 ml of cold chloroform was added 4-methylaminomethyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine (1.5 g, 0.0066 mole) and triethylamine (1.3 ml, 0.01 mole), followed by a solution of ethyl chloroformate (1.0 ml, 0.01 mole) in 5 ml of chloroform. After stirring at ambient temperature for five hours, the mixture was diluted with 50 ml ether, washed with water (2 ×), then dried (saturated sodium chloride, anhydrous magnesium sulfate). After filtering, the solvents were evaporated to a clear oil, 2 g, which was determined to be the desired carbamate intermediate; ir (chloroform): N-C(O)-O, 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 4.52 (s, 2H, CH_2), 5.23 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 6.11 (q, 2H, 2,3-pyrrolo), 6.66-7.36 (m, 4H, aromatic); ms: m/e 301 $(MH)^+$.

To a suspension of LAH (50% in oil, 0.6 g, 0.0065 mole) in 25 ml of cold THF was added a solution of the carbamate (1.0 g, 0.0033 mole) in 20 ml of THF. After stirring at ambient temperature for three hours, the mixture was quenched with 5 ml of saturated ammonium chloride solution, diluted with 50 ml of ether, then filtered. The filtrate was washed with water (2 ×), then dried (saturated sodium chloride, anhydrous magnesium sulfate). After filtering, the solvents were evaporated to a clear oil, which was dissolved in ether, then acidified to *p*H 1 with an ether solution of maleic acid. The resultant white precipitate was recrystallized from 2-propanol to yield white crystals, 0.5 g (40%), 160° dec; ms: (Cl) MH^+ 243; nmr (deuteriochloroform) (free base): δ 2.17 (s, 6H, $2CH_3$), 3.38 (s, 2H, α-CH_2), 5.22 (s, 2H, ring CH_2), 5.36 (s, 2H, ring CH_2), 5.93 (d, 1H, pyrrole), 6.15 (d, 1H, pyrrole), 6.66-7.28 (m, 4H, aromatic); ms: m/e 243 $(MH)^+$.

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot C_4H_4O_4$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.75; H, 6.20; N, 7.83.

b. A mixture of 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine **3** (3 g, 16.2 mmoles), paraformaldehyde (1.6 g), and dimethylamine hydrochloride (1.45 g, 17.8 mmoles) was refluxed in ethanol (50 ml) for 16 hours. The ethanol was then removed under vacuum and the resulting residue stirred with water, basified with dilute sodium hydroxide solution, and extracted with methylene dichloride. The methylene dichloride extract was dried (saturated sodium chloride wash, magnesium sulfate) and the solvent removed to give 3 g (12.4 mmoles, 77%) of an oil which was purified by flash chromatography (230-400 mesh silica gel, 5% methanol/dichloromethane), and converted to the maleate salt. Recrystallization from methanol/ether gave 2.5 g of white solid, mp 158-160°; nmr and ms identical with product from (a.).

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot C_4H_4O_4$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.71; H, 6.24; N, 7.84.

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