Synthesis of 5-Phenylpyrrolo[1,2-*b*][1,2,5]-triazepin-2(3*H*)-ones [1]

R. Richard L. Hamer*, Richard C. Effland and Joseph T. Klein

Hoechst-Roussel Pharmaceuticals Inc., Chemical Research Department, Somerville, New Jersey 08876

Francis P. Huger

Hoechst-Roussel Pharmaceuticals Inc., Department of Biochemistry, Somerville, New Jersey 08876

Jeffrey C. Wilker

Hoechst-Roussel Pharmaceuticals Inc., Department of Pharmacology, Somerville, New Jersey 08876

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The synthesis of a series of 5-phenylpyrrolo[1,2-*b*][1,2,5]triazepin-2(3*H*)-ones **1** as potential anxiolytic agents is described. Benzoylation of 1-phthalimidopyrrole, followed by hydrolysis, gave the 1-amino-2-benzoylpyrroles **3**. These were further functionalized to give the penultimate 1-aminoacetamido-2-benzoylpyrroles **8** and **9**, which were cyclized to the target pyrrolotriazepines **1**.

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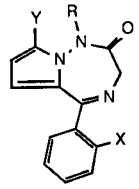
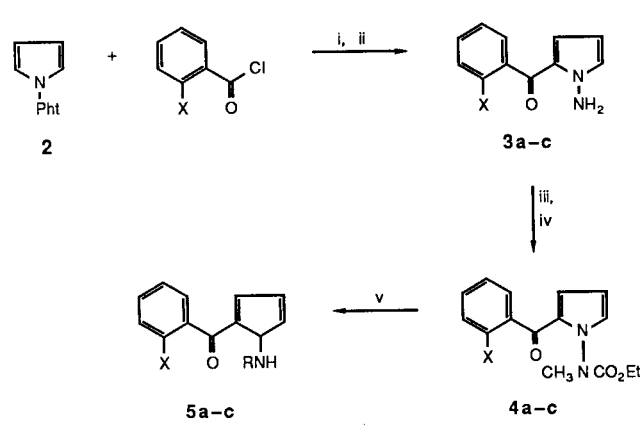
One current objective in anti-anxiety research is to develop compounds with improved pharmacological and clinical profiles over the traditional benzodiazepine anxiolytic drugs. From the standpoint of bioisosterism, a number of heteroaromatic diazepine derivatives have been recently prepared. These heterocycles include pyridine [2], thiophene [3a,b], pyrazole [4], thiazole [5], isoxazole [6], indole [7], and others [8]. As an extension of our continuing interest in pyrrole chemistry [9] and the bioisosteric effects of pyrrole-phenyl interchange, we prepared a series of 5-phenylpyrrolo[1,2-*b*][1,2,5]triazepin-2(3*H*)-ones **1a-g** as potential anxioselective anxiolytic agents.



R = H, CH_3
X = H, F, Cl
Y = H, Cl

As shown in Scheme I, 1-phthalimidopyrrole **2** [10], prepared by acidic condensation of 1-aminophthalimide with 2,5-dimethoxytetrahydrofuran, was acylated with various benzoyl chlorides in the presence of zinc chloride or tin(IV) chloride to give predominately the 2-acylated isomer. Stronger Lewis acids or elevated temperatures afforded polymeric material and a larger ratio of the 3-isomer respectively. Subsequent hydrolysis of the phthalimide group with aqueous methylamine in ethanol [11] gave the aminoketones **3a-c** in good overall yield. For the synthesis of 1-substituted pyrrolotriazepinones **1d-f** it was found advantageous to alkylate the pendant amino group prior to cyclization. To this end the aminoketones **3a-c** were acylated with ethyl chloroformate and then alkylated in the presence of milled potassium carbonate to afford carbamates **4a-c** which were hydrolyzed to give the *N*-alkylated aminopyrroles **5a-c** (Scheme I).

Scheme 1



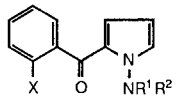
(i) $Zn(II)Cl_2$, DCE, 4 hours, 60°. (ii) 40% CH_3NH_2, EtOH, 2 hours, 25°. (iii) $ClCO_2Et$, $NaHCO_3$, DCM, 3 hours, 40°. (iv) CH_3I, K_2CO_3, DMF, 8 hours, 2! (v) KOH, EtOH, 18 hours, 80°.

With the exception of **9a** the penultimate aminoacetamides were prepared by straightforward homologation of the aminoketones **3a-c** and **5b-c** *via* condensation with *N*-(*t*-butoxycarbonyl)glycine (BOC-glycine) in the presence of dicyclohexylcarbodiimide affording the intermediate BOC protected amines **6a-c** and **7b-c**.

The BOC group was subsequently hydrolyzed in a protic solvent to the aminoacetamides **8a-c** and **9b-c** in high

Table I

2-Benzoylpyrrole Intermediates

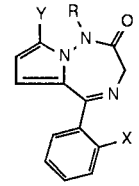


Compound No.	X	R^1	R_2 [a]	Yield, %	mp, °C	Recrystallization Solvent
3a	H	H	H	99	65-67	hexane
3b	F	H	H	93	44-47	hexane
3c	Cl	H	H	94	76-78	hexane
4a	H	CH_3	$CO_2CH_2CH_3$	94	50-52	ether-hexane
4b	F	CH_3	$CO_2CH_2CH_3$	97	64-66	dichloromethane
4c	Cl	CH_3	$CO_2CH_2CH_3$	57	54-56	dichloromethane
5a	H	CH_3	H	84	180-182	2-propanol
5b	F	CH_3	H	75	125-127	2-propanol
5c	Cl	CH_3	H	85	56-58	hexane
6a	H	H	$COCH_2NHBOC$	88	96-98	ethyl acetate-hexane
6b	F	H	$COCH_2NHBOC$	82	114-116	ethyl acetate-hexane
6c	Cl	H	$COCH_2NHBOC$	48	156-158	ethyl acetate-hexane
7b	F	CH_3	$COCH_2NHBOC$	56	112-114	ether
7c	Cl	CH_3	$COCH_2NHBOC$	68	131-133	ether
8a	H	H	$COCH_2NH_2$	74	218 dec	2-propanol
8b	F	H	$COCH_2NH_2$	86	114-116	2-propanol
8c	Cl	H	$COCH_2NH_2$	87	165-167	2-propanol
9c	H	CH_3	$COCH_2NH_2$	48	168-169	methanol
9b	F	CH_3	$COCH_2NH_2$	95	217-219	2-propanol
9c	Cl	CH_3	$COCH_2NH_2$	96	193-195	2-propanol

[a] BOC = *t*-Butoxycarbonyl.

Table II

5-Phenylpyrrolo[1,2-*b*][1,2,5]triazepin-2(3*H*)-ones



Compound No.	X	Y	R	Yield, %	mp, °C	Recrystallization Solvent
1a	H	H	H	17	199 dec	acetone
1b	F	H	H	26	189 dec	acetone
1c	Cl	H	H	13	215 dec	acetone
1d	H	H	CH_3	65	280 dec	acetone
1e	F	H	CH_3	76	210 dec	ethanol-ether
1f	Cl	H	CH_3	27	132-133	acetone
1g	F	Cl	CH_3	55	218 dec	2-propanol-ether

yields (Scheme II). The aminoacetamide **9a** was prepared by reaction of 1-amino-2-benzoylpyrrole **5a** with bromoacetyl bromide to give the bromoacetamide, which on treatment with sodium azide afforded the corresponding 2-azido-*N*-methyl-*N*-[2-benzoyl-1*H*-pyrrol-1-yl]acetamide. Reduction of the latter with platinum oxide gave **9a**. These aminoacetamides proved to be refractory to standard cyclization methods used in most diazepine syntheses. The target pyrrolotriazepinones were best prepared by cyclization of the aminoacetamide free bases in a refluxing solution of acetic acid and isopropanol. Chlorination of pyrrolotriazepinone **1e** with *N*-chlorosuccinimide gave substitution only at position 8 (**1g**). Characterization data for intermediates and the target compounds are given in Tables I through III.

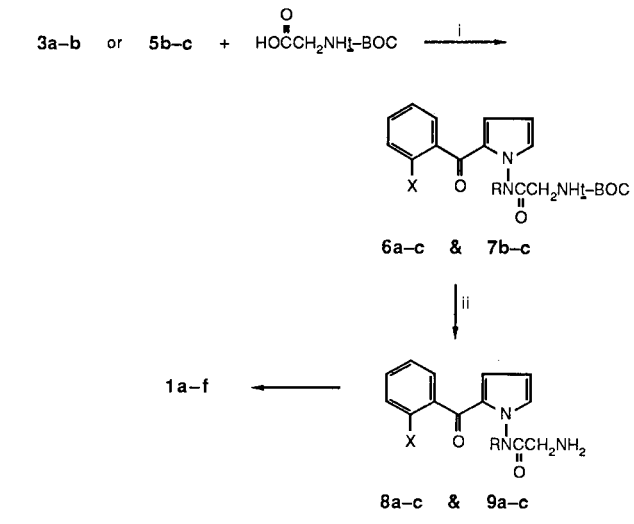
Table III

Elemental Analyses

Compound No.	Molecular Formula	Analyses, % Calcd. (% Found) C	H	N
1a	$C_{13}H_{11}N_3O$	69.31	4.92	18.65
		69.37	4.86	18.84
1b	$C_{13}H_{10}FN_3O$	64.19	4.14	17.28
		64.10	4.17	17.44
1c	$C_{13}H_{10}ClN_3O$	60.12	3.88	16.18
		60.47	4.00	16.39
1d	$C_{14}H_{13}N_3O\cdot HBr$	52.51	4.40	13.12
		52.57	4.55	13.01
1e	$C_{14}H_{12}FN_3O\cdot HCl$	57.24	4.45	14.30
		56.87	4.62	14.12
1f	$C_{14}H_{12}ClN_3O$	61.42	4.42	15.35
		61.57	4.43	15.75
1g	$C_{14}H_{11}ClFN_3O\cdot HCl$	51.23	3.68	12.80
		51.11	4.00	12.75
3a	$C_{11}H_{10}N_2O$	70.95	5.41	15.05
		71.11	5.27	14.98
3b	$C_{11}H_9FN_2O$	64.70	4.44	13.72
		64.69	4.64	13.53
3c	$C_{11}H_9ClN_2O$	59.87	4.11	12.69
		59.91	3.97	12.74
4a	$C_{15}H_{16}N_2O_3$	66.15	5.92	10.29
		66.28	6.05	10.26
4b	$C_{15}H_{15}FN_2O_3$	62.05	5.20	9.65
		62.11	5.19	9.65
4c	$C_{15}H_{15}ClN_2O_3$	58.73	4.93	9.13
		58.62	4.92	9.07
5a	$C_{12}H_{12}N_2O\cdot HBr$	51.26	4.66	9.96
		51.39	4.77	9.91
5b	$C_{12}H_{11}FN_2O$	66.04	5.08	12.83
		66.06	5.03	12.47
5c	$C_{12}H_{11}ClN_2O$	61.40	4.72	11.94
		61.43	4.86	11.91
6a	$C_{18}H_{21}N_3O_4$	62.95	6.16	12.13
		63.08	5.95	12.48
6b	$C_{18}H_{20}FN_3O_4$	59.82	5.57	11.62
		59.98	5.85	11.64
6c	$C_{18}H_{20}ClN_3O_4$	57.21	5.33	11.12
		57.33	5.58	11.03
7b	$C_{19}H_{22}FN_3O_4$	60.78	5.90	11.19
		60.79	5.69	11.13
7c	$C_{19}H_{22}ClN_3O_4$	58.23	5.66	10.72
		58.25	5.99	10.61
8a	$C_{13}H_{13}N_3O_2\cdot HCl$	55.81	5.04	15.02
		55.51	5.11	15.02
8b	$C_{13}H_{12}FN_3O_2\cdot HBr$	45.60	3.82	12.28
		45.20	4.14	12.04
8c	$C_{13}H_{12}ClN_3O_2\cdot HBr\cdot \frac{1}{2}H_2O$	42.47	3.83	11.43
		42.59	3.53	11.78
9a	$C_{14}H_{15}N_3O_2\cdot C_4H_4O$	57.90	5.13	11.25
		57.59	5.13	11.11
9b	$C_{14}H_{14}FN_3O_2\cdot HBr$	47.20	4.24	11.79
		47.32	4.33	11.95
9c	$C_{14}H_{14}ClN_3O_2\cdot HBr$	45.10	4.05	11.27
		44.75	4.05	11.18

Potential anxiolytic activity was evaluated *in vitro* by the ability of the compounds to displace ^{3}[H]-flunitrazepam from rat cortical homogenates [12]. Potential anticonvulsant activity was determined by measuring the inhibition of extensor tonus of mice subjected to electroshock [13]. As can be seen from Table IV, a separation of activities within the series was observed. Compounds **1a-g** were all active in displacing ^{3}[H]-flunitrazepam. Compounds **1e-g**, however, exhibited significant anticonvulsant activity as well [14]. Compound **1f** was the most potent of the series in both assays.

Scheme 2



(i) DCC, DCM, 5 hours, 25°. (ii) HBr, EtOAc, 1 hour, 35°.

(iii) CH_3CO_2H, 2-propanol

Table IV

Anxiolytic and Anticonvulsant Activities

	Bz Binding [a] (IC_{50} M)	SES [b] (ED_{50} mg/kg, i.p.) (95% CL)
1a	6.73×10^{-6}	>60
1b	5.86×10^{-7}	>60
1c	2.04×10^{-7}	>60
1d	3.40×10^{-7}	>60
1e	6.21×10^{-8}	43.6 (42.1-45.1)
1f	2.27×10^{-8}	17.9 (11.7-27.4)
1g	6.99×10^{-7}	36.1 (32.0-41.7)
Diazepam	9.60×10^{-9}	1.7

[a] ^{3}[H]-Flunitrazepam displacement from rat cortical homogenates. [b] Supramaximal electroshock assay in mice. ED_{50} values 95% confidence limits were calculated by computer probit analysis.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam SP3-200 Spectrophotometer. Nuclear magnetic resonance spectra were taken on a Jeol C-60HL or Varian 200 XL (where indicated) instrument. Chemical shifts are reported as δ units with tetramethylsilane as an internal standard. Mass spectral data were

determined with a Finnigan 4023 GC/MS/DS equipped with a INCOS data system. Elemental analyses were performed by Micro Tech Laboratories, Skokie, IL. Gravity and flash chromatographic purifications were performed using silica gel 60 as the solid phase (230-400 mesh) from EM Laboratories, Elmsford, NY. The hplc purifications were performed on a Waters Prep LC/System 500A with silica gel cartridges. Solvents were dried over 3 Å molecular sieves for reactions requiring anhydrous solvents.

(1-Amino-1*H*-pyrrol-2-yl)(2-chlorophenyl)methanone (**3c**).

Freshly pulverized zinc chloride (43.3 g, 320 mmoles) was added in one portion to a vigorously stirred mixture of 1-phthalimidopyrrole **2** (45 g, 210 mmoles) and 2-chlorobenzoyl chloride (37 g, 210 mmoles) in 500 ml of 1,2-dichloroethane. The reaction mixture was heated at 60° for 4 hours and then quenched with 700 ml of crushed ice and 500 ml of 1,2-dichloroethane. The organic layer was separated and washed with water, dried (magnesium sulfate), filtered, and concentrated to an oil. Flash chromatography of this oil (dichloromethane) gave 33.8 g (45%) of 2-[2-[2-chlorobenzoyl]-1*H*-pyrrol-1-yl]-1*H*-isoindole-1,3(2*H*)-dione.

This solid (31.5 g, 90 mmoles) was suspended in 350 ml of 95% ethanol and treated with 50 ml of a 40% aqueous methylamine solution over 10 minutes. After 2 hours of rapid stirring, the mixture was diluted with 400 ml of water and extracted with ether. The combined extracts were washed with water, dried (magnesium sulfate), filtered, and concentrated to an oil which solidified upon standing. Recrystallization of this solid from hexane gave 18.6 g (94%) of **3c** as a white powder, mp 76-78°; ir (chloroform): 1620 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.9 (s, 2H, NH_2), 5.9-6.2 (m, 1H, 4-β-pyrrole H), 6.35-6.55 (m, 1H, 3-β-pyrrole H), 7.05-7.25 (m, 1H, α-pyrrole H), 7.3-7.65 (m, 4H, ArH); ms: m/e 220 (M^+). Compounds **3a** and **3b** were prepared in a similar manner (Table I).

[2-[2-Chlorobenzoyl]-1*H*-pyrrol-1-yl]methylcarbamic Acid Ethyl Ester (**4c**).

Compound **3c** (32 g, 150 mmoles) was combined with sodium bicarbonate (30.2 g, 360 moles) in 400 ml of dichloromethane. Ethyl chloroformate (18.6 g, 170 mmoles) was added with vigorous stirring over 2 minutes and the resultant slurry heated under reflux for 2.5 hours. The mixture was quenched with 300 ml of water, separated, dried (magnesium sulfate), filtered, and concentrated to an oil. This oil slowly crystallized to give 32.8 g (77%) of 2-[2-chlorobenzoyl]-1*H*-pyrrol-1-ylcarbamic acid, ethyl ester. This solid carbamate (22 g, 75.1 mmoles), milled potassium carbonate (15.4 g, 110 mmoles), and methyl iodide (13 g, 120 mmoles) were combined in 100 ml of dry dimethylformamide and stirred at ambient temperature for 8 hours. The reaction was quenched with 1 liter of water and extracted with ether. The combined extracts were washed with water, dried (magnesium sulfate), filtered, and concentrated to afford a solid. Purification of this solid by preparative hplc (dichloromethane) gave 13.1 g (57%) of **4c** as white crystals, mp 54-56°; ir (chloroform); 1725 (NC=O), 1640 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.2 (t, 3H, CH_3), 3.45 (s, 3H, NCH_3), 4.2 (q, 2H, CH_2), 6.0-6.25 (m, 1H, 4-β-pyrrole H), 6.4-6.6 (m, 1H, 3-β-pyrrole H), 6.95-7.1 (m, 1H, α-pyrrole H), 7.2-7.5 (m, 4H, ArH); ms: m/e 307 (MH^+). Compounds **4a** and **4b** were prepared in a similar manner (Table I).

(2-Chlorophenyl)[1-(methylamino)-1*H*-pyrrol-2-yl]methanone (**5c**).

Compound **4c** (39.2 g, 130 mmoles) was dissolved in 100 ml of ethanol and 200 ml of water containing sodium hydroxide (25 g, 620 mmoles). The solution was heated under reflux for 18 hours followed by evaporation of the ethanol. The aqueous solution was extracted with ethyl acetate and the combined organic phase was dried (magnesium sulfate), filtered, and concentrated to give 28 g of an oil. Kugelrohr distillation of this oil at 125° (0.15 mm) gave a waxy solid. Trituration of this solid with hexane gave 25.5 g (85%) of **5c** as white crystals, mp 56-58°; ir (chloroform): 1620 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.92 (s, 3H, CH_3), 5.9 (bs, 1H, NH), 6.0-6.2 (m, 1H, 4-β-pyrrole H), 6.4-6.6 (m, 1H, 3-β-pyrrole H), 7.1-7.3 (m, 1H, α-pyrrole H), 7.4-7.6 (m, 4H, ArH); ms: m/e 234 (M^+). Compounds **5a** and **5b** were prepared in a similar manner (Table I).

[[[2-[2-Chlorobenzoyl]-1*H*-pyrrol-1-yl]methylamino]carbonyl]methylcarbamic Acid 2-Methylpropyl Ester (**7c**)

Compound **5c** (23.7 g, 100 mmoles) and *N*-(*t*-butoxycarbonyl)glycine (19.2 g, 110 mmoles) were combined in 250 ml of dichloromethane followed by addition of dicyclohexylcarbodiimide (23.7 g, 120 mmoles) in two portions over 3 minutes. The mixture was stirred at ambient temperature for 5 hours and was then filtered and concentrated to a yellow oil. Purification of this oil by preparative hplc (2:1 hexane-ethyl acetate) gave 28 g of a white solid. Recrystallization from ether gave 26.5 g (68%) of **7c** as white crystals, mp 131-133°; ir (chloroform): 1710-1690 (amide, carbamate (C=O), 1640 cm^{-1} (C=O) ^1H nmr (deuteriochloroform): δ 1.42 (s, 9H, $3CH_3$), 3.41 (s, 3H, NCH_3), 3.5-3.9 (m, 2H, CH_2), 5.3 (bs, 1H, NH), 6.2-6.4 (m, 1H, 4-β-pyrrole H), 6.5-6.7 (m, 1H, 3-β-pyrrole H), 7.05-7.2 (m, 1H, α-pyrrole H), 7.48 (s, 4H, ArH); ms: m/e 392 (MH^+). Compounds **6a-c** and **7b** were prepared in a similar manner (Table I).

2-Amino-*N*-methyl-*N*-[2-[2-chlorobenzoyl]pyrrol-1-yl]acetamide Hydrobromide (**9c**).

A stirred solution of **7c** (24 g, 61 mmoles) in 100 ml of ethyl acetate was treated with 60 ml of 1-propanol containing 12 ml of 48% hydrobromic acid. After 1 hour at 35° the solution was concentrated and the residue triturated with ether to give 23.2 g of a white powder. Recrystallization from 2-propanol gave 22 g (96%) of **9c** as white flocculent crystals, mp 193-195°; ir (potassium bromide); 3450, 3100, 3030-2800 (NH_3^+), 1680 (NC=O), 1630 cm^{-1} (C=O); ^1H nmr (methyl sulfoxide-d_6): δ 3.1-3.9 (m, 2H, CH_2), 3.36 (s, 3H, CH_3), 6.3-6.52 (m, 1H, 4-β-pyrrole H), 6.58-6.73 (m, 1H, 3-β-pyrrole H), 7.4-7.8 (m, 5H, 4ArH, α-pyrrole H), 8.1-8.5 (bs, 3H, NH_3); ms: m/e 292 (MH^+). Compounds **8a-c** and **9b** were prepared in a similar manner (Table I).

2-Amino-*N*-methyl-*N*-[2-benzoyl-1*H*-pyrrol-1-yl]acetamide Fumarate (**9a**).

A mixture of compound **5a** (14.9 g, 55 mmoles) and sodium bicarbonate (5.9 g, 71 mmoles) in 150 ml of dichloromethane was treated with a solution of bromoacetyl bromide (8.4 g, 42 mmoles) in 30 ml of dichloromethane over 30 minutes. After 22 hours at ambient temperature the mixture was washed with water, dried (magnesium sulfate), filtered, and concentrated to an oil which crystallized from ether-hexane to give 11.0 g (98%) of 2-bromo-*N*-[2-benzoyl-1*H*-pyrrol-1-yl]-*N*-methylacetamide as white crystals, mp 76-78°. A mixture of sodium azide (23.2 g, 350 mmoles) in 100 ml of dimethylformamide was treated with a solution of the above solid (10.2 g, 32 mmoles) in 30 ml of dimethylformamide and the resultant mixture was stirred at ambient temperature for 24 hours. This mixture was diluted with 800 ml of water then extracted with dichloromethane. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to give 8.2 g (82%) of 2-azido-*N*-methyl-*N*-[2-benzoyl-1*H*-pyrrol-1-yl]acetamide as a yellow solid which was used without further purification. The above azide (8.2 g, 29 mmoles) in 200 ml of methanol was hydrogenated in the presence of 250 mg of platinum oxide at 15 psi for 2 hours. The catalyst was removed by filtration and the filtrate was treated with fumaric acid (3.5 g, 30 mmole) and evaporated. The resulting solid was recrystallized from methanol-ether to give 5.2 g (48%) of **9a** as a white powder, mp 168-169°; ir (potassium bromide): 3400, 3200, 2950, 2800, 2600 (NH_3^+, CO_2H), 1710 (NC=O), 1630 cm^{-1} (C=O); ^1H nmr (methyl sulfoxide-d_6); δ 3.2-3.6 (m, 2H, CH_2), 3.3 (s, 3H, CH_3), 6.3-6.55 (m, 1H, 4-β-pyrrole H), 6.6 (s, 2H, CH=CH), 6.85-7.05 (m, 1H, 3-β-pyrrole H), 7.3-8.1 (m, 10H, 5ArH, α-pyrrole H, NH_2, $2CO_2H$; ms: m/e 257 (M^+).

5-(2-Chlorophenyl)-1-methy-1*H*-pyrrolo[1,2-*b*][1,2,5]triazepin-2(3*H*)-one (**1f**).

A solution containing the free base of **9c** (12.6 g, 43 mmoles) and glacial acetic acid (15 g, 250 mmoles) in 10 ml of 2-propanol was heated under reflux for 12 hours then concentrated to a dark oil. Flash chromatography of this oil (4:1 ethyl acetate-hexane) gave 3.2 g of a solid which was recrystallized from acetone to give 3.1 g (26%) of **1f** as white crystals, mp 132-133.5°; ir (chloroform): 1690 cm^{-1} (C=O); ^1H nmr

(methyl sulfoxide-d_6): δ 3.45 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 5.85-6.05 (m, 1H, β-pyrrole H), 6.1-6.35 (m, 1H, β-pyrrole H), 7.4-7.7 (m, 5H, 4ArH, α-pyrrole H); ms: m/e 274 (MH^+). Compounds **1a-e** were prepared in a similar manner (Table II).

8-Chloro-5-(2-(fluorophenyl)-1-methyl-1*H*-pyrrolo[1,2-*b*][1,2,5]triazepin-2(3*H*)-one Hydrochloride (**1g**).

A solution containing compound **1e** (3.3 g, 12.9 mmoles) and *N*-chlorosuccinimide (1.87 g, 14 mmoles) in 100 ml of dry tetrahydrofuran was stirred under reflux for 3 hours then concentrated. The residual oil was purified by flash chromatography (4:7 hexane-ethyl acetate) to give 2.1 g of an oil. This oil was treated with an excess of ethereal hydrogen chloride and the residue was recrystallized from 2-propanol-ether to give 2.3 g (55%) of **1g** as a white powder, mp 218° dec; ir (potassium bromide): 3400, 2500 (broad) (NH^+), 1710 cm^{-1} (C=O); ^1H nmr (methyl sulfoxide-d_6): (200 MH_z) δ 3.4 (s, 3H, CH_3), 4.45 (d, 1H, CH_2), 4.85 (d, 1H, CH_2), 6.8 (d, 1H, pyrrole H), 6.96 (d, 1H, pyrrole H), 7.4-7.6 (m, 2H, ArH), 7.8-8.0 (m, 2H, ArH), 11.3 (bs, 1H, NH^+); ms: m/e 291 (M^+).

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