Synthesis of Novel Pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepines. A Novel Heterocyclic Ring System

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The synthesis of novel pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepines **6-17** is described. Subsequent reactions on the parent system include reduction, Grignard addition, alkylation, acylation and carbamoylation.

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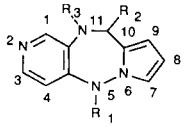
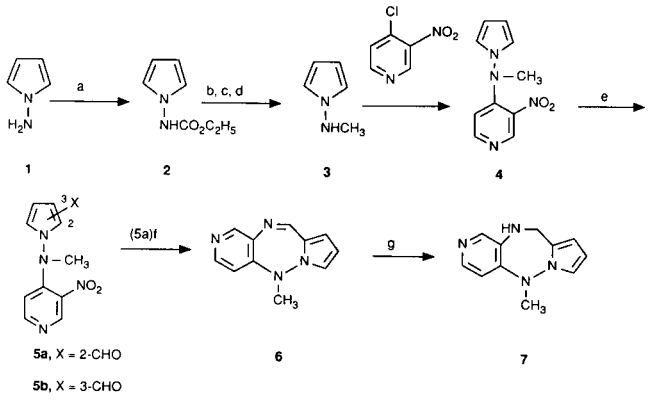
We recently reported the synthesis of the aminopyrrole containing heterocycles 5-phenylpyrrolo[1,2-*b*][1,2,5]triazepine-2(3*H*)-ones [1] and pyrrolo[1,2-*b*]cinnolines [2]. We now report the synthesis of a series of pyrido[3,4-*f*]pyrrolo-[1,2-*b*][1,2,5]triazepines **I**, another novel heterocyclic ring system incorporating the *N*-aminopyrrole moiety. This system lends itself to ready derivitization by substitution on nitrogen (*e.g.* N-5, N-11) or carbon (*e.g.* C-7 [3] or C-10).



I

As shown in Scheme I, 1-aminopyrrole **1** [4] was converted to the carbamate **2** by reaction with ethyl chloroformate. Treatment of **2** with potassium *t*-butoxide followed by methyl iodide gave the tertiary methylated carbamate which then was hydrolyzed to give 1-methylaminopyrrole **3**. Condensation of **3** with 4-chloro-3-nitropyridine [5] in dimethylformamide gave [*N*-methyl-*N*-(1*H*-pyrrol-1-yl)]-3-nitro-4-pyridinamine **4**. Formylation of **4** under Vilsmeier conditions gave the 2-aldehyde **5a**, along with a minor amount of the 3-aldehyde **5b**. Aldehyde **5a** cyclized spontaneously upon reduction of the nitro group with stannous chloride in tetrahydrofuran to give 5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine **6**. The imine **6** could be reduced with sodium borohydride to give the dihydro pyrrolotriazepine **7**, or reacted with Grignard reagents to give the C-10 adducts **8-13** (Scheme II). The dihydro **7** could be substituted at N-11 by acylation (**14**), formylation (**15**), carbamoylation (**16**) or alkylation (**17**).

Scheme I



Reagents:
a. ethyl chloroformate, dichloromethane sodium bicarbonate
b. potassium t-butoxide, THF
c. methyl iodide
d. NaOH, ethylene glycol
e. $POCl_3$/DMF
f. $SnCl_2 \cdot 2H_2O$, THF, HCl
g. $NaBH_4$, C_2H_5OH

Scheme II

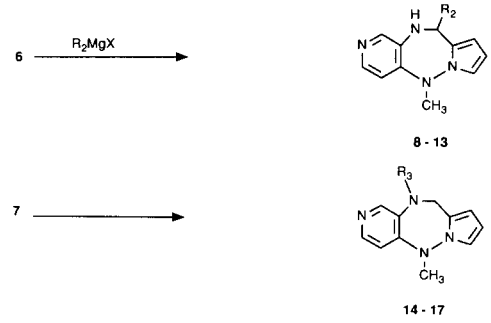
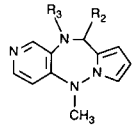


Table I



Compound No.	R_2	R_3
7	H	H
8	CH_3	H
9	C_6H_5	H
10	$(CH_2)_2C_6H_5$	H
11	4-(1-Methylpiperidinyl)	H
12	$(CH_2)_3N(CH_3)_2$	H
13	$(CH_2)_3N(C_2H_5)_2$	H
14	H	$COCH_3$
15	H	CHO
16	H	$CONHCH_3$
17	H	$(CH_2)_4$-4-(2-$CH_3OC_6H_4$)piperazine

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectral data were determined on a Finnigan 4023 GC/MS/DS equipped with a INCOS data system. The ^{1}H nmr spectra were obtained at 200 MHz using a Varian 200 XL with tetramethylsilane as an internal standard. The infrared spectra were recorded on a Pye Unicam SP3-200. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Illinois. Flash chromatographic separations 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.

[*N*-Methyl-*N*-(1*H*-pyrrol-1-yl)]-3-nitro-4-pyridinamine (**4**).

A mixture of sodium bicarbonate (15 g) and (*N*-amino)pyrrole (**1**) (9.2 g, 112 mmoles) in 50 ml of dichloromethane was treated over a period of fifteen minutes with ethyl chloroformate (13.0 g, 119 mmoles). The reaction mixture was then stirred at ambient temperature for four hours and filtered. The filtrate was washed with water followed by a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and filtered. Concentration afforded 17 g (98%) of *N*-(1*H*-pyrrol-1-yl)carbamic acid ethyl ester (**2**), mp 60-61°; ir (chloroform): ν 3430 cm^{-1} (NH), 1755 (C=O) cm^{-1}; ms: m/e 154 (M$^+$).

A cold solution of the secondary carbamate **2** (9 g, 58 mmoles) in 30 ml of tetrahydrofuran was treated with potassium *t*-butoxide (7.8 g) and then stirred at 5° for one hour. The mixture was then treated with a solution of 4.1 ml of methyl iodide in 10 ml of tetrahydrofuran and stirred at ambient temperature for four hours. The reaction mixture was then poured into 100 ml of water, stirred for five minutes and extracted with ethyl acetate. The organic layer was washed with water followed by a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate and filtered. Concentration afforded 9.4 g (96%) of *N*-methyl-*N*-(1*H*-pyrrol-1-yl)carbamic acid ethyl ester as an oil; ir (chloroform): ν 1720 cm^{-1} (C=O); ms: m/e 168 (M$^+$).

A solution of 9.4 g (55.9 mmoles) of this tertiary carbamate in 15 ml of ethylene glycol was treated with 10 ml of a 50% aqueous soluion of sodium hydroxide. After stirring at reflux for four hours, the reaction mixture was poured into 100 ml of water and extacted with ethyl acetate. The organic layer was washed with water followed by a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. Vacuum distillation of the resultant oil afforded 4.3 g (80%) of *N*-(methylamino)pyrrole (**3**) as an oil, bp 32-35° @ 1 mm Hg; ir (chloroform): ν 3340 cm^{-1} (NH); ms: m/e 96 (M$^+$).

A solution of *N*-(methylamino)pyrrole (**3**) (8.8 g, 91.5 mmoles) and 14.5 g (91.5 mmoles) of 4-chloro-3-nitropyridine in 200 ml of dimethylformamide was stirred at ambient temperature for 17 hours. The reaction mixture was then added to an aqueous sodium bicarbonate solution and extracted twice with diethyl ether. The combined organic layer was washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated with hexane to afford 15.6 g (78%) of [*N*-methyl-*N*-(1*H*-pyrrol-1-yl)]-3-nitro-4-pyridinamine (**4**), mp 91-99°. Treatment of 5.0 g of this product with ethereal hydrogen chloride yielded the corresponding hydrochloride salt. Recrystallization from isopropanol:methanol (3:1) afforded 3.4 g of [*N*-methyl-*N*-(1*H*-pyrrol-1-yl)]-3-nitro-4-pyridinamine hydrochloride, mp 235-236° dec; ^{1}H nmr (DMSO-d_6): δ 3.50 (s, 3H, N-CH_3), 6.16 (m, 2H, H-3 and H-4 pyrrole), 6.81 (d, 1H, H-5 pyridine), 6.98 (m, 2H, H-2 and H-5 pyrrole), 8.61 (d, 1H, H-6 pyridine), 9.10 (s, 1H, H-2 pyridine), 9.83 (broad s, 1H, exchanges with deuterium oxide); ms: m/e 218 (M$^+$).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$·HCl: C, 47.16; H, 4.35; N, 22.00. Found: C, 47.07; H, 4.19; N, 22.09.

10,11-Dihydro-5-methyl-5*H*-pyridol[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**7**).

Chilled dimethylformamide (5.5 ml) was treated with 7.5 ml of phosphorus oxychloride, stirred at ambient temperature ten minutes and then diluted with 10 ml of dichloroethane. The mixture was then treated with a solution of [*N*-methyl-*N*-(1*H*-pyrrol-1-yl)]-3-nitro-4-pyridinamine (**4**) (12 g, 55 mmoles) in 125 ml of dichloroethane. After stirring at 80° for four and one-half hours, the reaction was quenched with a solution of 45 g of sodium acetate trihydrate in 125 ml of water, refluxed at 80° for one hour, cooled, basified with sodium carbonate and extracted with dichloromethane. The organic layer was washed with an aqueous solution of sodium carbonate followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give an orange semi-solid. Purification by hplc (10% ethyl acetate/dichloromethane) gave 7.3 g (54%) of 1-[*N*-methyl-*N*-(3-nitro-4-pyridinyl)amino]pyrrole-2-carboxaldehyde (**5a**), mp 101-107°; ir (chloroform): ν 1680 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.40 (s, 3H, N-CH_3), 6.40 (m, 2H, H-4 pyrrole and H_5 pyridine), 7.10 (m, 2H, H-3 and H-5 pyrrole), 8.41 (d, 1H, H-6 pyridine), 8.72 (s, 1H, H-2 pyridine), 9.52 (s, 1H, C*H*O); ms: m/e 246 (M$^+$), and 2.35 g (17%) of 1-[*N*-methyl-*N*-(3-nitro-4-pyridinyl)-amino]pyrrole-3-carboxaldehyde (**5b**). The latter was further purified by recrystallization from isopropyl ether-methanol (5:1) to give a tan solid, mp 145-148°; ir (chloroform): ν 1690 (C=O), 1610, 1540, 1510, 1370, 1260 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.45 (s, 3H, N-CH_3), 6.46 (d, 1H, H-5 pyridine), 6.77 (m, 1H, H-4 pyrrole), 6.82 (m, 1H, H-5 pyrrole), 7.44 (m, 1H, H-2 pyrrole), 8.49 (d, 1H, H-6 pyridine), 8.84 (s, 1H, H-2 pyridine), 9.81 (s, 1H, C*H*O); ms: m/e 246 (M$^+$).

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.23; H, 4.09; N, 22.73.

To cold, concentrated hydrochloric acid (200 ml) was added, in the following order, 100 g of stannous chloride dihydrate, 200 ml of tetrahydrofuran, and a solution of 1-[*N*-methyl-*N*-(3-nitro-4-pyridinyl)amino]pyrrole-2-carboxaldehyde (**5a**) (28 g, 113.7 mmoles) in 150 ml of tetrahydrofuran. Upon completion of the addition, the reaction was stirred for ten minutes longer, poured into an aqueous solution of sodium hydroxide (200 g in 1 liter of water), stirred for five minutes and then extracted with ethyl acetate. The organic layer was washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. The resultant oil was purified by hplc (elution with ethyl acetate) to afford 10 g (38%) of 5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**6**) as an oil; ir (chloroform): ν 1610 cm^{-1} (C=N); ^{1}H nmr (deuteriochloroform): δ 3.08 (s, 3H, N-CH_3), 6.22 (m, 1H, H-8), 6.60 (m, 1H, H-9), 7.00 (s, 1H, H-7), 7.14 (d, 1H, H-4), 8.34 (s, 1H, H-10), 8.44 (d, 1H, H-3), 8.70 (s, 1H, H-1); ms: m/e 198 (M$^+$).

A solution of 4.2 g (21 mmoles) of 5-methyl-5*H*-pyridol-[3,4-*f*]-

pyrrolo[1,2-*b*][1,2,5]triazepine (**6**) in 75 ml of ethanol, was treated with 800 mg (21 mmoles) of sodium borohydride and stirred at ambient temperature for 18 hours. The solvent was then concentrated *in vacuo* and the residue taken up in water and extracted twice with ethyl acetate. The combined organics were washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 4.0 g (95%) of a white solid, mp 133-140°. Recrystallization from isopropyl ether:methanol (180:10) afforded 3.1 g (74%) of 10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*]-[1,2,5]triazepine (**7**), mp 135-140°; ^{1}H nmr (deuteriochloroform): δ 3.34 (s, 3H, N-C*H*$_3$), 4.34 (broad s, 1H, exchanges with deuterium oxide), 4.46 (s, 2H, H-10), 5.98 (m, 2H, H-7 and H-8), 6.79 (m, 1H, H-9), 6.84 (d, 1H, H-4), 7.82 (d, 1H, H-3), 7.82 (s, 1H, H-1); ms: m/e 200 (M$^+$).

Anal. Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.76; H, 6.18; N, 28.03.

10,11-Dihydro-5,10-dimethyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]-triazepine (**8**).

To 8.4 ml of a solution of methyl magnesium iodide (3.2 *M* in diethyl ether, diluted with 10 ml tetrahydrofuran) was added a solution of 4.1 g (20.7 mmoles) of 5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**6**) in 70 ml of tetrahydrofuran. After stirring at ambient temperature for 20 hours, the reaction mixture was quenched into 200 ml of an iced ammonium chloride solution and extracted twice with ethyl acetate. The combined organics were washed with water followed by a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The crude product was purified *via* flash chromatography (elution with diethyl ether) to afford a solid, recrystallization of which from toluene yielded 2.1 g (48%) of 10,11-dihydro-5,10-dimethyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**8**), mp 157-160°; ^{1}H nmr (deuteriochloroform): δ 1.61 (d, 3H, -C*H*$_3$), 3.35 (s, 3H, N-C*H*$_3$), 3.99 (broad s, 1H, exchanges with deuterium oxide), 5.02 (q, 1H, H-10), 5.94 (m, 1H, H-8), 6.02 (m, 1H, H-9), 6.79 (m, 1H, H-7), 6.82 (d, 1H, H-4), 7.84 (d, 1H, H-3), 7.84 (s, 1H, H-1); ms: m/e 214 (M$^+$).

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 66.94; H, 6.73; N, 26.23.

10,11-Dihydro-5-methyl-10-phenyl-5,10*H*-pyrido[3,4-*f*]pyrrolo-[1,2-*b*][1,2,5]triazepine (**9**).

Using the procedure described above for compound **8**, compound **9** was prepared from **6** and phenyl magnesium bromide in 79% chromatographed yield. Recrystallization of the chromatographed material from toluene gave a 64% yield of **9**, mp 200-203°; ^{1}H nmr (deuteriochloroform): δ 3.33 (s, 3H, N-C*H*$_3$), 4.38 (broad s, 1H, exchanges with deuterium oxide), 5.51 (broad s, 1H, H-10), 5.96 (m, 2H, H-8 and H-9), 6.84 (m, 1H, H-7), 6.85 (d, 1H, H-4), 7.48 (m, 5H, phenyl), 7.87 (d, 1H, H-3), 7.89 (s, 1H, H-1); ms; m/e 276 (M$^+$).

Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.91; H, 5.78; N, 20.12.

10,11-Dihydro-5-methyl-10-(2-phenylethyl)-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**10**).

To 2.8 g of magnesium turnings in 20 ml of diethyl ether and 20 ml of tetrahydrofuran was added 1 ml of 1,2-dibromoethane followed by 13.94 ml (102 mmoles) of 2-bromoethylbenzene. After initiating the reaction with external heat, the mixture was stirred at room temperature for one hour and then treated with a solution of 10.0 g (50 mmoles) of 5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo-[1,2-*b*][1,2,5]triazepine (**6**) in 100 ml of tetrahydrofuran. The reaction mixture was then stirred at room temperature for two hours, poured into an iced ammonium chloride solution, stirred for five minutes and extracted with ethyl acetate. The organic layer was washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. The concentrate (15.21 g) was purified by means of hplc (elution with ethyl acetate). Flash chromatography of the resultant oil (elution with 10% methanol/dichloromethane) afforded a solid (2.1 g) which was recrystallized from diethyl ether/-ethyl acetate (10:1) to yield 1.25 g of 10,11-dihydro-5-methyl-10-(2-phenylethyl)-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**10**), mp 92-94°; ^{1}H nmr (deuteriochloroform): δ 2.18, 2.48 (2 x m, 2H, C*H*$_2$CH$_2$C$_6$H$_5$), 2.94 (t, 2H, CH$_2$C*H*$_2$C$_6$H$_5$), 3.34 (s, 3H, N-CH$_3$), 3.90 (s, 1H, exchanges with deuterium oxide, NH), 4.80 (broad t, 1H, H-10), 5.96 (m, 1H, H-8), 6.05 (m, 1H, H-9), 6.82 (m, 1H, H-7), 6.82 (d, 1H, H-4), 7.30 (m, 5H, phenyl), 7.78 (s, 1H, H-1), 7.86 (d, 1H, H-3); ms: m/e 304 (M$^+$).

Anal. Calcd. for $C_{19}H_{20}N_4$: C, 75.00; H, 6.58; N, 18.42. Found: C, 74.68; H, 6.72; N, 18.27.

10,11-Dihydro-5-methyl-10-[(1-methyl)piperidin-4-yl]-5*H*-pyrido-[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**11**).

The Grignard reagent of 4-chloro-1-methylpiperidine was prepared and reacted with **6** using the above procedure described for the preparation of **10**, to give after hplc (elution with 50% methanol/dichloromethane) a 28% yield of off-white product, mp 230-235°. Recrystallization from ethyl acetate/methanol (20:1) gave pure **11**, mp 235-238°; ^{1}H nmr (deuteriochloroform): δ 1.42 (m, 2H, aliphatic), 1.96 (m, 5H, aliphatic), 2.30 (s, 3H, piperidine N-CH$_3$), 2.92 (broad t, 2H, aliphatic), 3.40 (s, 3H, N-CH$_3$), 4.28 (m, 2H, H-10 and exchangeable), 5.90 (m, 1H, H-8), 6.06 (m, 1H, H-9), 6.80 (m, 1H, H-7), 6.81 (d, 1H, H-4), 7.84 (s, 1H, H-1), 7.85 (d, 1H, H-3); ms: m/e 297 (M$^+$).

Anal. Calcd. for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55. Found: C, 68.46; H, 7.78; N, 23.49.

10,11-Dihydro-5-methyl-10-[3-(*N*,*N*-dimethylamino)propyl]-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**12**).

Compound **12** was obtained as an oil from the Grignard reagent of *N*,*N*-dimethylaminopropyl chloride, by the same method as that described for the preparation of **10**, in 50% yield after purification by hplc (elution with 50% methanol/dichloromethane). On standing the oil solidified to a tan solid, mp 77-79°; ^{1}H nmr (deuteriochloroform): δ 1.78 (m, 3H, aliphatic) 2.25 (s, 6H, N(CH$_3$)$_2$), 2.30 (m, 3H, aliphatic), 3.32 (s, 3H, N-CH$_3$), 4.77 (broad t, 1H, H-10), 5.89 (m, 2H, H-8 and NH), 6.00 (m, 1H, H-9), 6.76 (m, 1H, H-7), 6.77 (d, 1H, H-4), 7.77 (d, 1H, H-3), 7.80 (s, 1H, H-1); ms: m/e 286 (MH$^+$).

Anal. Calcd. for $C_{16}H_{23}N_5$: C, 67.34; H, 8.12; N, 24.54. Found: C, 67.02; H, 8.24; N, 24.40.

10-[3-(*N*,*N*-Diethylamino)propyl]-10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**13**).

Compound **13** was obtained as an oil, using the same procedure as that described for compound **10**, after purification by hplc (elution with 15% methanol/dichloromethane); ^{1}H nmr (deuteriochloroform): δ 1.06 (t, 6H, N(CH$_2$C*H*$_3$)$_2$), 1.80 (m, 3H, aliphatic), 2.24 (m, 1H, aliphatic), 2.58 (q, 4H, N(C*H*$_2$CH$_3$)$_2$), 2.60 (m,

2H, aliphatic), 3.36 (s, 3H, NCH_3), 4.84 (broad t, 1H, H-10), 5.51 (broad s, 1H, exchanges with deuterium oxide, N*H*), 5.91 (m, 1H, H-8), 6.04 (m, 1H, H-9), 6.81 (m, 1H, H-7), 6.83 (d, 1H, H-4), 7.83 (d, 1H, H-3), 7.87 (s, 1H, H-1); ms: m/e 314 (MH^+).

A portion was converted to the sesquifumarate salt (ethanol-ether), mp 170-172°.

Anal. Calcd. for $C_{18}H_{27}N_5 \cdot 1.5C_4H_4O_4$: C, 59.14; H, 6.78; N, 14.37. Found: C, 58.84; H, 7.05; N, 14.09.

11-Acetyl-10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*]-[1,2,5]triazepine Maleate (**14**).

A mixture of 20 ml of acetic anhydride and 10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (4.0 g, 20 mmoles) was stirred at room temperature for two hours. The mixture was then evaporated, the residue dissolved in water and the aqueous layer extracted with ethyl acetate. The organic layer was washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. The concentrate was purified by means of hplc (elution with ethyl acetate) to afford 2.3 g (48%) of 11-acetyl-10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine as an oil which solidified upon standing (mp 125-130°). The solid was dissolved in ethanol and acidified with an ethanol solution of maleic acid. Dilution with diethyl ether precipitated 2.25 g (31%) of **14**, mp 139-141°; ir (potassium bromide): ν 1680 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform + DMSO): δ 2.18 (broad d, 3H, COCH_3), 3.63 (broad s, 3H, NCH_3), 4.90 (broad s, 2H, H-10), 6.10 (m, 2H, H-8 and H-9), 6.32 (s, 2H, C*H*=C*H* maleate), 6.90 (m, 1H, H-7); 7.14 (broad m, 1H, H-4), 8.37 (broad d, 1H, H-3), 8.50 (broad s, 1H, H-1), 13.35 (broad s, 2H, exchanges with deuterium oxide, 2CO_2*H*); ms: m/e 242 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_4O \cdot C_4H_4O_4$: C, 56.98; H, 5.03; N, 15.64. Found: C, 56.75; H, 5.24; N, 15.43.

11-Formyl-10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*]-[1,2,5]triazepine Maleate (**15**).

A mixture of 2.57 ml of acetic anhydride and 6.42 ml of formic acid was stirred at 60° for one hour. The reaction mixture was then cooled to room temperature and treated with a solution of 10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (3.5 g, 17 mmoles) in 50 ml of tetrahydrofuran. After stirring at room temperature for one hour, the mixture was then poured into water and treated with an aqueous solution of sodium bicarbonate to *p*H 8. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. The resultant solid was purified by means of hplc (elution with ethyl acetate) to afford 3.2 g (83%) of a white solid, mp 133-135°. This material was converted to the maleate salt in ethanol to give 4.5 g of **15**, mp 157-159°; ir (chloroform): ν 1680 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform + DMSO): δ 3.56 (s, 3H, NCH_3), 4.96 (s, 2H, H-10), 6.04 (m, 1H, H-9), 6.12 (m, 1H, H-8), 6.35 (s, 2H, C*H*=C*H* maleate), 6.88 (m, 1H, H-7), 7.07 (d, 1H, H-4), 8.31 (s, 1H, H-1), 8.41 (d, 1H, H-3), 8.44 (s, 1H, C*H*O), 11.2 (broad s, 2H, exchanges with deuterium oxide, 2CO_2H); ms: m/e 228 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_4O \cdot C_4H_4O_4$: C, 55.81; H, 4.65; N, 16.28. Found: C, 55.79; H, 4.74; N, 16.38.

10,11-Dihydro-5-methyl-11-methylcarbamyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**16**).

A solution of 10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo-[1,2-*b*][1,2,5]triazepine (3.7 g, 18 mmoles) in benzene (100 ml) was treated with 1.6 ml of methyl isocyanate and then stirred at 70° for five hours. After cooling, the mixture was evaporated under reduced pressure and the residue was dissolved in water. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with water followed by a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by hplc (elution with 2.5% methanol/dichloromethane) gave 2.3 g (50%) of **16**, mp 197-200° dec. The maleate was formed in ethanol and the resulting solid was recrystallized from ethanol to give 1.8 g of 5,10-dihydro-*N*,5-dimethyl-11*H*-pyrido[3,4-*f*]-pyrrolo[1,2-*b*][1,2,5]triazepine-11-carboxamide maleate, mp 160-161°; ir (potassium bromide): ν 1670 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 2.70 (d, 3H, COCH_3), 3.62 (s, 3H, NCH_3), 4.84 (s, 2H, H-10), 6.00 (m, 1H, H-9), 6.12 (m, 1H, H-8), 6.26 (s, 2H, C*H*=C*H* maleate), 6.50 (m, 1H, exchanges with deuterium oxide, NH), 6.87 (m, 1H, H-7), 7.14 (d, 1H, H-4), 8.26 (d, 1H, H-3), 8.36 (s, 1H, H-1), 12.0 (bs, 2H, exchanges with deuterium oxide, 2CO_2H) ms: m/e 257 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_5O \cdot C_4H_4O_4$: C, 54.69; H, 5.09; N, 18.77. Found: C, 54.59; H, 5.23; N, 18.61.

10,11-Dihydro-11-{1-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (**17**).

To a suspension of sodium hydride (60% in oil, 1.0 g, 0.026 mole) in 10 ml of dry dimethylformamide at 0°, was added a solution of 10,11-dihydro-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,-5]triazepine (**7**) (4.6 g, 23 mmoles) in 50 ml of dimethylformamide.

After stirring at 0° for one hour, a solution of propargyl bromide (2.7 ml) in 10 ml of dimethylformamide was added, and the mixture was stirred at 0° for three hours, poured into 200 ml of water, stirred for five minutes, and then extracted with ethyl acetate. The organic layer was washed with water and dried (saturated sodium chloride, anhydrous magnesium sulfate).

After filtration, the material was concentrated to 3.9 g of dark oil, which was purified *via* hplc (elution with ethyl acetate). The desired fraction was concentrated to 2.4 g (44%) of 10,11-dihydro-11-(2-propynyl)-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]-triazepine as a light brown oil; ir (chloroform): ν 3300 cm^{-1} (C≡CH); ^{1}H nmr (deuteriochloroform): δ 2.30 (m, 1H, C≡C*H*), 3.40 (s, 3H, NCH_3), 3.78 (d, 2H, CH_2C≡C), 4.44 (s, 2H, H-10), 6.0 (m, 1H, H-8), 6.10 (m, 1H, H-9), 6.80 (m, 1H, H-7), 6.86 (d, 1H, H-4), 8.06 (d, 1H, H-3), 8.28 (s, 1H, H-1); ms: m/e 239 (M^+).

To 150 ml of *p*-dioxane were added 10,11-dihydro-11-(2-propynyl)-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine (2.3 g), 4-(2-methoxyphenyl)piperazine (2.1 g), paraformaldehyde (2.0 g) and cuprous chloride (0.02 g). After stirring at 80° for three hours, the mixture was concentrated to 6.9 g of brown oil, which was purified *via* hplc (elution with 5% methanol/dichloromethane). The desired fraction was concentrated to 4.3 g of 10,11-dihydro-11-[1-[4-(2-methoxyphenyl)piperazin-1-yl]-2-butynyl]-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine as a light brown oil; ms: m/e 442 (M^+).

To a slurry of 10% palladium on charcoal (2 g) in 5 ml ethanol was added a solution of 10,11-dihydro-11-{1-[4-(2-methoxyphenyl)-piperazin-1-yl)-2-butynyl}-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*]-[1,2,5]triazepine (4.0 g, 9 mmoles) in 245 ml of ethanol. The resultant mixture was hydrogenated at 50 PSI on a Paar apparatus for

four hours at room temperature. The mixture was then filtered and concentrated to an oil. Purification of the oil was accomplished by means of flash chromatography (elution with 5% methanol/dichloromethane) to afford 1.4 g (35%) of 10,11-dihydro-11-{1-[4-(2-methoxyphenyl)-piperazin-1-yl)-2-butyl}-5-methyl-5*H*-pyrido[3,4-*f*]pyrrolo[1,2-*b*][1,2,5]triazepine as an oil; ^{1}H nmr (deuteriochloroform): δ 1.6 (m, 4H, aliphatic), 2.44 (broad t, 2H, aliphatic), 2.66 (m, 4H, aliphatic), 3.12 (m, 6H, aliphatic), 3.36 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 4.32 (s, 2H, H-10), 6.00 (m, 2H, H-8 and H-9), 6.77 (m, 1H, H-7), 6.83 (d, 1H, H-4), 6.95 (m, 4H, phenyl), 7.92 (d, 1H, H-3), 8.10 (s, 1H, H-1); ms: m/e 447 (M^+).

Anal. Calcd. for $C_{26}H_{34}N_6O$: C, 69.96; H, 7.62; N, 18.83. Found: C, 69.54; H, 7.73; N, 18.45.

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