Synthesis and Salidiuretic Activity of 2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-*a*]pyridines and 5,6-Dihydro-4*H*-pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepines

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Starting from 2-hydrazino-3-(1-pyrrolyl)pyridine **3** a series of 2,3-dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-*a*]pyridines **49–50** and 5,6-dihydro-4*H*-pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepines **32–42** were synthesized and tested *p.o.* in rats for salidiuretic and renal vasodilator activity.

Keywords pyrrole; pyridine; triazolopyridine; triazepine; intramolecular cyclization; ¹H-NMR

In connection with our program on new heterocyclic compounds^{1–4)} with diuretic and antihypertensive activity, we were interested in the synthesis of triazolopyridines and analogues of 5-amino-8-(2-ethoxyethyl)-7-phenyl-5-triazolo[1,5-*c*]pyrimidine (bemitradine)^{5–13)} and we now report the synthesis and preliminary diuretic activity of 2,3-dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-*a*]pyridines and 5,6-dihydro-4*H*-pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepines.

Chemistry We have previously reported¹⁾ the synthesis of new structures such as 8-(1-pyrrolyl)-1,2,4-triazolo[4,3-*a*]pyridines **6** and 6*H*-pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepine **5** from 2-chloro-3-(1-pyrrolyl)pyridine **2** and from 2-hydrazino-3-(1-pyrrolyl)pyridine **3** as previously described.

The present study revealed that, when cyclization reactions were initiated from 2-hydrazino-3-(1-pyrrolyl)pyridine (**3**), they led either to dihydro-8-(1-pyrrolyl)triazolopyridines **8** or to a tricyclic dihydropyridopyrrolotriazepine system **9** and we have attempted to increase our knowledge about the parameters affecting the site of cyclization in order to obtain dihydropyrrolyltriazolopyridines or dihydropyridopyrrolotriazepines regiospecifically. Thus, treatment of 2-hydrazino-3-(1-pyrrolyl)pyridine (**3**) in hot EtOH with various alicyclic carbonyl derivatives afforded intermediate hydrazones **10–24**. In the same way,

treatment of **3** with aromatic carbonyl derivatives led to hydrazones **25–31**. Hydrazones **10–31**, being very unstable, were immediately involved without isolation in cyclization reactions. Two experimental procedures were used: treatment of a solution of hydrazone in EtOH by a slight excess of 30% hydrobromic acid, in acetic acid, or treatment of a solution in diethyl ether by gaseous hy-

Chart 1

Chart 2

Chart 3

Chart 4

TABLE I

No.	Dose mg/kg <i>p.o.</i>	Test of diuresis	Lipschitz natriuresis	Renal blood flow	Mean arterial pressure
32	100	0.92	1.50	Increase	Slight decrease
32	1	0.28	0.48	No effect	No effect
34	100	0.45	0.66	No effect	Decrease
45	100	0.47	0.13	No effect	No effect
46	100	0.17	0.88	No effect	Slight decrease
46	10	0.54	0.79	Not measured	Not measured
47	100	0.69	1.06	No effect	No effect
47	10	0.56	0.72	Not measured	Not measured
63	100	0.48	0.66	Not measured	Not measured
60	100	0.44	0.33	No effect	No effect
61	100	0.70	0.50	No effect	No effect

The figure under diuresis is the ratio between the mean volume of urine eliminated during the 5 h following gavage with the product to be tested and that for the 5 h following gavage with 1 g/kg of urea.

The figure under natriuresis is the ratio between the mean quantity of Na^+ eliminated during the 5 h following forcible feeding with the product to be tested and that for the 5 h following forcible feeding with 1 g/kg of urea.

drogen chloride.

There are two possible sites for cyclization, either the α -pyrrolic carbon or the pyridinic nitrogen, and the reaction orientation appears to be dependent on both the hydrazone-azine tautomerism and the size of the hydrazone substituents. Hydrazonepyridine tautomeric form A favors cyclization on the α -pyrrolic carbon probably because of the possibility of two free-rotating bonds pyridine $\text{C}_2\text{-NH}$ and NH-N= , which causes the system to be in favor of keeping the hydrazone group next to pyrrole ring.

TABLE II. $^1\text{H-NMR}(\text{DMSO-}d_6)$ Spectral Data for 5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepines 32—42

Compound	H1	H2	H3	H8	H9	H10
32	7.26	6.20	6.10	8.16	6.76	7.96
33	7.30	6.18	6.03	8.23	6.96	8.00
34	7.30	6.23	6.16	8.23	6.96	7.93
35	7.30	6.15	6.03	8.20	6.90	7.93
36	7.33	6.18	6.08	8.23	7.00	8.02
37	7.32	6.18	6.12	8.23	7.00	7.97
38	7.26	6.22	6.22	8.13	7.11	8.13
39	7.37	6.23	6.23	8.30	7.07	8.02
40	7.37	6.23	6.13	8.27	7.03	8.03
41	7.35	6.23	6.15	8.25	7.00	8.02
42	7.33	6.28	6.28	8.18	7.20	8.18

On the other hand, in the azinodihydropyridine form B, the structure is much more rigid and allows only one free rotating bond ($=\text{N-N=}$) which favors cyclization in dihydrotriazolopyridine.

This assumption is confirmed when hydrazone and azine structures were built with molecular models. Thus hydrazones 10—21, which carry small size aliphatic substituents, led to isolation of dihydropyridopyrrolotriaze-

TABLE III. ¹H-NMR(DMSO-*d*₆) Spectral Data for 5,6-Dihydro-4*H*-pyrido[2,3-*a*]pyrrolo[1,2-*c*]-1,2,5-triazepines **43**—**48**

Compound	H1	H2	H3	H8	H9	H10
43 ^{a)}	7.17	6.15	6.07	7.90	6.77	7.83
44	7.17	6.15	6.07	7.90	6.80	7.83
45	7.20	6.20	6.20	7.92	6.87	7.82
46	7.13	6.10	6.00	7.82	6.77	7.82
47	7.10	6.10	6.00	7.83	6.75	7.78
48	7.15	6.07	5.90	7.70	7.83	6.65

a) $J_{1,2} = 3.30$ Hz, $J_{1,3} = 1.5$ Hz, $J_{2,3} = 3.60$ Hz, $J_{9,10} = 7.80$ Hz, $J_{8,10} = 1.80$ Hz, $J_{8,9} = 4.80$ Hz.

TABLE IV. ¹H-NMR(DMSO-*d*₆) Spectral Data for 2,3-Dihydro-3-(3-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,5-*a*]pyridines **49**—**59**

Compound	H2' H5'	H3' H4'	H5	H6	H7
49	7.10	6.33	8.33	7.20	8.03
50	7.26	6.40	8.28	8.25	8.25
51	7.20	6.38	8.27	7.30	8.27
52	6.90	6.13	8.37	7.42	8.17
53	7.04	6.30	8.61	7.60	8.31
54	7.17	6.31	8.70	7.70	8.41
55	7.10	6.30	8.61	7.60	8.31
56	7.16	6.31	8.00	7.16	8.00
57	7.11	6.31	8.08	7.11	8.00
58	7.10	6.25	8.03	7.00	8.03
59	7.13	6.33	8.08	7.13	7.93

pine hydrochlorides **32**, **33**, **38**, **40**, dihydrochlorides **41** or hydrobromides **34**—**37**, **39** and **42**. On the other hand hydrazones with bulky substituents such as adamantane **24**, cycloheptane **22**, 2-methoxycyclohexane **21**, 3-methylcyclopentane **23**, or with aromatic substituents **25**—**31**, afforded dihydropyrrolyltriazolopyridine hydrochlorides **49**—**50** or hydrobromides **51**—**59**. Some free bases **60**—**65** were also obtained from the corresponding salts. The structures of these compounds were confirmed on the basis of the ¹H-nuclear magnetic resonance ¹H-NMR spectral analysis.

Biological Evaluation These molecules were studied in the Wistar rat (Sexal strain, males weighing about 250 g) from two points of view: existence of salidiuretic activity associated with a renal vasodilatory effect, or not associated with H.

1. Methods Salidiuretic Activity: The test of Lipschitz¹⁴⁾ modified according to Rupp¹⁵⁾ enables the evaluation, in the conscious rat, of the effect of a product to be tested, administered by gavage on the volume of urine and the renal elimination of sodium, compared with the effects of an oral loading of 1 g/kg of urea. For each dose

TABLE V. ¹H-NMR(DMSO-*d*₆) Spectral Data for 2,3-Dihydro-3-(3-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,5-*a*]pyridines **60**—**65**

Compound	H2' H5'	H3' H4'	H5	H6	H7
60	6.93	6.25	8.25	6.93	7.60
61	7.00	6.27	8.23	7.00	7.53
62	6.68	6.00	8.30	6.93	7.93
63	6.90	6.20	8.40	7.27	8.17
64	6.98	6.20	8.47	7.27	8.20
65	6.80	6.40	8.58	6.80	7.47

and each product, mean diuresis and natriuresis were measured (in a metabolism cage for 5 h, 8 rats) and the ratio between the effects of the product tested and those of the urea loading are calculated. If this ratio is above 0.81 for urine volume, it means that a diuretic effect can be assumed; similarly, a significant natriuretic effect can be assumed if the natriuresis ratio is above 0.72.¹⁶⁾

By way of comparison, under the same experimental conditions, the diuresis ratio was 11.5 ($n = 8$) for furosemide (100 mg/kg, *p.o.*), 1.27 ($n = 16$) for amiloride (100 mg/kg, *p.o.*) and 2.39 ($n = 16$) for triamterene (100 mg/kg, *p.o.*).

Renal Vasodilator Action: Under Inactin-induced anesthesia (100 mg/kg, *i.p.*), the renal blood flow was measured with an electromagnetic probe (Skalar transflow 601) placed on the left renal artery. Blood pressure was measured at the level of the carotid artery (Statham P23 Db transducer). These parameters were recorded for 30 min prior to and 240 min after the intragastric gavage of the drug tested (in suspension at a volume of 0.3 ml of an aqueous solution of 10% gumarabic).

2. Results Pyridopyrrolotriazepines **32**, **46** and **47** had weak but significant natriuretic effects. These were scarcely detectable with doses of 10 mg/kg, *p.o.*, and disappeared with a dose of 1 mg/kg. The salidiuretic effect of **32** was accompanied by renal vasodilatation and a slight decrease in peripheral vascular resistance with a dose of 100 mg/kg *p.o.*

This data suggests that the pyridopyrrolotriazepine tricyclic structure derivative **32** comprises a pharmacophore for the salidiuretic and vasodilator effects which is not encountered with the dihydropyrrolyltriazolopyridine bicyclic structure.

Experimental

Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Infrared (IR) spectra were recorded as KBr pellets on a Perkin-Elmer 257 G spectrophotometer, and ¹H-NMR spectra were obtained on a VARIAN EM 90 spectrometer for solution in dimethyl sulfoxide-*d*₆ (DMSO-*d*₆). Chemical shifts are expressed in ppm downfield from Me₄Si as an internal standard, and the *J* values are given in Hertz.

General Procedure for the Preparation of Hydrobromides and Hydrochlorides of 5,6-Dihydro-4*H*-pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepines **32—**42** and 2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-*a*]pyridines **49**—**59**** Method a: Preparation of Hydrobromides: x g (x' mol) of 2-hydrazino-3-(1-pyrrolyl)pyridine (**3**) were added to an absolute EtOH (100 ml) solution containing a 1.1 eq of carbonyl derivative. The reaction

mixture was refluxed for 2 h and the solvent was evaporated off. The obtained residual oil was dissolved in an absolute EtOH (5 ml), then 30% of hydrobromic acid in acetic acid (3 ml) was added. After being stirred at room temperature for 1 h, the precipitate was isolated, washed with diethyl ether (20 ml), dried and recrystallized from an appropriate solvent.

Method b: Preparation of Hydrochloride: Gaseous hydrogen chloride was bubbled through the obtained residual oil dissolved in anhydrous diethyl ether (80 ml) for 2 min. The precipitate was collected by filtration, washed with diethyl ether (20 ml), dried and recrystallized from an appropriate solvent.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-cyclohexane Hydrochloride (32) **3** (2 g, 11.5 mol) and cyclohexanone (1.1 g, 12.6 mmol) afforded **32** (2.12 g, 55%), mp 230 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 2660, 1640 (NH, NH₂⁺). Anal. Calcd for C₁₅H₁₉ClN₄: C, 61.95; H, 6.58; Cl, 12.19; N, 19.26. Found: C, 62.00; H, 6.60; Cl, 12.20; N, 19.30.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-1'-(2'-methyl cyclohexane) Hydrochloride (33) **3** (2 g, 11 mmol) and 2-methylcyclohexanone (1.3 g, 12.6 mmol) afforded **33** (0.059 g, 17%), mp 170 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3220, 3195, 2600 (NH, NH₂⁺). Anal. Calcd for C₁₆H₂₁ClN₄: C, 63.04; H, 6.94; Cl, 11.63; N, 18.38. Found: C, 63.30; H, 6.85; Cl, 11.87; N, 18.54.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-1'-(3'-methyl cyclohexane) Hydrobromide (34) **3** (2 g, 11.5 mmol) and 3-methylcyclohexanone (1.29 g, 12.6 mmol) afforded **34** (2.33 g, 58%), mp 238 °C (EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3160, 2670, 1640 (NH, NH₂⁺). Anal. Calcd for C₁₆H₂₁BrN₄: C, 55.02; H, 6.06; Br, 22.80; N, 16.04. Found: C, 54.89; H, 5.97; Br, 23.00; N, 16.06.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-1'-(4'-methyl cyclohexane) Hydrobromide (35) **3** (2 g, 11.5 mmol) and 4-methylcyclohexanone (1.29 g, 12.6 mmol) afforded **35** (2.30 g, 57%), mp 236 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3160, 2670, 1640 (NH, NH₂⁺). Anal. Calcd for C₁₆H₂₁BrN₄: C, 55.02; H, 6.06; Br, 22.88; N, 16.04. Found: C, 55.03; H, 6.12; Br, 22.79; N, 16.20.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-(tetrahydrofuran) Hydrobromide (36) **3** (2 g, 11.5 mmol) and 4H-tetrahydrofuran-4-one (1.126 g, 12.6 mmol) afforded **36** (1.3 g, 34%), mp 238 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3060, 3010, 2950, 2860, 1625 (NH, NH₂⁺). Anal. Calcd for C₁₄H₁₇BrN₄O: C, 49.87; H, 5.08; Br, 23.70; N, 16.61. Found: C, 49.78; H, 5.18; Br, 23.82; N, 16.67.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-(tetrahydrothiopyran) Hydrobromide (37) **3** (2 g, 11.5 mmol) and tetrahydrothiopyran-4-one (1.46 g, 12.6 mmol) afforded **37** (2.8 g, 69%), mp 244 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3150, 3100, 3040, 2960, 2900, 2790 (NH, NH₂⁺). Anal. Calcd for C₁₄H₁₇BrN₄S: C, 47.60; H, 4.85; Br, 22.62; S, 9.07. Found: C, 47.77; H, 4.97; Br, 22.41; S, 8.94.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-cyclopentane Hydrochloride (38) **3** (2 g, 11.5 mmol) and cyclopentanone (0.97 g, 12.6 mmol) afforded **38** (2 g, 63%), mp 238 °C (EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3190, 2650, 1630 (NH, NH₂⁺). Anal. Calcd for C₁₄H₁₇ClN₄: C, 60.75; H, 6.19; Cl, 12.81; N, 20.24. Found: C, 60.79; H, 6.18; Cl, 12.71; N, 20.44.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-3'-(tetrahydrothiophene) Hydrobromide (39) **3** (2 g, 11.5 mmol) and tetrahydrothiophen-3-one (1.29 g, 12.6 mmol) afforded **39** (1.7 g, 45%), mp 246 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3180, 3100, 3020, 2960, 2770, 2700, 1640 (NH, NH₂⁺). Anal. Calcd for C₁₃H₁₅BrN₄S: C, 46.03; H, 4.46; Br, 23.55; N, 16.51. Found: C, 46.09; H, 4.36; Br, 23.75; N, 16.45.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-1'-methylpiperidine Hydrochloride (40) **3** (2 g, 11.5 mmol) and 1-methylpiperidine-4-one (1.43 g, 12.6 mmol) afforded **40** (1.65 g, 42%), mp 225 °C (MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3075, 2940, 2700, 1630 (NH, NH₂⁺). Anal. Calcd for C₁₅H₂₁Cl₂N₅: C, 52.64; H, 6.18; Cl, 20.72; N, 20.46. Found: C, 52.56; H, 6.12; Cl, 21.00; N, 20.48.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-(1'-isopropylpiperidine) Dihydrochloride (41) **3** (2 g, 11.5 mmol) and 1-isopropylpiperidine-4-one (1.8 g, 12.6 mmol) afforded **41** (2.73 g, 64%), mp 265 °C (iso-PrOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3180, 3120, 2960, 2940, 2530, 1605 (NH, NH₂⁺). Anal. Calcd for C₁₇H₂₅Cl₂N₅: C, 55.14; H, 6.80; Cl, 18.91; N, 19.15. Found: C, 54.94; H, 6.71; Cl, 18.61; N, 19.31.

4-Cyclohexyl-5,6-dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine Hydrobromide (42) **3** (1.7 g, 9.7 mmol) and cyclohexane-4-carboxaldehyde (1.2 g, 10.6 mmol) afforded **42** (2.50 g, 73%), mp 234 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3180, 3090, 2930, 2850, 1630 (NH, NH₂⁺). Anal. Calcd for C₁₆H₂₁BrN₄: C, 55.02; H, 6.06; Br, 22.88; N, 16.04. Found: C,

54.84; H, 5.96; Br, 23.00; N, 15.96.

2,3-Dihydro-3H-3-(4-fluorophenyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrochloride Monohydrate (49) **3** (2.5 g, 14.7 mmol) and 4-fluorobenzaldehyde (2.01 g, 16.1 mmol) afforded **49** (2.6 g, 53%), mp 210 °C (iso-PrOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3440, 3320, 1635 (NH, NH₂⁺). Anal. Calcd for C₁₆H₁₆ClFN₄O: C, 54.74; H, 4.21; N, 10.78. Found: C, 57.68; H, 4.25; N, 10.60.

2,3-Dihydro-3-(4-fluorophenyl)-3-methyl-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrochloride (50) **3** (2.1 g, 12 mmol) and 4-fluoroacetophenone (1.83 g, 13.2 mmol) afforded **50** (2.2 g, 55%), mp 220 °C (iso-PrOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3320, 3260, 2800, 2700, 1630 (NH₂⁺). Anal. Calcd for C₁₇H₁₆ClFN₄: C, 61.66; H, 4.84; F, 5.74; N, 16.93. Found: C, 61.84; H, 4.85; F, 5.80; N, 17.00.

2,3-Dihydro-3-ethyl-3-(4'-fluorophenyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrobromide (51) **3** (2 g, 11.5 mmol) and 4-fluoropropiophenone (1.92 g, 12.6 mmol) afforded **51** (3.1 g, 70%), mp 240 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3440, 3340, 3320, 2960, 2860, 1630 (NH₂⁺). Anal. Calcd for C₁₈H₁₈BrFN₄: C, 55.34; H, 4.66; F, 4.88; N, 14.39. Found: C, 55.70; H, 4.67; F, 5.00; N, 14.41.

2,3-Dihydro-3-(4-fluorophenyl)-3-phenyl-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine (52) **3** (2.5 g, 14.4 mmol) and 4-fluorobenzophenone (2.87 g, 15.8 mmol) afforded **52** (2.8 g, 45%), mp 265 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300, 2820, 2720, 1630 (NH₂⁺). Anal. Calcd for C₂₂H₁₈BrFN₄: C, 60.41; H, 4.12; Br, 18.27. Found: C, 60.48; H, 4.15; Br, 18.47.

2,3-Dihydro-3H-3-(3-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrobromide (53) **3** (2 g, 11.5 mmol) and pyridine-3-carboxaldehyde (1.35 g, 12.6 mmol) afforded **53** (2.2 g, 56%), mp 240 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300, 2800, 1640 (NH₂⁺). Anal. Calcd for C₁₅H₁₄BrN₅: C, 52.34; H, 4.10; Br, 23.21; N, 20.35. Found: C, 52.26; H, 4.19; Br, 23.35; N, 20.14.

2,3-Dihydro-3-methyl-3-(3-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrobromide (54) **3** (2 g, 11.5 mmol) and 3-acetylpyridine (1.53 g, 12.6 mmol) afforded **54** (1.3 g, 32%), mp 236 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3100, 3030, 2900, 1630 (NH₂⁺). Anal. Calcd for C₁₆H₁₆BrN₅: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.64; H, 4.45; N, 19.43.

2,3-Dihydro-3-methyl-3-(4-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine Hydrobromide (55) **3** (2 g, 11.5 mmol) and 4-acetylpyridine (1.39 g, 12.6 mmol) afforded **55** (1.8 g, 36%), mp 270 °C (MeCN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3230, 2780 (NH₂⁺). Anal. Calcd for C₁₆H₁₆BrN₅: C, 53.63; H, 4.50; Br, 22.30; N, 19.55. Found: C, 53.33; H, 4.52; Br, 22.15; N, 19.49.

2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine-3-spiro-2'-adamantane Hydrobromide (56) **3** (2 g, 11.5 mmol) and adamantan-2-one (1.73 g, 12.6 mmol) afforded **56** (1.73 g, 22%), mp 260 °C (MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3100, 2920, 2800, 1625 (NH₂⁺). Anal. Calcd for C₁₉H₂₁BrN₄: C, 59.21; H, 5.49; N, 14.54. Found: C, 59.44; H, 5.50; N, 14.54.

2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine-3-spirocycloheptane Hydrobromide (57) **3** (2 g, 11.5 mmol) and cycloheptanone (1.29 g, 12.6 mmol) afforded **57** (1.1 g, 27%) mp 226 °C (EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3100, 2910, 2830 (NH₂⁺). Anal. Calcd for C₁₆H₂₁BrN₄: C, 55.02; H, 6.06; N, 16.04. Found: C, 55.21; H, 6.10; N, 16.12.

2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine-3-spiro-(2'-methoxycyclohexane) Hydrobromide (58) **3** (2 g, 11.5 mmol) and 2-methoxycyclohexanone (1.47 g, 12.6 mmol) afforded **58** (0.9 g, 21%), mp 140 °C (acetone). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3500, 3350, 2940, 1640 (NH₂⁺). Anal. Calcd for C₁₆H₂₁BrN₄O: C, 52.61; H, 5.79; N, 15.35. Found: C, 52.45; H, 5.80; N, 15.25.

2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine-3-spiro-(3'-methoxycyclopentane) Hydrobromide (59) **3** (2 g, 11.5 mmol) and 3-methoxycyclopentanone (1.13 g, 12.6 mmol) afforded **59** (2 g, 52%), mp 180 °C (EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3350, 2950, 1640 (NH₂⁺). Anal. Calcd for C₁₅H₁₉BrN₄: C, 53.74; H, 5.71; N, 16.71. Found: C, 53.60; H, 5.69; N, 16.69.

General Procedure for the Preparation of 5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepines and 2,3-Dihydro-8-(1-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridines x g of hydrobromide or hydrochloride (x mmol) were added to a 100 ml aqueous solution of saturated sodium hydrogen carbonate. After stirring at room temperature for 1 h, the obtained precipitate was collected by filtration, washed with 50 ml H₂O, dried and recrystallized in an appropriate solvent.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-tetrahydrofuran (43) **36** (2 g, 5.9 mmol). Yield (0.62 g, 41%), mp 210 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260, 3220 (NH). Anal. Calcd for C₁₄H₁₆N₄O: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.48; H, 6.29; N, 21.82.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-

tetrahydrothiopyran (44) 37 (1.4 g, 3.9 mmol). Yield (0.55 g, 51%) mp 170 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3270, 3215 (NH). *Anal.* Calcd for C₁₄H₁₆N₄S: C, 61.74; H, 5.92; N, 20.57; S, 11.27. Found: C, 61.76; H, 5.94; N, 20.58; S, 11.43.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-3'-tetrahydrothiophene (45) 39 (1.7 g, 5 mmol). Yield (0.5 g, 38%), mp 178 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260, 3220 (NH). *Anal.* Calcd for C₁₃H₁₄N₄S: C, 60.44; H, 5.46; N, 21.69; S, 12.41. Found: C, 60.20; H, 5.49; N, 21.63; S, 12.33.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-N-methylpiperidine (46) 40 (1.65 g, 4.7 mmol). Yield (0.8 g, 62%), mp 190 °C (CH₃CN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3220, 3100 (NH). *Anal.* Calcd for C₁₅H₁₉N₅: C, 66.89; H, 7.11; N, 26.00. Found: C, 67.00; H, 7.14; N, 26.01.

5,6-Dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine-4-spiro-4'-N-isopropylpiperidine (47) 41 (1.6 g, 4.3 mmol). Yield (0.5 g, 40%), mp 164 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260, 3230 (NH). *Anal.* Calcd for C₁₇H₂₃N₅: C, 68.66; H, 7.79; N, 23.55. Found: C, 68.68; H, 7.70; N, 23.60.

4-Cyclohexyl-5,6-dihydro-4H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine (48) 42 (1.65 g, 4.7 mmol). Yield (0.7 g, 55%), mp 116 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3280, 3220 (NH). *Anal.* Calcd for C₁₆H₂₀N₄: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.77; H, 7.54; N, 20.70.

2,3-Dihydro-3-(4-fluorophenyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,5-a]pyridine (60) 49 (0.2 g, 0.6 mmol). Yield (0.1 g, 57%), mp 90 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3330 (NH). *Anal.* Calcd for C₁₆H₁₃FN₄: C, 68.56; H, 4.67; F, 6.78; N, 19.99. Found: C, 68.52; H, 4.68; F, 6.62; N, 19.78.

2,3-Dihydro-3-(4-fluorophenyl)-3-methyl-8-(1-pyrrolyl)-4-1,2,4-triazolo[4,5-a]pyridine (61) 50 (2.2 g, 6.7 mmol). Yield (0.69 g, 35%), mp 120 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360 (NH). *Anal.* Calcd for C₁₇H₁₅FN₄: C, 69.37; H, 5.14; F, 6.45; N, 19.04. Found: C, 69.24; H, 5.16; F, 6.33; N, 19.05.

2,3-Dihydro-3-(4-fluorophenyl)-3-phenyl-8-(1-pyrrolyl)-1,2,4-triazolo[4,5-a]pyridine (62) 52 (1.5 g, 3.4 mmol). Yield (0.5 g, 42%), mp 160 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3320 (NH). *Anal.* Calcd for C₂₂H₁₇FN₄: C, 74.14; H, 4.81; F, 5.33; N, 15.72. Found: C, 74.20; H, 4.92; F, 5.28; N, 15.72.

2,3-Dihydro-3-(3-pyridyl)-8-(1'-pyrrolyl)-1,2,4-triazolo[4,5-a]pyridine (63) 53 (1 g, 2.9 mmol). Yield (0.35 g, 46%), mp 151 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3120 (NH). *Anal.* Calcd for C₁₅H₁₃N₅: C, 68.43; H, 4.98; N, 26.60. Found: C, 68.43; H, 5.02; N, 26.51.

2,3-Dihydro-3-(3-pyridyl)-8-(1'-pyrrolyl)-1,2,4-triazolo[4,5-a]pyridine pyridine (64) 54 (0.8 g, 2.2 mmol). Yield (0.3 g, 48%), mp 140 °C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3280 (NH), 1550, 1445, 1380, 1370, 660. *Anal.* Calcd for

C₁₆H₁₅N₅: C, 69.30; H, 5.45; N, 25.25. Found: C, 69.22; H, 5.42; N, 25.28.

2,3-Dihydro-3-methyl-3-(4-pyridyl)-8-(1-pyrrolyl)-1,2,4-triazolo[4,5-a]pyridine (65) 55 (1.5 g, 4.1 mmol). Yield (0.2 g, 17%), mp 126 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3335 (NH). *Anal.* Calcd for C₁₅H₁₅N₅: C, 69.30; H, 5.45; N, 25.25. Found: C, 69.29; H, 5.50; N, 25.28.

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