Synthesis of 7-(1-Pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazines

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The reactions of secondary amines (pyrrolidine, piperidine and morpholine) with 3,4,5-trichloropyridazine (**4**) was investigated. With **4** and excess amine, disubstitution occurred in good yield and selectively at positions 3 and 5. Treatment of **4** with 2 equivalents of the amine in ethanol afforded high yields of products resulting from monosubstitution at position 5. 3,4-Dichloro-5-(1-pyrrolidinyl)pyridazine (**6a**), resulting from **4** and 2 equivalents of pyrrolidine, was converted cleanly to 4-chloro-3-hydrazino-5-(1-pyrrolidinyl)pyridazine (**8**) with hydrazine hydrate. Pyridazine **8** was cyclized with formic acid to give a 1:1 complex (**9**) of formic acid and 8-chloro-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**13**). Triazolopyridazine **13** also formed a monohydrate (**12**) and a monohydrochloride salt (**14**). Catalytic hydrogenation of **9** gave 7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**3**), which was a target compound of this investigation.

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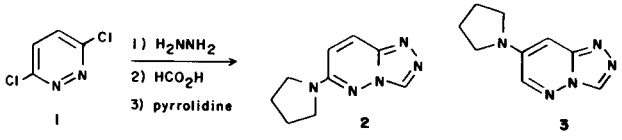
We recently needed samples of 6-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**2**) and its 7-(1-pyrrolidinyl) isomer **3** for a comparative pharmacological study. The preparation of **2** is known and initiates from 3,6-dichloropyridazine (**1**). Treatment of **1** with hydrazine and cyclization of the resulting 3-chloro-6-hydrazinopyridazine with formic acid yields 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine [1]. The latter affords **2** on treatment with pyrrolidine [2].



1 2 3

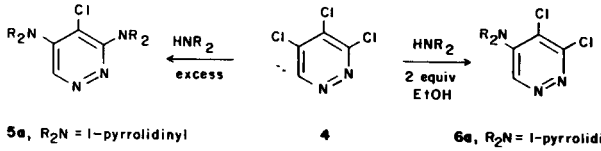
It appeared that 3,4,5-trichloropyridazine [3,6] could be an appropriate starting material for the heretofore unknown **3**, since Kuraishi and Castle [7] had used it as the starting material in their preparation of 7-amino-1,2,4-triazolo[4,3-*b*]pyridazine. These authors showed that 3,4,5-trichloropyridazine, when treated with ethanolic ammonia, produced a mixture of 4-amino-3,5-dichloropyridazine and 5-amino-3,4-dichloropyridazine, in isolated yields (after chromatography) of 35% and 38%, respectively. The latter isomer was used to prepare 7-amino-1,2,4-triazolo[4,3-*b*]pyridazine. Castle and co-workers have utilized the aminodichloropyridazines which they made to prepare several other heterocyclic ring systems [7-10].

Since little selectivity between positions 4 and 5 was observed in the ammonolysis of 3,4,5-trichloropyridazine (**4**) [7], we decided to investigate the reactions of **4** with secondary amines, as a starting point in our synthesis of **3**. Scheme I shows the results of such a study with pyrrolidine, piperidine and morpholine. Treatment of **4** with excesses of these amines gave products of disubstitution (**5a-c**). The specificity of these displacements for positions 3 and 5 was high, and the yields for these transformations were high, as can be seen from the Table in Scheme I.

Disubstitution reactions of **4** with other nucleophiles have produced pyridazines with substituents in adjacent positions. Thus, treatment of **4** with 2-aminothiophenol and 2-(methylamino)thiophenol afforded diazaphenothiazines [11,12]. In addition, when **4** was treated with two equivalents of benzyl mercaptide, 4,5-bis(benzylthio)-3-chloropyridazine resulted [13]. The latter structure was confirmed by an alternate synthesis [13].

The positions of disubstitution in **5a** were verified with an additional experiment. Hydrogenolysis of the chloro group by catalytic hydrogenation (Scheme II) gave 3,5-di-1-pyrrolidinylpyridazine (**7**), whose structure was unambiguous from its nmr spectrum. The coupling constant for the pyridazine hydrogens was 2.5 Hz, which clearly indicated a meta relationship. Interestingly, the hydrogen at the 4-position, which is strongly shielded in its ortho position

SCHEME I



5a, R_2N = 1-pyrrolidinyl
b, R_2N = 1-piperidinyl
c, R_2N = 4-morpholinyl

4

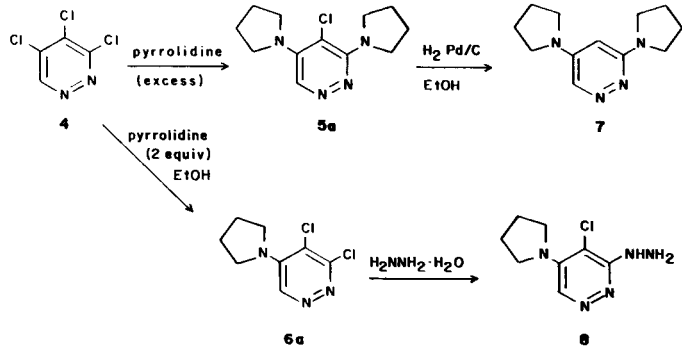
6a, R_2N = 1-pyrrolidinyl
b, R_2N = 1-piperidinyl
c, R_2N = 4-morpholinyl

Compound	Crude Yield (%)	Purity [a] (%)	Absolute Yield [b]	Recryst Yield (%)	Mp (°C)
5a	93	87	81	72 [c]	135-136
5b	97	80	78	52 [d]	81-83
5c	64	100	64	84 [e]	149.5-150
6a	98	78	76	48 [c]	86.5-88
6b	98	93	91	50 [c]	88-89
6c	82	93	76	56 [c]	105-107.5

[a] Determined by integrating all pyridazine proton signals present in the crude material and finding the area % of the signal corresponding to the compound of this table. [b] Determined from the product of columns 2 and 3. [c] Ethanol-water. [d] Hexane. [e] Crystallized directly from the reaction medium by the addition of water.

by both pyrrolidine rings, appears at δ 5.38 (deuteriochloroform), while the hydrogen at position 6 appears at δ 8.00.

SCHEME II



We next treated 3,4,5-trichloropyridazine (**4**) with 2 equivalents of the three amines in ethanol, to yield products of monosubstitution **6a-c**. Specificity for displacement at the 5-position was high (*vide infra*), and yields for these transformations were good (Scheme I). These results are particularly interesting when compared with the nonspecific amminolysis results with **4**.

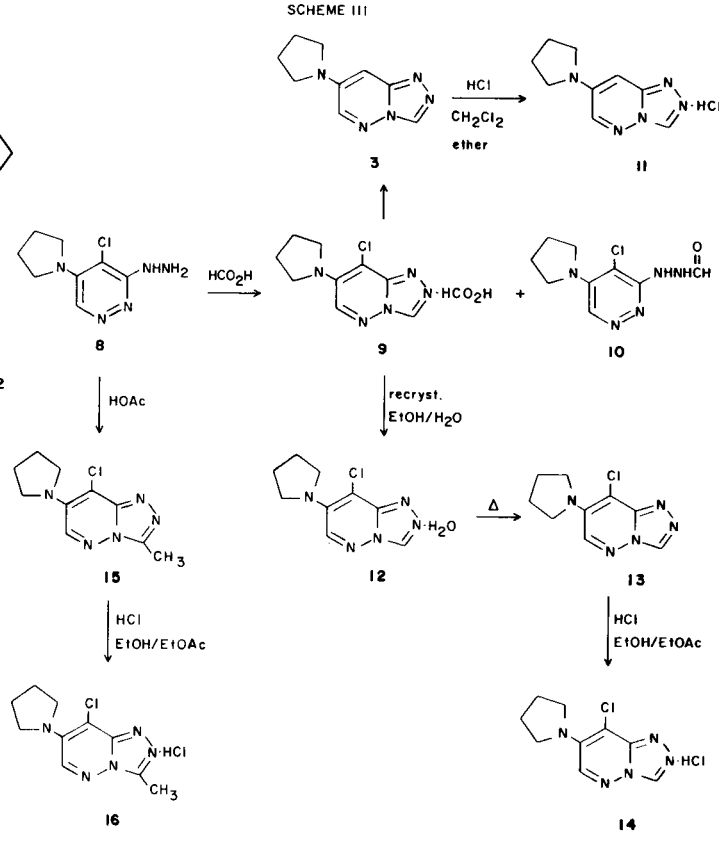
The structure assignments for **6a-c** were tentatively made at this point on the basis of nmr spectrometry. The pyridazine hydrogen in **6a**, for instance, appeared at δ 8.40 (deuteriochloroform), which was significantly farther upfield with respect to the pyridazine hydrogen of **4**, which appears at δ 9.40 (deuteriochloroform and dimethylsulfoxide-d_6) [14]. This shielding effect was consistent with structure **6a**, where the pyrrolidinyl group had been introduced ortho to the pyridazine hydrogen.

Having found that **6a** could be selectively and efficiently produced from **4**, we proceeded with the synthesis of triazolopyridazine **3**. Treatment of **6a** with hydrazine hydrate gave an 88% yield of a hydrazinopyridazine to which we assigned structure **8** (Scheme II), namely, 4-chloro-3-hydrazino-5-(1-pyrrolidinyl)pyridazine. In the nmr spectrum (dimethylsulfoxide-d_6) of **8** the pyridazine hydrogen appeared at δ 8.17. This additional shielding effect (with respect to that observed in going from **4** to **6a**) was consistent with the introduction of a second electron-donating group in the para position.

When hydrazinopyridazine **8** was treated with formic acid as shown in Scheme III, a mixture of products resulted. The major product, produced in 53% yield, was a 1:1 complex (**9**) of formic acid with 8-chloro-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine. Also produced was the formylhydrazinopyridazine **10**. Conversion of hydrazinopyridazine **8** to triazolopyridazine **9** clearly established the position of the hydrazino group in **8**.

Catalytic hydrogention of triazolopyridazine **9** with Pd/C led to 7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**3**), our target compound. The nmr spectrum (deuteriochloroform) left no doublet as to the position of the pyrrolidinyl group, since the coupling constant for the pyridazine hydrogens was 2.5 Hz. Also, the position of the pyrrolidinyl group in **8** was confirmed by this experiment. Interestingly, when **9** was recrystallized from ethanol-water, the monohydrate **12** resulted, which could be oven-dried to afford **13**. This conversion, by recrystallization, showed that triazolopyridazine **13** formed 1:1 complexes with solvent molecules and that **9** was not a true salt. However, triazolopyridazine **13** did form a monohydrochloride salt (**14**) upon treatment with hydrogen chloride, as did **3** (**11**).

SCHEME III



Hydrazinopyridazine **8** was also treated with acetic acid to produce the 3-methyl analog of **3** (**15**), which was then converted to monohydrochloride salt **16**. No complexation of **15** with acetic acid was observed.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B Spectrophotometer, nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analysis for C, H and N were performed by Dow Analytical Laboratories, Midland, MI.

4-Chloro-3,5-di-1-pyrrolidinylpyridazine (**5a**).

A 10.0 g (54.5 mmoles) quantity of 3,4,5-trichloropyridazine (**4**) (Aldrich) was added, over a 20 minute period, to 25 ml of pyrrolidine without external cooling. By the end of the addition the solution was at reflux. Reflux was maintained for 90 minutes. The solution was cooled

and the resulting slush was diluted with 100 ml of water. The pale yellow solid was collected and air-dried to yield 12.8 g (93%) of crude **5a**. Recrystallization (ethanol-water) gave 9.90 g (72%) of pure **5a**, mp 135-136°; ir (Nujol): 1555, 1340, 1110, 1030 cm^{-1}; nmr (deuteriochloroform): δ 8.20 (s, 1H, CH), 3.80-3.42 (m, 8H, both CH_2NCH_2 groups), 2.03-1.77 (m, 8H, remaining 4 CH_2 groups); ms (70 eV, electron impact): m/e 252 (molecular ion).

Anal. Calcd. for $C_{12}H_{17}ClN_4$: C, 57.02; H, 6.78; N, 22.17. Found: C, 56.80; H, 6.81; N, 22.48.

4-Chloro-3,5-di-1-piperidinylpyridazine (**5b**).

A 10.0 g (54.5 mmoles) quantity of (**4**) was added, over a 20 minute period, to 30 ml of piperidine. The addition was exothermic. The mixture was heated for 90 minutes on the steam bath, cooled and diluted with 100 ml of water. The resulting oil which separated solidified on cooling overnight in the refrigerator. The solid was collected, washed with water and air-dried to give 14.8 g (97%) of crude **5b**. Recrystallization (hexane) gave 7.90 g (52%) of pure **5b**, mp 81-83°; nmr (deuteriochloroform): δ 8.40 (s, 1H, pyridazine H), 3.50-3.03 (m, 8H, both CH_2NCH_2 groups), 1.93-1.47 (m, 12H, both $NCH_2CH_2CH_2CH_2$ groups); ms (70 eV, chemical ionization, methane): 281 ($M^+ + 1$), 309 ($M^+ + 29$), 321 ($M^+ + 41$).

Anal. Calcd. for $C_{14}H_{21}ClN_4$: C, 59.88; H, 7.54; N, 19.95. Found: C, 59.53; H, 7.36; N, 20.07.

4-Chloro-3,5-di-4-morpholinylpyridazine (**5c**).

To 30 ml of morpholine was added, over a 20 minute period, 10.0 g (54.5 mmoles) of (**4**). The hot mixture was then heated at reflux for 90 minutes during which time solution developed. After cooling and dilution with water (100 ml), the solution slowly deposited tan prisms which were collected and oven-dried to give 10.0 g (64%) of pure **5c**, mp 149.5-150°; nmr (deuteriochloroform): δ 8.50 (s, 1H, pyridazine H), 4.03-3.63 (m, 8H, both CH_2OCH_2 groups), 3.63-3.13 (m, 8H, both CH_2NCH_2 groups); ms: (70 eV, electron impact) m/e 284 (molecular ion).

Anal. Calcd. for $C_{12}H_{17}ClN_4O_2$: C, 50.61; H, 6.02; N, 19.68. Found: C, 50.63; H, 6.06; N, 19.46.

3,4-Dichloro-5-(1-pyrrolidinyl)pyridazine (**6a**).

To a solution of 100 g (0.544 mole) of 3,4,5-trichloropyridazine (**4**) in 400 ml of ethanol was added, dropwise, 77.5 g (1.09 moles) of pyrrolidine. The addition was exothermic, which initiated reflux, and icebath cooling was employed. After an hour of stirring, the solution was concentrated to a viscous oil which was triturated with water to produce a pale yellow solid. Collection and air-drying afforded 116 g (98%) of crude product. Recrystallization (ethanol-water) gave 57.0 g (48%) of **6a**, mp 86.5-88°; ir (Nujol): 1550, 1200 cm^{-1}; nmr (deuteriochloroform): δ 8.40 (s, 1H, pyridazine H), 3.87-3.57 (m, 4H, CH_2NCH_2), 2.18-1.92 (m, 4H, $NCH_2CH_2CH_2$).

Anal. Calcd. for $C_8H_9Cl_2N_3$: C, 44.06; H, 4.16; N, 19.27. Found: C, 44.14; H, 4.23; N, 19.44.

3,4-Dichloro-5-(1-piperidinyl)pyridazine (**6b**).

To a solution of 10.0 g (54.5 mmoles) of **4** in 50 ml of ethanol was added 9.28 g (0.109 mole) of piperidine over a 10 minute period. The addition was exothermic. After 1 hour of stirring, tlc indicated the absence of starting material and the mixture (a precipitate was present) was concentrated. The resulting semisolid was treated with 50 ml of water and oven-dried to give 12.4 g (98%) of crude **6b**. Recrystallization (ethanol-water) afforded 6.28 g (50%) of pure **6b**, mp 88-89°; nmr (deuteriochloroform): δ 8.63 (s, 1H, pyridazine H), 3.56-3.13 (m, 4H, CH_2NCH_2), 2.03-1.50 (m, 6H, $NCH_2CH_2CH_2CH_2$); ms: (70 eV, chemical ionization, methane) 232 ($M^+ + 1$), 260 ($M^+ + 29$), 272 ($M^+ + 41$).

Anal. Calcd. for $C_9H_{11}Cl_2N_3$: C, 46.57; H, 4.78; N, 18.10. Found: C, 46.65; H, 4.77; N, 18.36.

3,4-Dichloro-5-(4-morpholinyl)pyridazine (**6c**).

To a solution of 10.0 g (54.5 mmoles) of **4** in 50 ml of ethanol was added 9.50 g (0.109 mole) of morpholine over a 10 minute period. The addition was only mildly exothermic. After 1 hour of stirring, tlc showed the absence of **4**. The mixture (a precipitate had formed) was concentrated, and the residue was triturated with water (50 ml). The resulting solid was collected, washed with water and air-dried to yield 10.5 g (82%) of crude **6c**. Recrystallization (ethanol-water) gave 7.22 g (56%) of pure **6c**, mp 105-107.5°; nmr (deuteriochloroform): δ 8.65 (s, 1H, pyridazine H), 4.03-3.65 (m, 4H, CH_2OCH_2), 3.65-3.20 (m, 4H, CH_2NCH_2); ms: (70 eV, chemical ionization, methane) 234 ($M^+ + 1$), 262 ($M^+ + 29$), 274 ($M^+ + 41$).

Anal. Calcd. for $C_8H_9Cl_2N_3O$: C, 41.05; H, 3.87; N, 17.95. Found: C, 41.40; H, 3.78; N, 17.85.

3,5-Di-1-pyrrolidinylpyridazine (**7**).

A solution of 6.00 g (23.7 mmoles) of **5a** in 100 ml of ethanol was hydrogenated in a Parr apparatus at 50 psi for 1.5 hours in the presence of 10% Pd/C. The catalyst was removed by filtration and the filtrate was concentrated. The resulting amber oil was partitioned between aqueous sodium carbonate and methylene chloride, and the organic phase was concentrated to leave 4.91 g (95%) of **7**, mp 171-180°; mp 183-185° (toluene-hexane); ir (potassium bromide): 1620, 1415, 1350, 1305, 1105, 995, 820 cm^{-1}; nmr (deuteriochloroform): δ 8.00 (d, J = 2.5 Hz, 1H, H at 6-position), 5.38 (d, J = 2.5 Hz, 1H, H at 4-position), 3.70-3.10 (m, 8H, both CH_2NCH_2 groups), 2.33-1.74 (m, 8H, both $NCH_2CH_2CH_2CH_2$ groups); ms: (70 eV, electron impact) m/e 218 (molecular ion).

Anal. Calcd. for $C_{12}H_{18}N_4$: C, 66.02; H, 8.31; N, 25.67. Found: C, 66.10; H, 8.26; N, 25.66.

4-Chloro-3-hydrazino-5-(1-pyrrolidinyl)pyridazine (**8**).

A mixture of 15.0 g (68.8 mmoles) of **7** and 200 ml of 95% hydrazine was heated to reflux. The resulting solution was cooled in an icebath to afford, after collection and air-drying, 13.0 g (88%) of **8**, mp 189-192° (dec); ir (Nujol): 3330 and 3210 (NH), 1575 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.17 (s, 1H, pyridazine H), 6.22 (broad s, 1H, NH), 4.03 (broad s, 2H, NH_2), 3.85-3.53 (m, 4H, CH_2NCH_2), 2.20-1.87 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, chemical ionization, methane) 214 ($M^+ + 1$), 242 ($M^+ + 29$), 254 ($M^+ + 41$).

Anal. Calcd. for $C_8H_{12}ClN_5$: C, 44.96; H, 5.66; N, 32.78. Found: C, 45.00; H, 5.68; N, 32.96.

Treatment of **8** with Formic Acid.

A solution of 49.9 g (23.4 mmoles) of **8** in 250 ml of formic acid was heated at reflux for 1 hour. Concentration led to a slurry (yellow crystals were present) which was diluted with water (200 ml). The yellow crystals were collected, washed with water and oven-dried to yield 32.2 g (53%) of a 1:1 complex (**9**) of formic acid and 8-chloro-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine, mp 163-165° (formic acid-ether); ir (Nujol): 3150 (CH), 3200-2300 (OH), 1695 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.39 (s, 1H, HCO_2H), 8.45 (s, 1H, H at 3-position), 8.17 (s, 1H, H at 6-position), 4.02 (broad signal, 1H, HCO_2H), 3.95-3.47 (m, 4H, CH_2NCH_2), 2.13-1.74 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, chemical ionization, methane); 224 ($M^+ + 1$), 252 ($M^+ + 29$), 264 ($M^+ + 41$).

Anal. Calcd. for $C_9H_{10}ClN_5 \cdot HCO_2H$: C, 44.53; H, 4.49; N, 25.97. Found: C, 44.60; H, 4.51; N, 26.25.

The filtrate was basified with potassium carbonate solution and the resulting pale green solid was collected, washed with water and air-dried to yield 17.4 g of material, which was a mixture of **10** (R_f = .10) and **12** (R_f = .33) as indicated by tlc (silica gel; 9:1::chloroform:methanol). Recrystallization of an aliquot from ethanol gave a green solid (which displayed a single spot of R_f = .10 on tlc), which proved to be 2-[4-chloro-5-(1-pyrrolidinyl)-3-pyridazinyl]hydrazine carboxaldehyde (**10**), mp 184-184.5°; ir (Nujol): 3325 and 3175 (NH), 1690 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.17 (s, 1H, CH), 8.00 (s, 1H, CH), 3.90-3.43 (m, 4H, CH_2NCH_2), 2.13-1.77 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, chemical ionization, methane) 242 ($M^+ + 1$), 270 ($M^+ + 29$), 282 ($M^+ + 41$).

Anal. Calcd. for $C_9H_{12}ClN_5O$: C, 44.72; H, 5.01; N, 28.98. Found: C, 44.75; H, 4.97; N, 28.98.

A sample of **9** when recrystallized from ethanol-water, gave hydrate **12**, mp 204-205.5°; ir (Nujol): 3470 and 3385 (OH), 3125 (CH), 1620, 1605, 1495 cm^{-1}; nmr (deuteriochloroform and dimethylsulfoxide-d_6): δ 8.95 (s, 1H, H at 3-position), 8.24 (s, 1H, H at 6-position), 3.97-3.53 (m, 4H,

CH_2NCH_2), 3.37 (s, 2H, H_2O), 2.20-1.80 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, chemical ionization, methane) 224 ($M^+ + 1$), 252 ($M^+ + 29$), 264 ($M^+ + 41$).

Anal. Calcd. for $C_9H_{10}ClN_5 \cdot H_2O$: C, 44.72; H, 5.01; N, 28.98. Found: C, 44.90; H, 5.06; N, 29.13.

Hydrate **12** was dried in a vacuum oven to produce **13**, mp 206-207°; ir (Nujol): 3125 (CH), 1620, 1605, 1495 cm^{-1}.

Anal. Calcd. for $C_9H_{10}ClN_5$: C, 48.33; H, 4.51; N, 31.31. Found: C, 48.50; H, 4.68; N, 31.31.

7-(1-Pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**3**).

A solution of 5.39 g (20.0 mmoles) of **9** in 200 ml of methanol containing 50 mg of 10% Pd/C was hydrogenated at 50 psi in a Parr apparatus for 5.5 hours. The catalyst was removed by filtration and the filtrate was concentrated to a viscous oil. The resulting solid was collected and recrystallized from water (100 ml) to yield 3.05 g (85%) of **3** as short, yellow needles, mp 238-240°; ir (Nujol): 3115 (CH), 1625 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 8.77 (s, 1H, H at 3-position), 8.03 (d, J = 2.5 Hz, 1H, H at 6-position), 6.49 (d, J = 2.5 Hz, 1H, H at 8-position), 3.60-3.14 (m, 4H, CH_2NCH_2), 2.23-1.80 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, electron impact) m/e 189 (molecular ion).

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.12; H, 5.86; N, 37.02. Found: C, 57.20; H, 5.84; N, 37.30.

7-(1-Pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine Monohydrochloride (**11**).

To a solution of 2.75 g (14.5 mmoles) of **3** in 75 ml of methylene chloride was added excess ethereal hydrogen chloride. The pale yellow solid was collected and recrystallized from methanol-ethyl acetate to give **11** as white needles, mp 238-240°; ir (Nujol): 3650-2000 (NH^+), 1635 (C=N), 1585, 1500 cm^{-1}; nmr (deuterium oxide with sodium 2,2,-dimethyl-2-silapentane-5-sulfonate internal standard): δ 9.10 (s, 1H, H at 3-position), 8.70 (d, J = 2.5 Hz, 1H, H at 6-position), 6.80 (d, J = 2.5 Hz, 1H, H at 8-position), 4.00-3.20 (m, 4H, CH_2NCH_2), 2.37-1.94 (m, 4H, $NCH_2CH_2CH_2$).

Anal. Calcd. for $C_9H_{11}N_5 \cdot HCl$: C, 47.89; H, 5.36; N, 31.03. Found: C, 48.10; H, 5.48; N, 31.24.

8-Chloro-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine Monohydrochloride (**14**).

A solution of 4.72 g (21.1 mmoles) of **13** in 200 ml of warm ethanol was diluted with 100 ml of ethyl acetate. Addition of excess ethereal hydrogen chloride caused a rapid precipitation of white crystals which were collected and air-dried to give 4.46 g (94%) of **14**, mp 244-245° (dec); ir (Nujol): 2700-2000 (NH^+), 1625 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 12.04 (broad s, 1H, NH^+), 9.70 (s, 1H, H at 3-position), 8.77 (s, 1H, H at 6-position), 4.00-3.70 (m, 4H, CH_2NCH_2), 2.17-1.85 (m, 4H, $NCH_2CH_2CH_2$).

Anal. Calcd. for $C_9H_{10}ClN_5 \cdot HCl$: C, 41.55; H, 4.26; N, 26.92. Found: C, 41.70; H, 4.33; N, 26.88.

8-Chloro-3-methyl-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**15**).

A solution of 12.8 g (60.0 mmoles) of **8** in 100 ml of acetic acid was heated at reflux for 2.5 hours. The solution was concentrated to a yellow solid which was triturated with water, collected and air-dried to yield 14.2 g (99%) of **15**, mp 166.5-168° (ethanol-water); ir (Nujol): 3050 (CH), 1605, 1485, 1355, 1310 cm^{-1}; nmr (deuteriochloroform): δ 7.97 (s, 1H, H at 6-position), 3.90-3.60 (m, 4H, CH_2NCH_2), 2.67 (s, 3H, CH_3), 2.14-1.93 (m, 4H, $NCH_2CH_2CH_2$); ms: (70 eV, electron impact) m/e 237 (molecular ion).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.70; H, 5.21; N, 29.42.

8-Chloro-3-methyl-7-(1-pyrrolidinyl)-1,2,4-triazolo[4,3-*b*]pyridazine Hydrochloride (**16**).

A solution of 10.9 g (45.9 mmoles) of **15** in 100 ml of ethanol was diluted with 100 ml of ethyl acetate and treated with excess ethereal hydrogen chloride. Crystallization occurred slowly. The white crystals were collected and air-dried to yield 9.64 g (77%) of **16**, mp 221-224° (dec); ir (Nujol): 2800-2200 (NH^+), 1615 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.00 (broad s, 1H, NH^+), 8.83 (s, 1H, H at 6-position), 4.03-3.75 (m, 4H, CH_2NCH_2), 2.67 (s, 3H, CH_3), 2.12-1.85 (m, 4H, $NCH_2CH_2CH_2$).

Anal. Calcd. for $C_{10}H_{12}ClN_5 \cdot HCl$: C, 43.81; H, 4.78; N, 25.55. Found: C, 43.60; H, 4.83; N, 25.65.

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[3] 3,4,5-Trichloropyridazine is available commercially, and can be prepared from mucochloric acid. Thus, treatment of mucochloric acid with semicarbazide followed by hydrolysis of the resulting product with acetic acid gives 4,5-dichloro-4-pyridazinone [4], which is then converted to 3,4,5-trichloropyridazine with phosphorus oxychloride [5].

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