Annelated Piperazinyl-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines

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Tricyclic analogs of piperazinylthiopyrano[3,2-*d*]pyrimidine hypoglycemic agents were prepared. The angular tricyclic systems, 8,9-dihydro-7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine and 8,9-dihydro-7*H*-tetrazolo[1,5-*a*]thiopyrano[2,3-*e*]pyrimidine derivatives were synthesized from 2,4-dichloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine in three step sequences. Derivatives of the linear tricyclic system, 5,6-dihydro-7*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]pyrimidine, were prepared by condensation of 3-amino-1,2,4-triazole with ethyl 3-oxo-tetrahydropyran-2-carboxylate. The tricyclic heteroaryl-piperazines lacked significant hypoglycemic activity.

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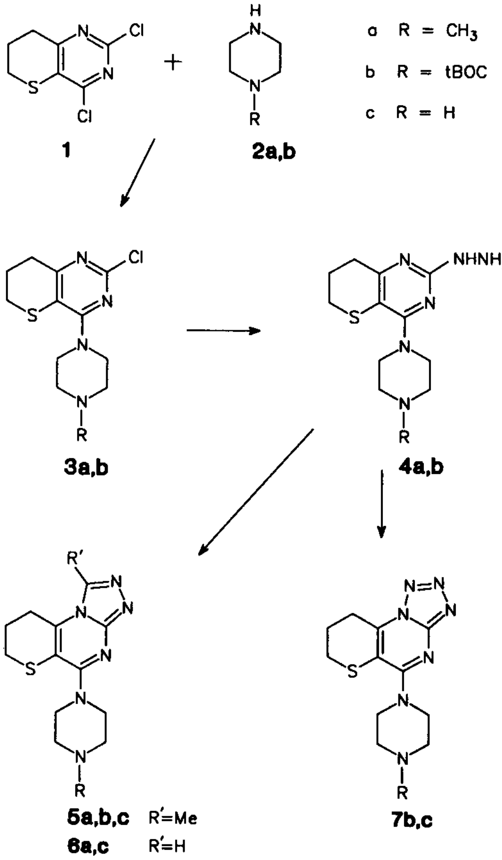
The antidiabetic properties of heteraromatic piperazines are well known [1-3]. Recently the promising hypoglycemic properties of some piperazine-containing amino-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine derivatives were reported [4,5]. We were interested in the structure activity correlation of this hypoglycemic activity, particularly with regard to certain annelated 7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines.

Scheme 1



The syntheses of the angular tricyclic analogs was undertaken from the known bicyclic 2,4-dichloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine [6] and the intent was to prepare the 2-hydrazino derivative as an intermediate for ring closure to the triazolo or tetrazolo structure. However, since the chlorine at the 4-position of the pyrimidine is more readily displaced than that at the 2-position, the introduction of 1-methylpiperazine or a blocked piperazine was undertaken first. The mono *t*-butyloxycarbonyl (*t*-BOC)-protected piperazine derivative (**2b**, [7]) was prepared by treatment of piperazine with di-*t*-butyldicarbonate, followed by separation from the unwanted bis-*t*-BOC by-product by crystallization. Introduction of 1-methylpiperazine (**2a**) or mono-*t*-BOC-piperazine (**2b**) occurred smoothly at the 4-position with minimal amounts of 2,4-disubstitution occurring under the reaction conditions employed. The resulting 4-piperazinyl-substituted heterocycles **3** could then be treated with hydrazine in refluxing isoamyl alcohol to displace the 2-chloro functionality. Ring closure of the hydrazino compound **4** with triethyl orthoacetate or with triethyl orthoformate at elevated temperature or by diazotization in dioxane gave tricyclic derivatives with an annelated triazole or tetrazole ring, **5** and **6** or **7**, respectively. Removal of the *t*-BOC group from **5b**, **6b** or **7b** was smoothly effected with hydrochloric acid.

Ring closure of **4** to the tricyclics **5-7** could each occur in two ways depending on whether N1 or N3 was the closure site. In each case nmr and thin layer chromatography showed only a single product in the ring closure reaction. Isolation of the ring closure products, crystallization and evaluation by single crystal X-ray diffraction (Figure 1) established that ring closure occurred on N1 to produce the angular 7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine (**5**) and 7*H*-tetrazolo[1,5-*a*]thiopyrano[2,3-*e*]pyrimidine systems (**7**) and not the linear isomers. This is consistent with the hypothesis that N1 is the most basic (and nucleophilic) of the two heteroaromatic nitrogens. The X-ray analysis of the dimaleate salt of the 2-amino-substituted bicyclic system (**8**, MTP-1403) [4] provided additional confirmation of the

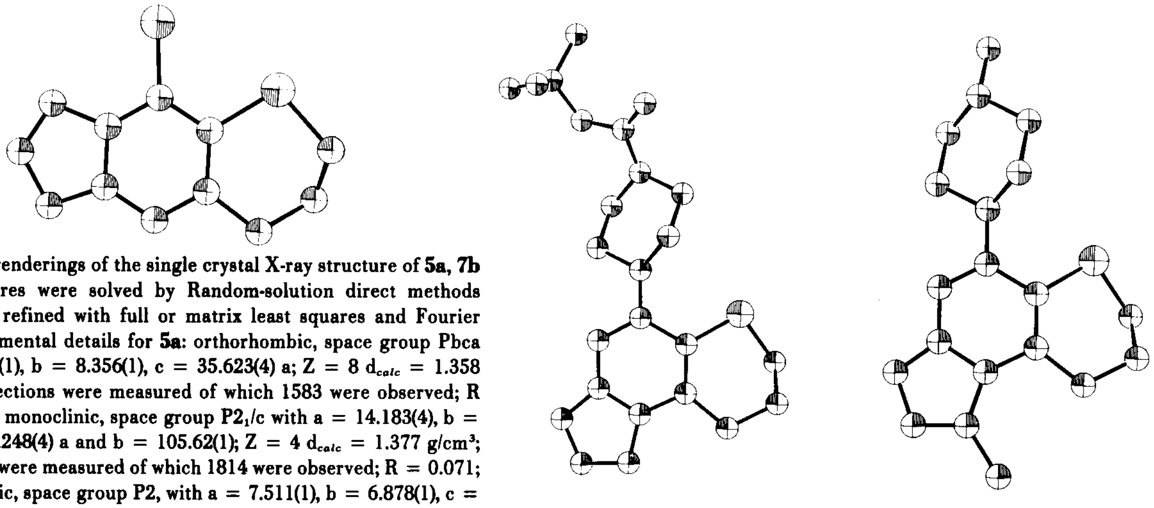


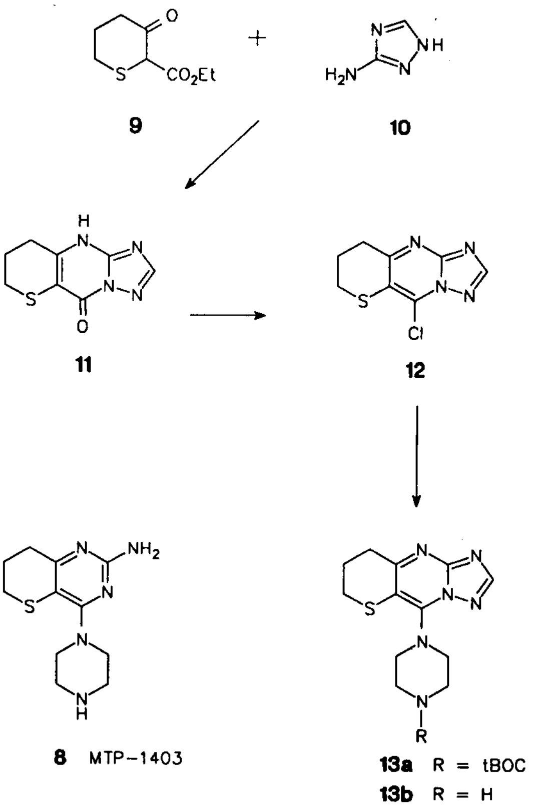
Figure 1. Ortep renderings of the single crystal X-ray structure of **5a**, **7b** and **12**. Structures were solved by Random-solution direct methods (SHELX76) and refined with full or matrix least squares and Fourier methods. Experimental details for **5a**: orthorhombic, space group Pbca with a = 10.000(1), b = 8.356(1), c = 35.623(4) a; Z = 8 d_{calc} = 1.358 g/cm^3; 2043 reflections were measured of which 1583 were observed; R = 0.043; for **7b**: monoclinic, space group $P2_1/c$ with a = 14.183(4), b = 8.201(3), c = 16.248(4) a and b = 105.62(1); Z = 4 d_{calc} = 1.377 g/cm^3; 2792 reflections were measured of which 1814 were observed; R = 0.071; for **12**: monoclinic, space group P2, with a = 7.511(1), b = 6.878(1), c = 9.741(1) a and b = 112.02; Z = 2 d_{calc} = 1.614 g/cm^3; 696 reflections measured of which 642 were observed [I > 3s(I)]; R-0.064.

more basic site as it showed that N1 was the site of heteroaromatic protonation [8]. The piperazinylthiopyranopyrimidines, whether annelated or not, seem to possess some common structural features: (a) the heteroaromatic systems are all essentially planar except for the methylene carbons of the thiopyran which are above and below the plane of the pyrimidine ring and (b) the carbon-nitrogen bond connecting the aromatic system with the piperazine is somewhat shortened and the normally pyramidal piperazine nitrogen is somewhat flattened presumably due to some electron release from the piperazine nitrogen and corresponding double bond character in the attachment to the heterocycle.

Access to the isomeric linear triazolo system would be predicted to be possible utilizing chemistry first investigated by Bulow and Haas [9]. They condensed 3-amino-1,2,4-triazole (**10**) with *β*-ketoesters to prepare triazolo[2,3-*a*]pyrimidines. After the ambiguity of the structure assignment of this ring system was emphasized [10], other workers [11,12] confirmed the original structure assignment and showed that isomeric triazolo[4,3-*a*]pyrimidines (prepared from one carbon cyclization reagents and hydrazinopyrimidines) rearranged [13] to the [2,3-*a*] system under acidic conditions.

The reaction of ethyl 3-oxotetrahydrothiopyran-2-carboxylate (**9** [14], structure confirmed in [15]) with **10** could produce any or all of four tricyclic products depending on the mode of ring closure. In fact, the reaction gave only one detectable product, 5,6-dihydro-9-oxo-7*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]pyrimidine (**11**). The structure was confirmed as the linear tricyclic product, analogous to the Bulow and Haas closure product, by X-ray analysis (Figure 1) of the 9-chloro-derivative (**12**), produced by chlorination of **11** with phosphorus oxychloride/dimethylaniline. The functionalized piperazine was introduced by the usual method; nucleophilic displacement of chloride from **12** with **2a** or **2b** and deprotection gave **13a,b**.

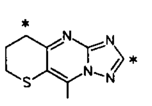
Scheme 2



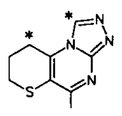
An investigation of ^{13}C magnetic resonance shifts of aromatic carbons of **6c** and **13b** was consistent with the X-ray structures. In the case of phenanthrene compared with anthracene, a 7 ppm upfield shift is observed at the γ (C-4) position in the angular system relative to anthracene. A similar steric phenomenon was seen in this series; examination of Table I shows a similar upfield shift for the starred (*) carbons of the angular system (**6c**) relative to the linear one (**13b**), a 21 Hz upfield shift for the γ position in the thiopyran and 8.2 Hz for the corresponding position in the triazole.

Table 1

^{13}C Parameters for Thiopyrano[2,3-*e*][1,2,4-triazolo[4,3-*a*]pyrimidine and Thiopyrano[3,2-*d*][1,2,4-triazolo][2,3-*a*]pyrimidine Derivatives (ppm)



13



6

	$-SCH_2-CH_2-{}^*CH_2-$			$-{}^*CH=$
6c	28.0	22.5	26.0	133 (d)
13b	28.0	23.2	34.2	154 (dd)

Examination of the tricyclic derivatives in an oral glucose tolerance test in genetically obese, insulin-resistant mice (ob/ob) analogous to the system described in [4] showed no significant effects at concentrations as high as 100 mg/kg with compound **8** as a positive control.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Microanalyses were performed by the Analytical Section of these laboratories. The ^1H nmr spectra were obtained on a Varian XL-200 spectrometer using tetramethylsilane as an internal standard. The electron-impact mass spectra were determined with a LKB-9000 mass spectrometer (70 eV) or a Varian MAT-731 (FAB) instrument. Infrared spectra were obtained on a Perkin-Elmer infracord spectrometer determined as mulls in series 11-41 Halocarbon oil from 4000 to 1300 cm^{-1} and in Nujol from 650 to 1300 cm^{-1}. Ultraviolet spectra were obtained with a Perkin-Elmer UV spectrophotometer in methanol solution.

1-(*t*-Butoxycarbonyl)piperazine (**2b**).

To a solution of piperazine (66.85 g, 0.776 mole) in water (808 ml) and *t*-butyl alcohol (924 ml) containing 2.5 *N* aqueous sodium hydroxide solution (122 ml) at 10° was added di-*t*-butyl bicarbnate (67.22 g, 0.308 mole) over a period of 30 minutes. The resulting mixture was stirred at 25° for 1 hour, and then the clear solution was concentrated to remove *t*-butanol. The white solid which separated was filtered to yield 18 grams of bis (*t*-butoxycarbonyl)piperazine, mp 161-162.5°; ^1H nmr (deuteriochloroform): δ 1.42 (s, 18H, CH_3), 3.38 (s, 8H, CH_2).

Anal. Calcd. for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.81; H, 9.11; N, 9.92.

The filtrates were combined and extracted three times with chloroform. The combined extract was washed with water, saturated brine, dried over magnesium sulfate, and concentrated to give a light yellow liquid. The white solids which separated on cooling were dried in high vacuum to yield 94.1 g (65%) of 1-(*t*-butoxycarbonyl)piperazine (**2b**), mp 48-49° (lit [7], mp 42.5-45°); ^1H nmr (deuteriochloroform): δ 1.42 (s, 9H, CH_3), 1.88 (s, 1H, NH, deuterium oxide exchangeable), 2.80 (m, 4H, CH_2NH), 3.38 (m, 4H, CH_2N-CO).

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.12; H, 9.50; N, 15.25.

2-Hydrazino-7,8-dihydro-4-(4-*t*-butoxycarbonyl-1-piperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**4b**).

A solution of 5 g (0.0226 mole), of 2,4-dichloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**1**) in chloroform (20 ml) was treated slowly at 0° with triethylamine (3.16 ml, 0.0226 mole). To this stirred mixture was added dropwise over a period of 25 minutes a solution of **2b** (4.21 g, 0.0226 mole) in chloroform (10 ml). After an additional 30 minutes at 0°, the solution was diluted with chloroform (25 ml) and extracted with 5% sodium bicarbonate solution (25 ml). After drying and concentration to dryness, the waxy solid was triturated with warm ethyl ether (50 ml). The ethereal solution was concentrated to 15 ml and was then treated with petroleum ether (35-60°) at 35° until cloudy. Crystallization over 2 days gave **3b** as a pale colored solid, mp 86-88° (5.79 g, 69%); tlc showed a single spot, R_f 0.50 (Analtech SGF plates developed with hexanes: ethyl acetate [4:1]); ^1H nmr (deuteriochloroform): δ 1.30 (s, 9H), 2.03-2.34 (m, 2H), 2.71-3.02 (m, 4H), 3.40 (broad s, 8H).

This *t*-BOC derivative (2 g, 0.0054 mole) was dissolved in isoamyl alcohol (10 ml) and hydrazine hydrate (2 g) was added. The solution was stirred at 130° for one hour after which the solvent was removed *in vacuo*. The residue was dissolved in chloroform, extracted successively with 5% sodium bicarbonate solution and water, dried over magnesium sulfate and concentrated to dryness. After drying *in vacuo* for four hours, ethyl ether (1 ml) was added to give a creamy colored solid (1.76 g, 89%), mp 142-143°; ms: (EI, 70 ev), m/e 366 (M^+, base); ^1H nmr (deuteriochloroform): δ 1.46 (s, 9H, tBu), 2.17 (quint, 2H, CH_2), 2.60 (br s, 1H, NH), 2.76 (t, 2H, CH_2), 2.88 (m, 2H, CH_2), 3.36 (m, 4H, CH_2's), 3.51 (m, 4H, CH_2's), 3.90 (br s, 2H, NH_2).

Anal. Calcd. for $C_{15}H_{26}N_6SO_2$: C, 52.44; H, 7.15; N, 22.93; S, 8.75. Found: C, 52.51; H, 7.09; N, 22.80; S, 8.47.

8,9-Dihydro-1-methyl-5-(4-methyl-1-piperazinyl)-7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine (**5a**).

Following the procedure for the synthesis of **3b**, 2.0 g (9.0 mmoles) of **1** and 1-methylpiperazine (3.6 g, 36.0 mmoles) gave 1.6 g (62%) of 2-chloro-7,8-dihydro-4-(4-methyl-1-piperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**3a**), mp 85-87° (lit [6], 88-90°); tlc: R_f 0.25 (Analtech SGF plate developed with ethyl acetate).

Analogous to the preparation of **4b**, **4a** was prepared from 1.5 g (5.3 mmoles) of **3a** and hydrazine hydrate (1.5 g) in refluxing isoamyl alcohol (10 ml), 0.67 g (42%) of 2-hydrazino-7,8-dihydro-4-(4-methyl-1-piperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**4a**) was obtained; ms: (EI, 70 ev) m/e 280 (M^+); tlc: R_f 0.5 (Analtech SGF plate developed with dichloromethane-methanol [40:1]); ^1H nmr (deuteriochloroform): δ 2.18 (s, 2H), 2.33 (s, 3H), 2.53 (m 4H), 2.77 (t, 2H), 2.89 (t, 2H), 3.48 (m, 4H), 3.88 (m, m, 2H), 5.94 (m, 1H).

Following the procedure for the synthesis of **5b**, 281 mg (1.0 mmole) of **4b** and 2 ml of triethyl orthoacetate in 6 ml of *n*-butanol, gave 274 mg (90%) of 8,9-dihydro-1-methyl-5-(4-methyl-1-piperazinyl)-7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo[4,3-*a*]-

pyrimidine (**5a**). Recrystallization from isopropanol gave material with mp 210-212°; ms: (EI 70 eV) m/e 304 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 1.67 (br s, 2H, NH's), 2.36 (s, 3H, Me), 2.53 (m, 4H, CH_2's), 2.86 (s, 3H, Me), 2.93 (m, 2H, CH_2), 3.24 (t, 2H, CH_2), 3.49 (m, 4H, CH_2's); uv: λ max 250 nm (log ε 4.28) and 319 nm (log ε 3.71); the dihydrochloride salt had mp 280-282° dec.

Anal. Calcd. for $C_{14}H_{20}N_6S$: C, 55.23; H, 6.62; N, 27.61; S, 10.53. Found: C, 54.91; H, 6.40; N, 27.88; S, 10.21.

Anal. Calcd. for $C_{14}H_{20}N_6S{\cdot}2HCl{\cdot}2H_2O$: C, 40.68; H, 6.28; N, 20.33; S, 7.76; Cl, 17.15. Found: C, 41.00; H, 5.97; N, 20.25; S, 7.83; Cl, 17.18.

8,9-Dihydro-1-methyl-5-(4-*t*-butoxycarbonyl-1-piperazinyl)-7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine (**5b**).

Compound **4b** (200 mg, 0.54 mmole) and 2 ml of triethyl orthoacetate were heated under reflux with *n*-butanol (6 ml) for 20 hours. The reaction mixture was evaporated and the solid residue was treated with ethyl ether to give 172.5 mg (82%) of **5b**, mp 225-226° dec; ms: (EI, 70 eV) m/e 390 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 9H, tBu), 2.34 (quint, 2H, CH_2), 2.87 (s, 3H, Me), 2.95 (m, 2H, CH_2), 3.25 (t, 2H, CH_2), 3.40 (m, 4H, CH_2's), 3.54 (m, 4H, CH_2's); uv: λ max 253 nm (log ε 4.37) and 311 nm (log ε 3.82).

Anal. Calcd. for $C_{18}H_{26}N_6SO_2$: C, 55.36; H, 6.71; N, 21.52; S, 8.21. Found: C, 54.96; H, 6.54; N, 21.26; S, 7.97.

8,9-Dihydro-1-methyl-5-(1-piperazinyl)-7*H*-thiopyrano[2,3-*e*]-[1,2,4]triazolo[4,3-*a*]pyrimidine (**5c**).

A solution of 120 mg (0.3 mmole) of **5b** in 6 ml of 10% hydrochloric acid was refluxed for 1 hour, after which time it was concentrated by rotary evaporation. The solids which separated were recrystallized from methanol-ether to give a light tan solid of **5c** (89 mg, 78%), mp 255-256° dec; ms: (EI, 70 eV) m/e 290 (M$^+$); ^{1}H nmr (deuterium oxide): δ 2.43 (m, 2H, CH_2), 2.96 (s, 3H, Me), 3.11 (m, 2H, CH_2), 3.50 (m, 6H, CH_2's), 4.07 (m, 4H, CH_2's).

Anal. Calcd. for $C_{13}H_{18}N_6S{\cdot}2HCl{\cdot}H_2O$: C, 40.94; H, 5.82; N, 22.04. Found: C, 40.49; H, 5.87; N, 22.00.

8,9-Dihydro-5-(4-methyl-1-piperazinyl)-7*H*-thiopyrano[2,3-*e*]-[1,2,4]triazolo[4,3-*a*]pyrimidine Dihydrochloride (**6a**).

A mixture of **4a** (0.50 g, 1.8 mmoles) and triethyl orthoformate (5 g) in 2-methoxyethyl ether (3 ml) was heated at 130° for 16 hours under nitrogen. The solvents were removed *in vacuo* and the brown residue was chromatographed on basic alumina (20 ml), eluting with dichloromethane:methanol (40:1, 75 ml fractions). Fractions 4 and 5 were combined and concentrated to a dark oil (0.52 g) which solidified upon standing. Recrystallization from 2-propanol containing a trace of hydrochloric acid gave the desired product, mp 270-275° dec; ms: (EI, 70 eV) m/e 290 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 2.37 (s, 3H, Me), 2.4-2.5 (m, 4H, CH_2's), 2.60 (m, 4H, CH_2's), 3.01 (t, 2H, CH_2), 3.05 (t, 2H, CH_2), 3.60 (m, 4H, CH_2's), 8.48 (s, 1H, H-1).

Anal. Calcd. for $C_{13}H_{18}N_6S{\cdot}2HCl{\cdot}H_2O$: C, 40.95; H, 5.82; N, 22.04; S, 8.41; Cl, 18.60. Found: C, 40.79; H, 5.83; N, 21.56; S, 8.25; Cl, 18.08.

8,9-Dihydro-5-(1-piperazinyl)-7*H*-thiopyrano[2,3-*e*][1,2,4]triazolo-[4,3-*a*]pyrimidine (**6c**).

A mixture of **4b** (1.17 g, 3.2 mmoles), triethyl orthoformate (10 g) and 2-methoxyethyl ether (6 ml) was heated at 130° for 16 hours under nitrogen. The solvents were removed *in vacuo* and the brown residue was applied to a flash column of basic alumina (20 x 3 cm). Elution with dichloromethane (200 ml) was followed with dichloromethane-methanol mixtures (0.5% methanol, 300 ml and 2.5% methanol, 500 ml). Combination and concentration of fractions containing the major product [R$_f$ 0.30 on silica gel, dichloromethane:methanol (40:1)] gave an oil (1.2 g) which was cautiously warmed in 1.0 *N* hydrochloric acid (5 ml). After gas evolution had subsided (15 minutes) heating was continued until the boiling temperature was reached. The solution was concentrated *in vacuo* to a gum, flushed with methanol, and then triturated with isopropanol (10 ml). The resulting solid was filtered, washed with ether, and dried *in vacuo* to furnish the product as a tan solid (0.55 g, 50%), mp 230-235°; ^{1}H nmr (deuterium oxide): δ 2.50 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.28 (t, 2H, CH_2), 3.56 (t, 4H, CH_2's), 4.16 (t, 4H, CH_2's), 9.10 (s, 1H, H-1).

Anal. Calcd. for $C_{12}H_{16}N_6S{\cdot}2HCl{\cdot}H_2O$: C, 39.24; H, 5.49; N, 22.88; Cl, 19.30. Found: C, 39.56; H, 5.42; N, 22.56; Cl, 19.94.

8,9-Dihydro-5-(4-*t*-butoxycarbonyl-1-piperazinyl)-7*H*-tetrazolo-[1,5-*a*]thiopyrano[2,3-*e*]pyrimidine (**7b**).

A solution of sodium nitrite (1 g) in 2 ml of water was added dropwise to a stirred mixture of **4b** (371 mg, 1.0 mmole) in 10 ml of acetic acid-dioxane (1:1) at room temperature. The mixture was stirred at room temperature for 16 hours. The solvent was evaporated, and water was added. The yellow-orange solid residue so obtained was crystallized from aqueous ethanol to obtain 357 mg (95%) of 8,9-dihydro-5-(4-*t*-butoxycarbonyl-1-piperazinyl)-7*H*-tetrazolo[1,5-*a*]thiopyrano[2,3-*e*]pyrimidine, mp 170-171°; ir showed no azide absorption at 2130 cm^{-1}; ms: (EI, 70 eV) m/e 377 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 1.47 (s, 9H, tBu), 2.20 (quint, 2H, CH_2), 2.42 (m, 4H, CH_2's), 2.84 (t, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.04 (m, 2H, CH_2), 3.36 (t, 4H, CH_2); uv: λ max 252 nm (log ε 4.51) and 310 nm (log ε 3.94).

Anal. Calcd. for $C_{16}H_{23}N_7SO_2$: C, 50.91; H, 6.14; N, 25.98; S, 8.50. Found: C, 50.53; H, 5.89; N, 25.61; S, 8.34.

8,9-Dihydro-5-(1-piperazinyl)-7*H*-tetrazolo[1,5-*a*]thiopyrano[2,3-*e*]-pyrimidine (**7c**).

This compound was prepared in a manner similar to the synthesis of **5c**. From 215 mg (0.57 mmole) of **7b**, 152 mg (76%) of 8,9-dihydro-5-(1-piperazinyl)-7*H*-tetrazolo[1,5-*a*]thiopyrano[2,3-*e*]-pyrimidine dihydrochloride (**7c**) was obtained, mp 206-208° dec; ms: (EI, 70 eV) m/e 277 (M$^+$); ^{1}H nmr (deuterium oxide): δ 2.46 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.40 (t, 2H, CH_2), 3.57 (m, 4H, CH_2's), 3.94 (m, 4H, CH_2's).

Anal. Calcd. for $C_{11}H_{15}N_7S{\cdot}2HCl$: C, 37.72; H, 4.89; N, 27.99. Found: C, 37.64; H, 4.79; N, 28.06.

5,6-Dihydro-9-hydroxy-7*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]-pyrimidine (**11**).

To 5.0 g (0.0266 mole) of ethyl 3-oxotetrahydrothiopyran-2-carboxylate (**9**) in ethanol (70 ml) was added 3-amino-1,2,4-triazole (**10**, 2.19 g, 0.026 mole). The mixture was heated under reflux for 15 hours during which time total dissolution occurred after 10-15 minutes and then a white solid formed. The reaction was cooled to room temperature and the solid was filtered off, washed with cold ethanol and dried to give 3.12 g (0.015 mole), 56% yield) of tlc pure product (Analtech silica gel plates developed with chloroform:methanol:water [40:10:1]). An analytical sample was obtained by treatment of this material with boiling methanol and the insoluble solid which remained was washed with ether and dried *in vacuo*; ms: (EI, 70 eV) m/e 208 (M^+); ^1H nmr (DMSO-d_6): δ 2.08 (m, 2H, CH_2), 2.78 (t, 2H, J = 7 Hz, CH_2), 2.93-2.99 (m, 2H, CH_2), 8.20 (s, 1H, H2).

Anal. Calcd. for $C_8H_8N_4O_1S_1$: C, 46.14; H, 3.87; N, 26.91. Found: C, 46.21; H, 3.94; N, 26.69.

9-Chloro-5,6-dihydro-7*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]pyrimidine (**12**).

A suspension of **11** (2.08 g, 0.010 mole) in freshly distilled phosphorus oxychoride (12 ml) was heated under reflux under nitrogen for 1.5 hours but dissolution did not occur. Diethylaniline (1 ml) was added and dissolution occurred immediately to give an amber colored solution which was heated under reflux for an additional hour before being cooled to room temperature. The reaction mixture was evaporated to dryness and ice-water (70 ml) was carefully added (exotherm) to the residue. A solution was formed which upon the addition of more ice deposited an off-white solid precipitate which was filtered off and washed well with ice-water. Drying on the filter pad gave 1.66 g (0.0073 mole, 73% yield) of tlc pure product (Analtech silica gel plates developed with chloroform:methanol:water [40:10:1]). An analytical and X-ray crystallographic sample was obtained by recrystallization from aqueous methanol; ms: (EI, 70 eV) m/e 226, 228 (M^+); ^1H nmr (deuteriochloroform): δ 2.31 (d of t, 2H, J = 6.5 Hz, CH_2), 3.12-3.21 (2 t's, 4H, each J = 6.5 Hz, 2 CH_2's), 8.41 (s, 1H, H2).

Anal. Calcd. for $C_8H_7N_4S_1Cl_1$: C, 42.39; H, 3.11; N, 24.72. Found: C, 42.48; H, 3.25; N, 24.76.

9-(1-[4-*t*-Butoxycarbonyl]piperazinyl)-5,6-dihydro-7*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]pyrimidine (**13a**).

Compound **12** (1.0 g, 4.42 mmoles) was suspended in isoamyl alcohol (20 ml) and **2b** (3.29 g, 17.69 mmoles) was added. This mixture was heated at reflux temperature under nitrogen for 2 hours and then allowed to stand at room temperature for 2 hours before being evaporated to dryness. The tan residue so obtained was dissolved in dichloromethane (60 ml) and extracted with 10% aqueous sodium carbonate (3 x 60 ml). The organic phase was dried over sodium sulfate, filtered and evaporated to a brown syrup (5.56 g). Ether (15 ml) was added to this residue and the mixture was allowed to stand at room temperature overnight. Crystallization occurred and the crystals were filtered and washed well with ether to give 1.64 g (69%) of material which was slightly contaminated with **2b**. An analytical sample was obtained by chromatography on a column of silica gel 60 (2.2 x 32.0 cm) developed in acetone; ms: (EI, 70 eV) m/e 376 (M^+); ^1H nmr (deuteriochloroform): δ 1.53 (s, 9H, $C(CH_3)_3$), 2.29 (d of t, 2H, J = 6.5 Hz, CH_2), 3.06 (t, 2H, J = 6.5 Hz, CH_2), 3.14 (t, 2H, J = 6.5 Hz, CH_2), 3.58-3.74 (m, 8H, piperazine CH_2's), 8.33 (s, H2).

Anal. Calcd. for $C_{17}H_{24}O_2S_1$: C, 54.24; H, 6.43; N, 22.32. Found: C, 54.50; H, 6.40; N, 22.40.

5,6-Dihydro-7*H*-9-(1-piperazinyl)-thiopyrano[3,2-*d*][1,2,4]triazolo[2,3-*a*]pyrimidine (**13b**).

Compound **13a** (0.390 g, 1.04 mmoles) was dissolved in trifluoroacetic acid (12 ml) and allowed to stand at room temperature for 45 minutes before being evaporated to dryness under a stream of nitrogen. The residue so obtained was then reevaporated to dryness several times from water *in vacuo* to give a pale yellow residue which was afterwards dissolved in a little water and passed onto a Dowex 1 x 2 (OH^-) column (2.0 x 23.0 cm). The column was developed with water and fractions containing the required product were pooled and evaporated to dryness to give 0.180 mg (0.65 mmole, 63% yield) of analytically pure product as a white solid; ms: (EI, 70 eV) m/e 276 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_6S_1$: C, 52.15; H, 5.84; N, 30.41. Found: C, 52.41; H, 5.92; N, 30.37.

A portion (0.140 g, 0.51 mmole) was converted into the monohydrochloride salt by dissolution in ethanol (5 ml) and addition of methanolic hydrogen chloride (0.7 ml). This mixture was concentrated under a stream of nitrogen to approximately 4 ml when crystallization commenced. The crystals so formed were collected by centrifugation, washed with cold ethanol (2 x 5 ml) and ether (2 x 5 ml), and dried *in vacuo* to give 0.110 g (0.32 mmole) of **13c** hydrochloride; ^1H nmr (deuterium oxide): δ 2.28 (d of t, 2H, J = 6.5 Hz, CH_2), 3.09 (t, 2H, J = 6.5 Hz, CH_2), 3.14 (t, 2H, J = 6.5 Hz, CH_2), 3.56 (m, 4H, piperazine CH_2's), 3.94 (m, 4H, piperazine CH_2's), 8.41 (s, H2).

Anal. Calcd. for $C_{12}H_{16}N_6S_1 \cdot HCl \cdot 0.5H_2O$: C, 44.79; H, 5.48; N, 26.11. Found: C, 45.11; H, 5.51; N, 25.89.

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