of unlabeled ligands were employed: 1 μM atropine for muscarinic cholinergic receptors, 1 μM phentolamine for α-adrenergic receptors, and 1 μM (+)-butaclamol for dopaminergic receptors. Logarithmic Hill plots were used to determine pIC_{50} (negative logarithm of the concentration required to inhibit specific binding by 50%) values, which were converted to IC_{50} values. At least 5 points on the decline of the curve were employed for each plot.

Acknowledgment. We thank Marla Bliss for technical assistance in performing the [^{3}H]norepinephrine and [^{3}H]serotonin uptake experiments and B. H. C. Westerink for expert help with the norepinephrine assays. Support of part of the research in the form of PHS Fellowship MH 07507 (to A.R.M.) and Grant NS14997 is also gratefully acknowledged. H.I.Y. is a recipient of Research Scientist Development Award MH 00095 from the National Institute of Mental Health.

6-(Substituted-amino)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines and 4-(Substituted-amino)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with Potential Antianxiety Activity

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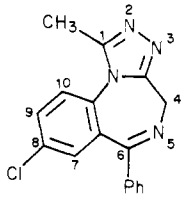
A series of 6-(substituted-amino)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was prepared for pharmacological evaluation, and, because of an interesting chemical isomerization, a similar series of 4-(substituted-amino)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was also obtained. Pharmacological evaluation of these compounds demonstrated that 8-chloro-1-methyl-6-piperidino-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**10**) had interesting activity in tests useful for detecting antianxiety activity, while the corresponding 4-piperidino derivative (**15**) had little activity in these tests. A brief discussion of a possible mechanism for the isomerization is also included.

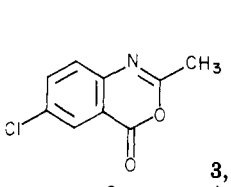
The 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines [viz., alprazolam (**1**)] have been shown to have



1

interesting antianxiety activity both in experimental animals[1] and in man.[2] Our discovery[3,4] that analogues of **1** with a variety of substituents at C-1 had an activity profile in the CNS screen that was different than that found for the anxiolytics prompted us to study the effect of substitution at other sites of the 4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine ring system. This report details our preparation of a series of compounds with nitrogen substituents in place of the C-6 phenyl. Because of some interesting and unexpected chemistry associated with this system, a series of analogues with amino substituents at C-4 was also obtained.

Entry into this series was provided by the reaction of 7-chloro-3-methyl-1*H*-2,4-benzoxazin-1-one[5] (**2**) with formic acid hydrazide to give the triazolobenzoic acid **3** using reaction conditions previously reported by Reid and Peters[6] for the unsubstituted system. The methyl ester (**4**), obtained from **3** with diazomethane, was hydroxymethylated in 74% yield with paraformaldehyde in xylene.[7] Thionyl chloride conversion of the resulting alcohol



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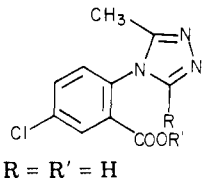
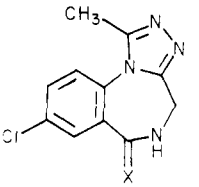
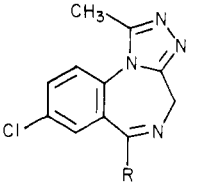


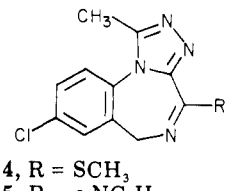
3, R = R′ = H
4, R = H; R′ = CH_3
5, R = CH_2OH; R′ = CH_3
6, R = CH_2Cl; R′ = CH_3



7, X = O
8, X = S



9, R = SCH_3
10, R = c-NC_5H_{10}
11, R = c-$N(CH_2CH_2)_2O$
12, R = c-NC_6H_{12}
13, R = $NH(CH_2)_5CH_3$



14, R = SCH_3
15, R = c-NC_5H_{10}
16, R = c-$N(CH_2CH_2)_2O$
17, R = c-NC_6H_{12}

(**5**) to the chloride (**6**) was followed by ammonolysis in the presence of potassium iodide to give the lactam (**7**). The electrophilic thiolactam (**8**) was then prepared by the reaction of **7** with phosphorus pentasulfide in refluxing pyridine. Amines reacted with **8** only with difficulty. Thus, the reaction of **8** with piperidine required 18 h at reflux with the amine as solvent. With the less nucleophilic morpholine, 20 h of reflux was required to give a 38% yield of the product (**11**). (Results for other amines in this reaction are recorded in Table I.) The reaction of **8** with hexamethylenimine was particularly difficult and, suprisingly, **13** was obtained in addition to the expected product **12**. The structure of **13**, which must have resulted from a reductive cleavage of the hexamethylenimine ring, was confirmed by an independent condensation of **8** with *n*-hexylamine to give **13** in 80% yield. In an attempt to increase the reactivity of the thiolactam system and perhaps also avoid the hexamethylenimine ring cleavage reaction, **8** was alkylated with methyl iodide and sodium

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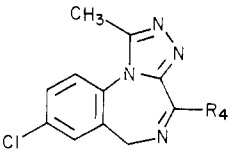
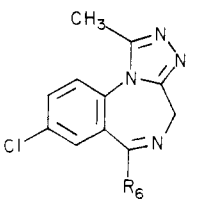
Table I. Physical and Analytical Data for the *s*-Triazolo[4,3-*a*][1,4]benzodiazepines

no.	R_4	R_6	procedure	yield, %	mp, °C	recrystn solvent	formula	anal.
10		c-NC_5H_{10}	A[b]	56.7[a]	248-249.5	MeOH-EtOAc	$C_{16}H_{18}ClN_5$	C, H, Cl, N
			B[b]	16.6				
			C[b]	8.8				
11		c-$N(CH_2CH_2)_2O$	A[d]	38.1	243-253	CH_2Cl_2-MeOH-EtOAc	$C_{15}H_{16}ClN_5O$	C, H, Cl, N
			B[c]	6.0				
			D[b]	23.0				
12		c-NC_6H_{12}	A[e]	11	253.5-254.5	MeOH-EtOAc	$C_{17}H_{20}ClN_5$	C, H, Cl, N
			B[g]	4.1				
13		$NH(CH_2)_5CH_3$	A[e]	16.5	211.5-213.5	MeOH-EtOAc	$C_{17}H_{22}ClN_5$	C, H, Cl, N
			A[f]	79.9				
15	c-NC_5H_{10}		B[b]	34.7	191.5-192			
			C[b]	29.1	203.5-205.5	MeOH-EtOAc	$C_{16}H_{18}ClN_5$	C, H, Cl, N
16	c-$N(CH_2CH_2)_2O$		B[c]	2.3	191-191.5	CH_2Cl_2-EtOAc	$C_{15}H_{16}ClN_5O$	C, H, Cl, N
			D[b]	45.6				
17	c-NC_6H_{12}		B[g]	24.5	180-182	EtOAc-Sk B	$C_{17}H_{20}ClN_5$	C, H, Cl, N
18		c-NC_4H_8	A[h]	50.7	223-225	CH_2Cl_2-EtOAc	$C_{15}H_{16}ClN_5$	C, H, N; Cl[i]
			B[j]	10.8				
19	c-NC_4H_8		B[j]	18.4	216-217	CH_2Cl_2-EtOAc-Sk B	$C_{15}H_{16}ClN_5$	C, H, N; Cl[k]
20		c-$N(CH_2CH_2)_2N$-CH_3	A[l]	60.5	287-290	CH_2Cl_2-EtOAc	$C_{16}H_{19}ClN_6$	C, H, N; Cl[m]
			B[n]	2.6				
21	c-$N(CH_2CH_2)_2N$-CH_3		B[n]	8.6	194-196	CH_2Cl_2-EtOAc	$C_{16}H_{19}ClN_6$	C, H, Cl, N
22		c-$N(CH_2CH_2)_2N$-Ph	A[o]	26.6	315-317 dec	CH_2Cl_2-EtOAc	$C_{21}H_{21}ClN_6$	C, H, Cl, N
23		c-NC_5H_8	A[p]	53.9	224-225	CH_2Cl_2-EtOAc	$C_{16}H_{16}ClN_5$	C, H, Cl, N
24		c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	A[q]	59.3	246-249	CH_2Cl_2-EtOAc	$C_{17}H_{21}ClN_6O$	C, H, Cl; N[r]

[a] Crude product. [b] See Experimental Section. [c] Compound 9 refluxed for 6 days with morpholine; product chromatographed on silica gel with 3% MeOH-$CHCl_3$. [d] Reaction of 8 with refluxing morpholine for 20 h. [e] Reaction of 8 with hexamethylenimine at 130 °C for 43 h with a slow stream of N_2 flowing through the reaction mixture; products purified by silica gel chromatography with mixtures of MeOH and $CHCl_3$ containing 2.5-5% MeOH. [f] Reaction of 8 with *n*-hexylamine at 135 °C for 18 h. [g] Reaction of 9 with hexamethylenimine at 120 °C for 24 h and 150 °C for 39 h; product purified by silica gel chromatography with 2% MeOH-$CHCl_3$. [h] Reaction of 8 with refluxing pyrrolidine for 10 h. [i] Cl: calcd, 11.75; found, 12.19. [j] Reaction of 9 with refluxing pyrrolidine for 25 h; products isolated by silica gel chromatography with 3% MeOH-$CHCl_3$. [k] Cl: calcd, 11.75; found, 12.19. [l] Reaction of 8 with 1-methylpiperazine at 130 °C for 24 h. [m] Cl: calcd, 10.72; found, 11.25. [n] Reaction of 9 with refluxing 1-methylpiperazine for 19 h; products purified by silica gel chromatography with mixtures of MeOH and $CHCl_3$ containing 5 to 100% MeOH. [o] Reaction of 8 with 3 equiv of 1-phenylpiperazine in refluxing 1-butanol for 4 days. [p] Reaction of 8 with refluxing 1,2,3,6-tetrahydropyridine for 32 h. [q] Reaction of 8 with 1-(2-hydroxyethyl)piperazine at 150 °C for 24 h. [r] N: calcd, 23.29; found, 22.80.

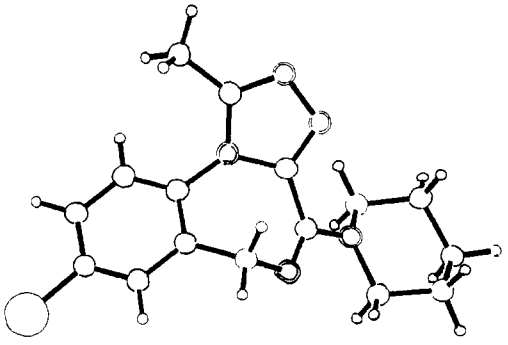
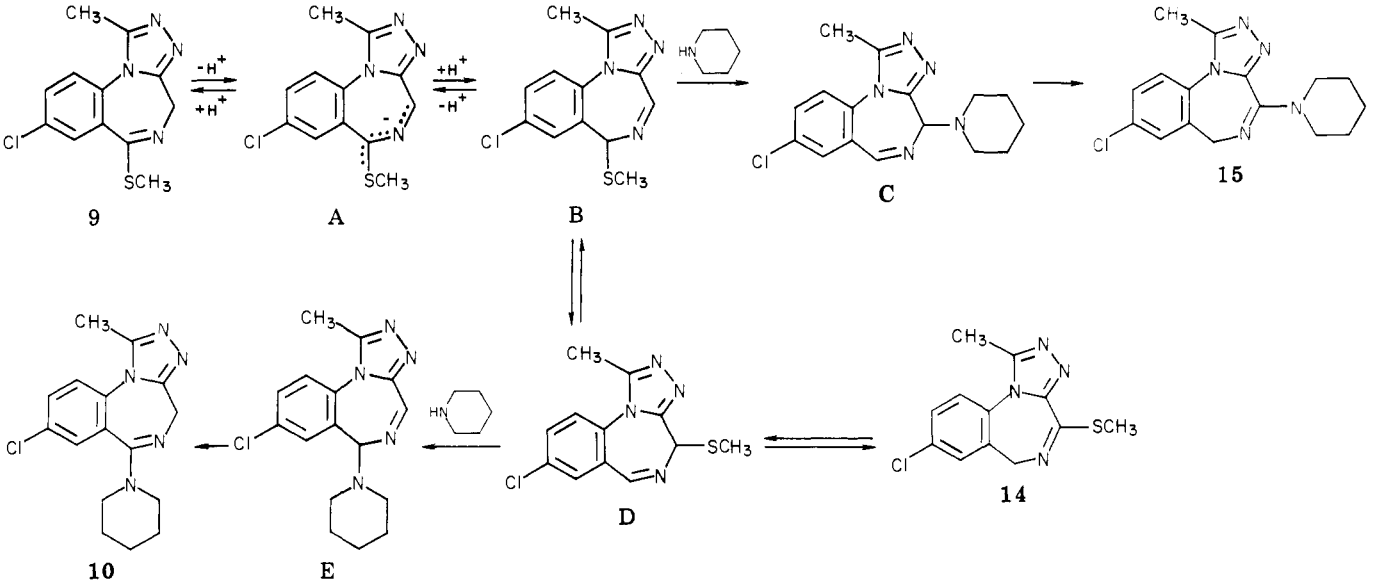


Figure 1. Computer drawing of compound **15** from X-ray data.

hydroxide. The resulting thioether **9** was then subjected to hot hexamethylenimine. In this case, the expected product (**12**) was obtained in only minor amounts; the major product was the isomeric derivative (**17**). [None of the ring-opened product (**13**) was obtained.] Other amines behaved similarly (Table I), and for convenience the reaction of **9** with piperidine was studied in more detail. Thus, the reaction of **9** with refluxing piperidine for 48 h gave a mixture of **10** and **15** in 17 and 35% yields, respectively. The structure of **15** was supported by spectral data and fully substantiated by an X-ray crystallographic analysis (Figure 1).[8] With morpholine this reaction was very sluggish. After refluxing **9** with morpholine for 6 days,

(8) David J. DuChamp, unpublished results. The crystal data were as follows: space group $C2/c$, $z = 8$, $a = 17.306(6)$ Å, $b = 10.853(3)$ Å, $c = 17.087(4)$ Å, $\beta = 104.11(3)$ Å, D (calcd) = 1.35 g/cm^3. Data were collected at low temperature (−150 °C); a trial structure was obtained by direct methods and refined by least squares to an agreement index (R) of 0.047 for the 892 reflections, with observed intensities greater than 3 standard deviations. Hydrogen parameters were in the calculations but were not refined.

Scheme I



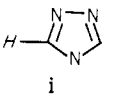
although most of the starting material had been consumed, the total yield of products 11 and 16 was only about 8%, with the major product being the unisomerized compound 11. Based on mechanistic considerations (see below), we repeated this reaction in the presence of the strong nonnucleophilic base 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU); after a relatively short reaction time (22 h), we obtained 16 and 11 in 46 and 23% yields, respectively. This result suggests that the rearrangement reaction is initiated by base and that morpholine was not sufficiently basic for this purpose. A possible mechanism for this reaction is shown for piperidine in Scheme I. Base abstraction of the relatively acidic C-4 proton of 9, which is flanked by both the electronegative triazole ring and the imine nitrogen, would give an allylic anion (A). A similar anion has recently been proposed for the base-catalyzed isomerization of an allyl sulfide.[9] Reprotonation of A could occur at either C-4 or C-6 to give 9 or B, respectively. We propose that B is the transient intermediate that condenses with amines in an S_N2'-like process with elimination of methanethiol to give, via C, the observed C-4 substituted products (viz., 15). If B is in fact the required intermediate for the production of 15, it implies that a second, isomeric, intermediate (D) would be required for the facile formation of the "normal" product 10 from 9. Evidence in support of this suggestion was obtained by treating 9 with a nonnucleophilic base. Thus, when 9 was allowed to react with DBU at 100 °C in Me_2SO, a mixture was obtained from which 9 (46%) and 14 (23%) were isolated by silica gel chromatography. We propose that this interconversion may have been accomplished by the thioallylic rearrangment of intermediates B and D. The thermal thioallylic rearrangement of allyl phenyl sulfide has been reported;[10] this type of rearrangement has also been used synthetically.[11] From this discussion it might be expected that 14 would also react with amines to give a mixture of the C-4 and C-6 substituted products. In fact, when 14 was allowed to react with hot piperidine, a mixture of 10 (9%) and 15 (29%) was obtained.

Pharmacology. Results. A discussion of the screen used to evaluate these compounds has been presented.[1,3] The pharmacological data for the 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines and 6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines are presented in Table II. Data for alprazolam (1) and diazepam (25) are included for comparison. It will be noted that, although 8-chloro-1-methyl-6-piperidino-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (10) had interesting activity in tests (P, B, γ-B, and HS) indicating antianxiety activity (compare 10 with 1 and 25), the 1,2,5,6-tetrahydro-1-pyridinyl derivative (23) was less active and other members of this series had little activity in these tests. In the isomeric 6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine series, little activity was found in the screen for central nervous system activity.

Experimental Section

Chemistry. Melting points taken in a capillary tube are corrected. The structures of all compounds were supported by IR, UV, and NMR spectra. IR spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer; UV spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A 60A or XL 100 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were obtained with a Varian MAT CH 7 or LKB spectrometer. The analytical results obtained were within ±0.4% of the theoretical values if not otherwise stated. The silica gel used for chromatography was obtained from E. Merck A. G., Darmstadt, Germany. Skellysolve B (Sk B) is a commercial hexane, bp 60–70 °C, made by Skelly Oil Co., Kansas City, MO.

5-Chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzoic Acid (3). A stirred mixture of 7-chloro-3-methyl-1*H*-2,4-benzoxazin-1-one (2)[5] (1.96 g, 0.01 mol), formic acid hydrazide (0.661 g, 0.011 mol), and EtOH (20 mL) was refluxed, under N_2, for 1 h 50 min, cooled, and concentrated in vacuo. The residue was crystallized from MeOH to give 1.52 g of 3, mp 251.5–253.5 °C dec. The analytical sample had mp 254–255 °C; UV (EtOH) end absorption, λ_{max} 281 nm (ε 1150), inflections 224 (11 650), 287 (1050); NMR [$(CD_3)_2NCDO$] δ 2.25 (s, 3, CH_3), 8.6 (s, 1, i). Anal. ($C_{10}H_8ClN_3O_2$) C, H, Cl, N.



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Methyl 5-Chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)-benzoate. (4). A stirred suspension of 3 (77 g) in CH_2Cl_2 (1500 mL) was cooled in an ice bath and treated with an excess of diazomethane, prepared from 75 g of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine. The solid quickly dissolved to give a colorless solution. This was washed with dilute $NaHCO_3$ and water, dried

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Table II. Pharmacological Data for the *s*-Triazolo[4,3-*a*][1,4]benzodiazepines[a]

no.	Tr	nicotine TE	nicotine D	pentylene-tetrazole (P)	bicuculline TE (B)	γ-butyro-lactone (γ-B)	hypoxic stress (HS)
1[e]	0.6	0.02	0.02	0.1	0.2	0.08	0.2
10	0.3	0.4	0.4	1.1	0.7	0.9	0.3
11	>100	80	71	c	c	c	c
12	>100	>100	>100	c	c	c	c
13	>100	>100	>100	c	c	c	c
15	>100	>100	>100	c	c	c	c
16	>100	>100	>100	40	>50	>50	>50
17	>100	>100	>100	c	c	c	c
18	>100	18	18	>50	>50	7.4	>50
19	>6	>6	>6	>6[b]	>6	>6	>6
20	>100	>100	>100	c	c	c	c
21	>100	>100	>100	>50	>50	40	40
22	>100	>100	>100	c	c	c	c
23	10	0.6	0.5	3	4	4	3
24	>100	>100	>100	c	c	c	c
25[d]	7	0.28	0.28	0.1	2.6	0.035	0.2

[a] Values are ED_{50} expressed in mg/kg. [b] Lethal at 12.5 mg/kg. [c] Not tested. [d] Diazepam, obtained from Hoffman-LaRoche, Inc. [e] Alprazolam.

(Na_2SO_4), and concentrated. The residue was crystallized from benzene–Skelly B to give 60.8 g of **4**, mp 89–91.5 °C. The analytical sample had mp 86–88.5 °C; UV (EtOH) λ_{max} 206 nm (ε 39900), 283 (1350), inflections 225 (10950), 291 (1200); IR (Nujol) 1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.27 (s, 3, C-CH_3), 3.75 (s, 3, O-CH_3).

Methyl 5-Chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzoate. (5). A stirred mixture of **4** (0.504 g, 0.002 mol), paraformaldehyde (0.6 g), and xylene (10 mL) was warmed, under N_2, in an oil bath maintained at 115–124 °C for 1 h 15 min and then concentrated in vacuo. The residue was crystallized from EtOH–EtOAc to give 0.233 g, mp 163–165 °C, and 0.183 g, mp 157–159 °C, of **5**. The analytical sample was recrystallized from MeOH–EtOAc and had mp 165–166.5 °C; UV (EtOH) λ_{max} 204 nm (ε 42600), 283 (1250), inflection 225 (10800); IR (Nujol) 3240 cm^{-1} (OH), 1735 (C=O); NMR [$(CD_3)_2NCDO$] δ 2.17 (s, 3, C-CH_3), 3.73 (s, 3, O-CH_3), 4.47 (s, 2, CH_2-OH). Anal. ($C_{12}H_{12}ClN_3O_3$) C, H, Cl, N.

Methyl 5-Chloro-2-[3-(chloromethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzoate. (6). Compound **5** (21.83 g, 0.0776 mol) was added with cooling and stirring to 205 mL of thionyl chloride. The resulting solution was warmed, under N_2, to 55 °C during 65 min and maintained at 55–67 °C for an additional 1 h 35 min. It was then concentrated in vacuo. The residue was mixed with dry benzene and concentrated. The resulting mixture was poured into ice–water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The solid residue was dissolved in CH_2Cl_2–EtOAc and filtered through a small pad of silica gel. The filtrate was concentrated in vacuo, replacing the CH_2Cl_2 by EtOAc. The resulting EtOAc solution was treated with Skelly B and allowed to crystallize at 4 °C to give 18.37 g of **6**, mp 123–124 °C. A second crop, 0.922 g, mp 120–120.5 °C, was obtained by concentrating the mother liquors. The analytical sample was crystallized from EtOAc–Skelly B and had mp 124.5–126 °C; UV (EtOH) λ_{max} 206 nm (ε 47200), 281 (1300), inflections 227 (12350), 288 (1150); IR (Nujol) 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.21 (s, 3, C-CH_3), 3.75 (s, 3, O-CH_3), 4.49 (q, 2, J_{AB} = 13 Hz, CH_2-Cl).

8-Chloro-5,6-dihydro-1-methyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-6-one (7). A stirred solution of **6** (300 mg, 1 mmol) in THF (10 mL) was cooled, under N_2, in an ice bath and treated with 8 mL of a saturated solution of NH_3 in MeOH. The mixture was kept in the ice bath for 20 min and at ambient temperature for 18 h. The mixture was concentrated in vacuo, and the residue was mixed with water and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from MeOH–EtOAc to give 0.169 g, mp 253.5–255.5 °C, and 0.026 g, mp 251–252.5 °C, of **7**. The analytical sample had mp 263–264 °C; UV (EtOH) λ_{max} 212 nm (ε 36450), 236 (17350), 283 (1500), inflection 291 (1350); IR (Nujol) 3320 cm^{-1} (NH), 1655 (C=O); NMR [$(CD_3)_2NCDO$] δ 2.66 (s, 3, CH_3), 4.53 (m, 2, C-4 H_2). Anal. ($C_{11}H_9ClN_4O$) C, H, Cl, N.

8-Chloro-4,5-dihydro-1-methyl-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-6-thione (8). A stirred mixture of **7** (24.87 g, 0.1 mol) and dry pyridine (1420 mL) was treated with P_2S_5 (24.45 g, 0.11 mol) and refluxed for 2.5 h, under N_2. The mixture was cooled and concentrated in vacuo, and the residue was mixed with water and $CHCl_3$. The mixture was neutralized with $NaHCO_3$, and the solid was collected by filtration. This solid was washed with $CHCl_3$ and recrystallized from $CHCl_3$–MeOH–EtOAc to give 20.31 g, mp 303–308 °C, of **8**. Additional product was obtained from the $CHCl_3$ filtrates, which were washed with brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from $CHCl_3$–MeOH–EtOAc to give 2.93 g, mp 298–303 °C, and 0.78 g, mp 302–305 °C, of **8** (91% overall yield). The analytical sample was recrystallized from CH_2Cl_2–MeOH and had mp 306–308 °C; UV (EtOH) λ_{max} 223 nm (ε 31500), 316 (7700); IR (Nujol) 3150 cm^{-1} (NH); NMR [$(CD_3)_2NCDO$] δ 2.64 (s, 3, CH_3), 4.67 (q, 2, J_{AB} = 15 Hz, C-4 H_2). Anal. ($C_{11}H_9ClN_4S$) C, H, Cl, N, S.

8-Chloro-1-methyl-6-(methylthio)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9). An ice-cold, stirred mixture of **8** (13.2 g, 0.05 mol) in MeOH (75 mL) was treated with 55 mL of 0.945 N NaOH. The ice bath was removed and, after 10 min, methyl iodide (3.11 mL, 0.05 mol) was added to the solution. About 5 min after this addition the mixture solidified. It was kept at ambient temperature for 1 h, mixed with ice–water, and stirred for 10 min. The solid was collected by filtration, washed with water, and dried to give 12.0 g of **9**, mp 244–249 °C. The analytical sample was recrystallized from CH_2Cl_2–EtOAc and had mp 247.5–249 °C; UV (EtOH) λ_{max} 218 nm (ε 35850), 241 (12450), 275 (3550), inflections 220 (34800), 286 (3400), 295 (2850); NMR ($CDCl_3$) δ 2.40 (s, 3, S-CH_3), 2.62 (s, 3, C-CH_3), 4.06, 5.33 (2 d, 2, J_{AB} = 13 Hz, C-4 H_2). Anal. ($C_{12}H_{11}ClN_4S$) C, H, Cl, N, S.

8-Chloro-1-methyl-6-piperidino-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (10). Procedure A. A stirred solution of **8** (2.65 g, 0.01 mol) and piperidine (25 mL) was refluxed for 18 h, under N_2. The solution was mixed with cold water and extracted with CH_2Cl_2. The extract was washed with water and then brine, dried (Na_2SO_4), and concentrated in vacuo. The solid residue was mixed with EtOAc and collected by filtration; it was recrystallized from CH_2Cl_2–MeOH–EtOAc to give 1.39 g, mp 238–243 °C, and 0.40 g, mp 225–232 °C, of crude **10**.

A sample of this material was dissolved in CH_2Cl_2, washed with dilute $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. The residue was crystallized from MeOH–EtOAc to give **10**: mp 248–249.5 °C; UV (EtOH) λ_{max} 213 nm (ε 41550), 294 (3450), inflections 237 (14600), 287 (3350); NMR ($CDCl_3$) δ 1.6 (br s, 6, C-CH_2-C), 2.61 (s, 3, C-CH_3), 3.15 (br s, 4, N-CH_2-C), 3.8, 4.92 (2 d, 2, J_{AB} = 13 Hz, C-4 H_2).

Reaction of 8-Chloro-1-methyl-6-(methylthio)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9) with Piperidine. Procedure B. A stirred mixture of **9** (2.79 g, 0.01 mol) and piperidine (20 mL) was refluxed gently for 48 h. A slow stream of nitrogen was bubbled through the mixture during this period. The cooled mixture was poured into water and extracted with $CHCl_3$. The

extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silca gel (200 g) with mixtures of MeOH and $CHCl_3$ containing 3–5% MeOH. The first product eluted from the column was crystallized from MeOH–EtOAc to give 0.974 g, mp 204–206.5 °C, and 0.123 g, mp 202–204 °C, of 8-chloro-1-methyl-4-piperidino-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**15**). The analytical sample had mp 191.5–192 °C; however, when the melt was cooled slowly it solidified and then remelted at 203.5–205.5 °C: UV (EtOH) end absorption, λ_{max} 264 nm (6800), 273 (6450), 276 (6400), 283 (6250), inflections 221 (18 200), 230 (17 300), 258 (7400), 267 (6700); IR (Nujol) 3040 cm^{-1} (=CH), 1585, 1495 (C=C, C=N); NMR ($CDCl_3$, 100 MHz) δ 1.61 (br s, 6, C-CH_2-C), 2.64 (s, 3, CH_3), 3.41 (br s, 4, N-CH_2-C), 3.91, 4.37 (2 d, 2, J_{AB} = 13 Hz, C-6 H_2).

The second product eluted from the column was crystallized from MeOH–EtOAc to give 0.358 g, mp 249.5–251.5 °C, and 0.166 g, mp 249.5–251 °C, of **10**. The IR (Nujol) spectrum of this material was identical with that of an authentic sample.

Reaction of 8-Chloro-1-methyl-4-(methylthio)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (14) with Piperidine. Procedure C. A stirred mixture of **14** (0.443 g, 1.59 mmol) in piperidine (4 mL) was kept at 115–117 °C, under N_2, for 20 h with a slow stream of N_2 passing through the mixture. It was then mixed with water and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (25 g) with 3% MeOH–$CHCl_3$. The first product eluted from the column was crystallized from MeOH–EtOAc (Darco) to give 0.051 g, mp 190.5–203.5 °C, and 0.095 g, mp 189–190 °C, of **15**. The mixture melting points of the first and second crops with the analytical sample were 200.5–205 and 203–205 °C, respectively. This material was identical with the authentic sample by TLC on silica gel with 5% MeOH–$CHCl_3$. The two crops were combined and recrystallized from MeOH–EtOAc to give 0.126 g, mp 189.5–190.5 °C. The mixture melting point of this material with the analytical sample was 189.5–205.5 °C.

The second product eluted from the column was crystallized from MeOH–EtOAc (Darco) to give 0.044 g of **10**, mp 248–249 °C. The IR (Nujol) spectrum of this material was identical with that of an authentic sample.

Reaction of 8-Chloro-1-methyl-6-(methylthio)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9) with Morpholine and DBU. Procedure D. A stirred mixture of **9** (2.79 g, 0.01 mol), morpholine (20 mL), and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU; 1.52 g, 0.01 mol) was refluxed for 22 h with a slow stream of N_2 bubbling through the mixture. It was then concentrated in vacuo. The residue was chromatographed on silica gel (160 g) with 3% MeOH–$CHCl_3$. The first material eluted was crystallized from CH_2Cl_2–EtOAc–Skelly B to give 1.45 g of **16**, mp 187–188.5 °C. This material was identical with the authentic sample by TLC on silica gel with 5% MeOH–$CHCl_3$. The mixture melting point was undepressed. The second compound eluted from the column was crystallized from CH_2Cl_2–EtOAc to gve 0.73 g of **11**, mp 257–258.5 °C. This material was identical with the authentic sample by IR (Nujol) and TLC (5% MeOH–$CHCl_3$ on silica gel) comparison.

Reaction of 8-Chloro-1-methyl-6-(methylthio)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9) with DBU. A stirred mixture of **9** (1.2 g, 0.004 mol) in dry Me_2SO (9 mL) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU; 0.608 g, 0.004 mol). It was kept at ambient temperature for 1 h 15 min, warmed slowly to 100 °C during about 2 h, and kept at 100 °C for 3 h 45 min; it was then poured onto crushed ice and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (75 g) with 2% MeOH–$CHCl_3$. The first compound eluted was crystallized from CH_2Cl_2–EtOAc to give 0.203 g, mp 248.5–250 °C, and 0.051 g, mp 248.5–250 °C (22.7% yield), of 8-chloro-1-methyl-4-(methylthio)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**14**). The analytical sample had mp 249.5–250.5 °C; UV (EtOH) end absorption, λ_{max} 223 nm (ϵ 20 350), inflections 243 (12 300), 269 (7500), 277 (6050), 284 (5000); NMR ($CDCl_3$, 100 MHz) δ 2.42 (s, 3, S-CH_3), 2.72 (s, 3, C-CH_3), 4.28, 4.77 (2 br s, 2, C-6 H_2); NMR [$(CD_3)_2NCDO$, 100 MHz, 25 °C] δ 4.4, 4.93 (2 br s, 2, C-6 H_2), NMR [$(CD_3)_2NCDO$, 100 MHz, 100 °C] δ 4.58 (s, 2, C-6 H_2); MS *m/e* (relative intensity) 278 (999.9), 245 (196.7), 238 (299.3), 232 (441.4). Anal. ($C_{12}H_{11}ClN_4S$) C, H, N, S; Cl: calcd, 12.72; found, 12.25.

The second compound eluted from the column was crystallized from CH_2Cl_2–EtOAc to give 0.369 g, mp 248.5–251 °C, and 0.141 g, mp 248.5–250 °C (45.6% yield), of recovered **9**. The IR (Nujol) spectrum of this material was identical with that of an authentic sample. The mixture melting point with **14** was 211–242 °C.

Pharmacology. Methods. Carworth Farms male albino mice (CF-1) weighing 18–22 g were used for all studies reported here. Unless otherwise indicated, the test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered ip to groups of four or six mice per dose, at multiple dose levels distributed at 0.3 log intervals. Procedures for measuring the effect of test compounds on the loss of traction (Tr); antagonism of nicotine-induced tonic–extensor convulsions (TE) and death (D), pentylenetetrazole-induced clonic convulsions (P), and bicuculline-induced tonic–extensor convulsions (B); potentiation of γ-butyrolactone-induced sleep (γ-B); and prolongation of hypoxic survival time (HS) have been described previously.[1,3,12,13] ED_{50} values were calculated by the method of Spearman and Karber.[14]

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