after drying and evaporation of the solvent were chromatographed on 25 g of silica gel using 1:1 benzene–ethyl acetate as eluent. the desired product crystallized slowly from ether–pentane to give 0.648 g (51%) of colorless crystals, mp 138–139 °C.

Biological Methods. Antagonism of *d*-Amphetamine-Induced Symptoms in Rats. Neuroleptic effects in vivo were estimated by the blockade of amphetamine stereotypy. Rats were placed individually in covered plastic compartments; after a brief period of acclimation in the cages, the rats in groups of five were treated intraperitoneally with compounds at doses separated by 0.5 log unit (i.e., ..., 1, 3.2, 10, 32, ... mg/kg). They were subsequently treated 1, 5, and 24 h later with *d*-amphetamine sulfate, 5 mg/kg ip. One hour after each amphetamine challenge, each rat was assessed for its most characteristic behavior on a six-point scale.[27] These ratings represent increasing degrees of drug effect,[28] and the time of rating chosen coincides with the peak effect of amphetamine.[14] Scores were dichotomized (cf. ref 27), and approximate ED_{50} values were determined, based on the quantal data. Doses are expressed in terms of the hydrochloride salts.

[^{3}H]Spiroperidol Binding to Dopamine Receptor. The method was adapted from that of Burt, Creese, and Snyder.[29] Rats (Sprague–Dawley CD males, 250–300 g, Charles River Laboratories, Wilmington, MA) were decapitated, and brains were immediately dissected to recover the corpus striatum. The latter was homogenized in 40 volumes of ice-cold 50 mM Tris-HCl [tris(hydroxymethyl)aminomethane hydrochloride] buffer, pH 7.7, with a Brinkmann Polytron PT-10. The homogenate was centrifuged twice at 50000*g* for 10 min at 0–4 °C with rehomogenization of the intermediate pellet in fresh Tris buffer (same volume) in the Polytron., The final pellet was gently resuspended in 90 volumes of cold 50 mM Tris-HCl buffer, pH 7.6, containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, and 10 μM pargyline. The tissue suspension was placed in a 37 °C water bath for 5 min and kept ice cold until use. The incubation mixture consisted of 0.02 mL of inhibitor solution or vehicle, 1.0 mL of tissue preparation, and 0.10 mL of [^{3}H]spiroperidol solution (New England Nuclear, 23.6 Ci/mmol), prepared so as to obtain a 0.5 nM final concentration. Tubes were incubated in sequence for 10 min at 37 °C in groups of three, after which 0.9 mL from each incubation tube was filtered through Whatman GF/B filters under vacuum. After washing twice with 5 mL of cold Tris-HCl, pH 7.7, buffer, each filter was placed in a scintillation vial with 10 mL of Aquasol-2 (New England Nuclear), and each vial was vortexed. Samples were kept at room temperature overnight before determination of radioactivity in a liquid scintillation counter. Binding was calculated as fmol of [^{3}H]spiroperidol bound/mg of protein. Controls (vehicle or 10^{-7} M *l*-butaclamol), blank (10^{-7} M *d*-butaclamol), and inhibitor solutions (four concentrations) were run in triplicate. The concentration that reduced binding by 50% (IC_{50}) was estimated on semilog paper. The IC_{50} values in Table I represent means of two to three runs. Insoluble drugs were dissolved in ethanol (1–2% ethanol in final incubation mixture).

Acknowledgment. The authors are grateful to Mrs. C. T. Lewis and R. B. Drolet, M. L. Elliot, A. H. Gager, C. W. Scott, A. A. Sini, and R. L. Taylor for expert technical assistance.

(27) A. Weissman, B. K. Koe, and S. S. Tenen, *J. Pharmacol. Exp. Ther.*, 151, 339 (1966).
(28) R. M. Quinton and G. Halliwell, *Nature (London)*, 200, 178 (1963).
(29) D. R. Burt, I. Creese, and S. H. Snyder, *Mol. Pharmacol.*, 12, 800 (1976).

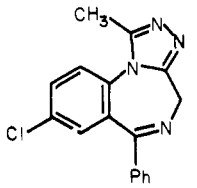
8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with Substituents at C-4

Jackson B. Hester, Jr.,* Allan D. Rudzik, and Philip F. VonVoigtlander

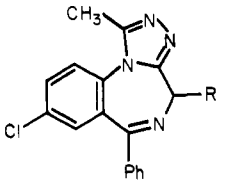
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. *Received December 7, 1979*

A series of 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with substituents at C-4 was prepared and evaluated for antianxiety potential. It was found that substitution at this position generally decreased the activity in this series.

Our interest in the antianxiety activity of the 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines [viz., alprazolam (1)][1,2] prompted us to study the structure–activity relationships of members of this series with substituents at C-4. Of particular interest in this regard were the 4-hydroxy derivatives (viz., 8) which, based on the experience with diazepam,[3] were potential metabolites. In this report we present our methods for the synthesis of these compounds and their pharmacological activity.



1



2, R = $COOC_2H_5$
3, R = CH_3
4, R = NH_2
5, R = CH_2COOH
6, R = CH_2CH_2COOH
7, R = $OC(=O)CH_3$
8, R = OH

Our discovery that the carboxylic acid derived from ester **2** was easily decarboxylated made it possible to activate the 4 position of **1** for electrophilic reactions via the ester. Subsequent hydrolysis and decarboxylation of this activating function would then give the desired monosubstituted products. The ester (**2**) was prepared in 56% yield by the reaction of **1** with diethyl carbonate and sodium hydride. Alkylation was readily accomplished by the reaction of **2** with sodium hydride and an appropriate alkyl halide. Thus, with methyl iodide, **9** was obtained in 72% yield; subsequent sodium hydroxide hydrolysis, followed by decarboxylation of the acid, gave **3** in 63% yield. Compounds **5** and **6** were prepared in a similar manner. The reaction of **2** with *O*-(2,4-dinitrophenyl)hydroxylamine and sodium hydride gave **10** in 77% yield. Sodium hy-

(1) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, 14, 1078 (1971).
(2) T. M. Itil, N. Polvan, S. Egilmez, B. Saletu, and J. Marasa, *Curr. Ther. Res. Clin. Exp.*, 15, 603 (1973).
(3) M. A. Schwartz, B. A. Koechlin, E. Postma, S. Palmer, and G. Krol, *J. Pharmacol. Exp. Ther.*, 149, 423 (1965).

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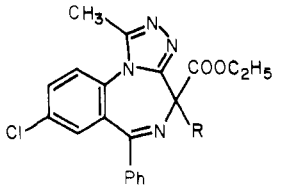
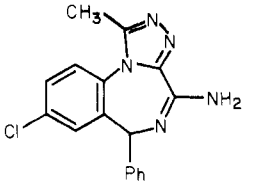


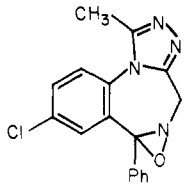


9, R = CH_3
10, R = NH_2
11, R = $CH_2COOC_2H_5$
12, R = $CH_2CH_2COOC_2H_5$

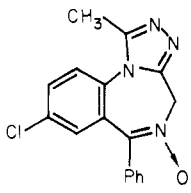
13

droxide hydrolysis of this material was, however, complicated by the sensitivity of 4 to base. Thus brief exposure of **10** to sodium hydroxide gave **13** as the only isolable product. Decarboethoxylation of **10** to give 4 was accomplished under mild conditions by barium hydroxide hydrolysis, followed by acidification with sulfuric acid. A clean conversion of **4** to **13** could be carried out with sodium methoxide in methanol.[4]

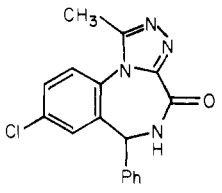
A now standard method for the preparation of the 5-phenyl-3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (viz., oxazepam) employs the Polonovski rearrangement of the N-4 oxides.[5] In order to utilize this method for the preparation of **8**, we attempted to prepare the N-5 oxide **15** by the reaction of **1** with *m*-chloroperoxybenzoic acid



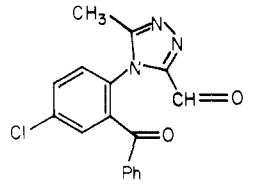
14



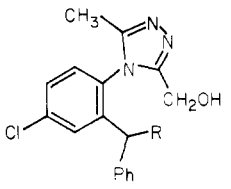
15



16



17



18, R = NH_2
19, R = OH (isomer A)
20, R = OH (isomer B)

in ethanol. The major product (35% yield) of this reaction was, however, the oxazirine (**14**), with **15** being obtained in only 6% yield.[6] In addition, the conversion of **14** to **15** be heating proved to be inefficient. It was found, however, that the keto aldehyde **17** could be obtained in 88% yield by the reaction of **14** with dimethylamine in methanol.[7] The subsequent reaction of **17** with ethanolic ammonia gave the desired 4-hydroxy derivative (**8**) in 51% yield. Since **17** had previously been obtained by the oxidation of 7-chloro-1-methyl-6-phenyl-*s*-triazolo[4,3-*a*]-quinoline,[8] the latter starting material could also be used for the preparation of **8** if desired. For comparison purposes, **15** was prepared by the reaction of 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide with acethydrazide and converted to **7** with acetic anhydride. Mild sodium hydroxide hydrolysis of the ester gave **8** in 85% yield.[9] The structure of this alcohol was further substantiated by its conversion back to **7** with acetic anhydride in pyridine. A facile rearrangement of **8** to **16** was accomplished with sodium hydroxide in a manner similar to that reported for oxazepam.[5] Surprisingly, the sodium borohydride reduction of **8** gave the amino alcohol **18**. Assignment of structure **18** was based on a comparison with the products obtained from the sodium borohydride reduction of the keto aldehyde **17**. In the latter case, we obtained a pair of diastereomeric diols (**19** and **20**) which were isolated by fractional crystallization.[10] The NMR spectra of these diastereomers were interesting in that the hydroxymethylene protons of **19** were represented by an AB pattern with doublets centered at δ 3.56 and 4.14, while the analogous protons of **20** were represented by a singlet at δ 4.55.[11] The NMR spectrum of **18** was similar to that of **19**, with the hydroxymethylene protons being represented by AB doublets centered at δ 3.30 and 3.95; the proton on the benzylic carbon adjacent to the amine, however, was represented by a singlet at δ 4.82 compared to the corresponding proton of **19** which was found at δ 5.51 due to the enhanced deshielding effect of the hydroxyl substituent.

Pharmacological Results and Discussion

The tests used for evaluating the pharmacological activity of this series of compounds in mice have been described previously.[1] The results are recorded in Table II and compared with those for the unsubstituted analogue (alprazolam, **1**). In general, we found that substitution at C-4 was detrimental to activity. The 4-methyl derivative (**3**) which was the most active compound in this series was an effective antagonist of pentylenetetrazole-induced clonic convulsions; however, it appeared to be somewhat less active than **1** on the traction response (Tr) and for antagonizing nicotine-induced tonic–extensor convulsions (TE) and death (D). Unlike observations for the corresponding 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivative, oxazepam,[12] hydroxyl substitution at C-4 markedly reduced the activity in this series (compare **8** with **1**); this compound was even less active than the corresponding acetate ester (**7**) or the amine (**4**). The double-bond tautomers **13** and **16** of compounds **4** and **8**, respectively, had little activity in these test systems. However, both the N-5 oxide **15** and especially the oxazirine (**14**) had interesting activity.

Experimental Section

Melting points taken in a capillary tube are corrected. The structures of the compounds were supported by IR, UV, and NMR

(4) A similar tautomerization of the 3-amino-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones has been described; see ref 7.
(5) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
(6) 8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 5-oxide has been obtained in 71% yield by the chloroperoxybenzoic acid oxidation of N-5 in CH_2Cl_2: K. Meguro and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 2375 (1973).
(7) Compare the related oxazirine chemistry in the 7-chloro-1,3-dihydro-6-phenyl-2*H*-1,4-benzodiazepin-2-one series: R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Org. Chem.*, **36**, 1064 (1971).
(8) J. B. Hester, Jr., *J. Heterocycl. Chem.*, in press.
(9) A similar preparation of **8** from **15** has recently been reported; see ref 15.
(10) Diastereomeric products from a similar asymetric system have been reported: M. Gall, R. A. Lahti, A. D. Rudzik, D. J. DuChamp, C. Chidester, and T. Scahill, *J. Med. Chem.*, **21**, 542 (1978).
(11) An explanation for this phenomenon might be that in one diastereomer (**19**) rotation about the triazol–hydroxymethylene bond is restricted by hydrogen bonding between the alcohols while in the other (**20**) this is not the case.
(12) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).
(13) T. Sheradsky, *J. Heterocycl. Chem.*, **4**, 413 (1967).
(14) M. Gall, B. V. Kamdar, and R. J. Collins, *J. Med. Chem.*, **21**, 1290 (1978).

Table I. Physical and Analytical Data for the 1-Methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines

no.	procedure	yield, %	mp, °C	recrystn solvent	formula	anal.
2	*a*	56	223-224 dec	CH_2Cl_2-EtOH	$C_{20}H_{17}ClN_4O_2$	C, H, Cl, N
3	B[a]	63.3	199-200.5	EtOAc-Sk B	$C_{18}H_{15}ClN_4$	H, Cl, N; C[e]
4	*a*	63	208-209 dec	MeOH-EtOAc	$C_{17}H_{14}ClN_5$	C, H, Cl, N
5	C[a]	59.6	292-303 dec	CH_2Cl_2-MeOH	$C_{19}H_{15}ClN_4O_2$	C, H, Cl, N
6	C[f]	59.5	216-217.5	CH_2Cl_2-EtOAc	$C_{21}H_{19}ClN_4O_2$	C, H, Cl, N
7	*a*	36	235.5-236.5	EtOAc-Sk B	$C_{19}H_{15}ClN_4O_2$	C, H, Cl; N[g]
8	*a*		245.5-246.5	$CHCl_3$-EtOH	$C_{17}H_{13}ClN_4O \cdot C_2H_5OH$	C, H, Cl; N[a]
9	A[a]	72.4	175.5-176.5	EtOAc-Sk B	$C_{21}H_{19}ClN_4O_2$	C, H, Cl, N
10	A[d]	77	177.5-178	EtOAc-Sk B	$C_{20}H_{18}ClN_5O_2$	C, H, Cl, N
11	A[b]	70.4	177-179.5	CH_2Cl_2-EtOAc-Sk B	$C_{24}H_{23}ClN_4O_2$	C, H, Cl, N
12	A[c]	47.9	152.5-154	CH_2Cl_2-EtOAc-Sk B	$C_{26}H_{27}ClN_4O_4$	C, H, Cl, N
13	*a*		279-280 dec	MeOH	$C_{17}H_{14}ClN_5$	C, H, Cl, N
14	*a*	34.7	167-167.5	EtOAc	$C_{17}H_{13}ClN_4O$	C, H, Cl, N
15	*a*		281-282	MeOH-EtOAc	$C_{17}H_{13}ClN_4O$	C, H, Cl, N
16	*a*	64.5	308-309	EtOH-$CHCl_3$	$C_{17}H_{13}ClN_4O$	C, H, Cl, N

[a] See Experimental Section. [b] Reaction with ethyl bromoacetate at 23 °C for 17 h; product purified by silica gel chromatography with 2% MeOH-$CHCl_3$. [c] Reaction with ethyl 4-bromobutyrate at 23 °C for 17 h; product purified by silica gel chromatography with 2% MeOH-$CHCl_3$. [d] Reaction with *O*-(2,4-dinitrophenyl)hydroxylamine[13] at 23 °C for 2 h. [e] C: calcd, 66.97; found, 66.44. [f] Product isolated by silica gel chromatography with 5% MeOH-2% HOAc-$CHCl_3$. [g] N: calcd, 15.28; found, 14.79.

Table II. Pharmacological Data[a] for the 1-Methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines

			nicotine		
no.	LRR[c]	TR[d]	TE	D	pentylenetetrazole
1[e]	>100	0.6	0.02	0.02	0.2
2	>100	>100	50	45	>100
3	>200	1.8	0.056	0.056	0.1
4	>100	18	0.36	0.63	3.5
5	>200	13	0.9	0.9	5
6	>200	>200	89	89	>50
7	>200	18	1.0	1.0	8.9
8[b]	>50	23	4.0	4.0	8.9
9	>200	112	16	18	40
10	>200	159	3.1	4.5	32
11	>200	>200	>200	>200	>50
12	>100	>100	>100	>100	>50
13	>200	>200	40	40	>100
14	>25	2.5	0.12	0.12	0.2
15	>200	10	0.2	0.2	1.8
16	>100	>100	>100	>100	>25

[a] Values are ED_{50} values expressed in mg/kg. [b] Some of these data have been reported previously; see ref 14. [c] Loss of righting reflex. [d] Loss of traction. [e] Alprazolam.

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 CH7 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.

8-Chloro-1,4-dimethyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-4-carboxylic Acid Ethyl Ester (9). Procedure A. An ice-cold stirred solution of **2** (3.81 g, 0.01 mol) in DMF (50 mL) was treated with NaH (0.462 g, 0.11 mol of a 57% mineral oil suspension) and kept in the ice bath for 15 min and at ambient temperature for 1 h 50 min. It was then cooled in an ice bath, treated with CH_3I (1.56 g, 0.011 mol), and kept at ambient temperature for 2 h 15 min, at 100–105 °C for 2 h, and at ambient temperature for 18 h. This mixture was concentrated in vacuo. The residue was mixed with water, neutralized with HOAc, and extracted with CH_2Cl_2. The extract was dried (Na_2CO_3) and concentrated. The residue was crystallized from EtOAc–Skelly B to give 2.86 g of **9**, mp 183–185 °C. The analytical sample had mp 175.5–176.5 °C; UV (EtOH) end absorption, λ_{max} 223 nm (*e* 38300), inflections 250 (14150), 270 (7000), 290 (3800); IR (Nujol) 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (t, 3, *J* = 7 Hz, CH_2CH_3), 2.40 (s, 3, 4-CH_3), 2.62 (s, 3, 1-CH_3), 3.77 (q, 2, *J* = 7 Hz, CH_2CH_3).

8-Chloro-1,4-dimethyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (3). Procedure B. A solution of **9** (4.47 g, 0.0113 mol) in 95% EtOH (140 mL) was treated with 1 N NaOH (33.9 mL), refluxed under N_2 for 5 h, and concentrated in vacuo. A solution of the residue in brine was neutralized with HCl and extracted with $CHCl_3$. The extract was dried (K_2CO_3) and concentrated in vacuo. The residue was crystallized from EtOAc–Skelly B to give 2.31 g of **3**, mp 197–198.5 °C. The analytical sample had mp 199–200.5 °C; UV (EtOH) λ_{max} 223 nm (ε 40950), inflections 245 (15600), 270 (5650), 290 (2708); NMR ($CDCl_3$) δ 2.1 (d, 3, *J* = 7 Hz, $CHCH_3$), 2.63 (s, 3, CCH_3), 4.21 (q, 1, $CHCH_3$).

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-4-acetic Acid (5). Procedure C. A stirred mixture of **11** (3.5 g, 0.00769 mol), 95% EtOH (77 mL), and 1.0 N NaOH (23.1 mL) was refluxed for 18 h and concentrated in vacuo. The residue was mixed with ice–water (80 mL), treated with 1.14 N HCl (20.3 mL), and warmed on the steam bath for 40 min. This mixture was cooled, neutralized to pH 2.5 with a little $NaHCO_3$, and filtered. The solid was washed with water, dried in vacuo, and recrystallized from CH_2Cl_2–MeOH to give 1.68 g of **5**, mp 294–295 °C.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-4-carboxylic Acid Ethyl Ester (2). A stirred mixture of **1** (61.8 g, 0.20 mol) and diethyl carbonate (1 L) was treated successively with NaH (8.43 g of a 57% suspension in mineral oil) and EtOH (2 mL). It was then refluxed under N_2 for 1.5 h, cooled, and concentrated in vacuo. The residue was treated with 1 L of ice–water which contained 0.2 mol of HCl and extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated. The residual solid was boiled with EtOAc and collected by filtration. It was recrystallized from CH_2Cl_2–EtOH to give 35.7 (mp 224–225 °C dec) and 6.98 g (mp 210–214 °C dec) of **2**. The analytical sample had mp 223–224 °C dec; UV (EtOH) λ_{max} 223 nm (ε 38450), inflections 247 (14450), 260 (7200), 290 (3650); IR (Nujol) 1750, 1710 (w) cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.93, 1.39 (2 t, 3, *J* = 7 Hz, CH_2CH_3), 2.60, 2.64 (2 s, 3, CH_3), 3.88, 4.50 (q, q, 2, *J* = 7 Hz, CH_2CH_3), 4.92, 6.50 (2 s, 1, C_4 H).

4-Amino-8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (4). A stirred solution of **10** (3.96 g, 0.01 mol) in ethanol (125 mL) was treated with 33.6 mL of 0.327 N barium hydroxide and kept at ambient temperature for 1 h. It was then concentrated in vacuo, and the residue was dissolved in water and neutralized with 10 mL of 1.037 N sulfuric acid. The solid barium sulfate was collected by filtration and washed with water. The combined filtrate was concentrated in vacuo. The residue was dissolved in absolute ethanol, and the solution was

concentrated in vacuo. The resulting material was crystallized from MeOH–EtOAc to give 2.04 g of 4, mp 208 °C dec. The analytical sample had mp 208–209 °C dec; UV (EtOH) λ_{max} 223 nm (ϵ 39 200), inflections 247 (14 700), 265 (7000), 290 (3400); IR (Nujol) 3440, 3330 (NH), 1600, 1575, 1560, 1530, 1485 cm^{-1} (C=N, C=C); NMR ($CDCl_3$) δ 2.63 (s, 3, CH_3), 2.79 (br s, 2, NH_2), 5.06 (s, 1, C_4 H).

8-Chloro-4-hydroxy-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine Acetate (7). A stirred mixture of 15 (2.39 g, 0.00734 mol), acetic anhydride (11.8 mL), and AcOH (7 mL) was warmed on the steam bath under N_2 for 30 min and concentrated in vacuo. The residue was suspended in water, neutralized (pH 7) with dilute Na_2CO_3, and extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated. Crystallization of the residue from EtOAc gave 0.96 g (36%) of 7, mp 233.5–235 °C. A second crop, 0.55 g, mp 225–227 °C, was also obtained. The analytical sample was crystallized from EtOAc–Skellysolve B and had mp 235.5–236.5 °C (lit.[15] mp 229–230 °C dec); UV (EtOH) λ_{max} 223 nm (ϵ 38 300), inflections 248 (13 750), 270 (6850), 290 (4100); IR (Nujol) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.37 [s, 3, C(=O)CH_3], 2.61 (s, 3, 1-CH_3), 6.66 (s, 1, C_4 H).

8-Chloro-4-hydroxy-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine Acetate (7) from 8. Compound 8 (0.10 g, 0.27 mol) was added to an ice-cold, stirred solution of Ac_2O (0.5 mL) in pyridine (2.5 mL), and the mixture was stirred at ambient temperature, under N_2, for 18 h. It was then poured into water and extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated in vacuo. The residue was crystallized from EtOAc to give 0.070 g (70.7%) of 7, mp 234–235 °C. The product was identical with the authentic sample by IR, UV, and NMR spectral comparison.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-4-ol Ethanol Solvate (8) from 7. A stirred suspension of 7 (2.60 g, 0.007 mol) in 95% EtOH (130 mL) was cooled in an ice bath, under N_2, and treated dropwise during 1 h 50 min with a solution of 1 N NaOH (7.28 mL) in water (26 mL). The solution was kept in the ice bath for an additional hour, poured into ice–water, treated with a little brine, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was crystallized from $CHCl_3$–EtOH to give 2.20 g (84.7%) of 8, mp 242 °C dec. The analytical sample had mp 245.5–246.5 °C[17] (lit.[15] mp 245.5 °C dec); UV (EtOH) λ_{max} 223 nm (ϵ 34 150), inflections 246 (13 200), 266 (6150), 275 (4900), 285 (3650), 298 (2050); NMR ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, $HOCH_2CH_3$), 2.60 (s, 3, CH_3), 3.74 (q, 2, J = 7 Hz, $HOCH_2CH_3$), 5.63 (s, 1, C_4 H); MS m/e 324, 309, 295. Anal. Calcd for $C_{17}H_{13}ClN_4O\cdot C_2H_5OH$: C, 61.53; H, 5.16; Cl, 9.56; N, 15.11; EtOH, 12.42. Found: C, 61.68; H, 5.32; Cl, 9.71; N, 14.30; EtOH, 9.25.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-4-ol Ethanol Solvate (8) from 17. Compound 17 (0.326 g, 0.001 mol) was added to 95% EtOH (25 mL) which had been saturated at ambient temperature with NH_3. The resulting mixture was stirred for 5 h and concentrated in vacuo at 25–30 °C. The residue was crystallized from EtOH to give 0.189 g (51%) of 8, mp 238.5–239 °C dec. This material was identical with the authentic sample by IR, UV, and NMR comparison.

4-Amino-8-chloro-1-methyl-6-phenyl-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13) from 10. A stirred suspension of 10 (0.792 g, 0.002 mol) in ethanol (25 mL) was treated with 2.5 mL of 1 N NaOH and kept at ambient temperature for 1 h 50 min. It was then concentrated in vacuo. A solution of the residue in water was neutralized to pH 6.8 with dilute HCl and then concentrated in vacuo. The residue was mixed with absolute EtOH and concentrated. The resulting material was extracted with $CHCl_3$. The product obtained from the $CHCl_3$ extract was crystallized first from MeOH–EtOH and then from MeOH to give 0.282 g (43.5%) of 13, mp 278–279.5 °C dec. The analytical sample had mp 279–280 °C dec; UV (EtOH) end absorption, λ_{max} 283 nm (ϵ 2950), inflection 274 (3800); IR (Nujol) 3480, 3300, 3240, 3120 (NH), 1650 cm^{-1} (C=N); NMR [$(CD_3)_2NCDO$] δ 2.75 (s, 3, CH_3), 5.40 (s, 1, C_6 H); MS m/e 323, 322, 308, 307.

4-Amino-8-chloro-1-methyl-6-phenyl-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13) from 4. A small piece of Na was dissolved in MeOH (5 mL) and the stirred solution was cooled in an ice bath, under N_2, and treated with 0.323 g (0.001 mol) of 4. The mixture was allowed to come to ambient temperature and stand for 7 h. It was then diluted with ice–water. The solid was collected by filtration, washed with water, dried in vacuo, and crystallized from MeOH to give 0.211 g (65.2%) of 13, mp 274.5–276 °C. This material was identical with the authentic sample by IR, NMR, and UV comparison.

Reaction of 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (1) with *m*-Chloroperoxybenzoic Acid. A stirred solution of 1 (1.00 g, 0.00324 mol) in absolute EtOH was cooled in an ice bath and treated with *m*-chloroperoxybenzoic acid (1.12 g, 0.00648 mol). The mixture was allowed to remain in the ice bath for 6 h and to stand at ambient temperature for 18 h. It was then concentrated in vacuo; the residue was suspended in cold, dilute K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with water, dried (K_2CO_3), and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with mixtures of MeOH–$CHCl_3$ containing 5–10% MeOH. The first compound eluted was crystallized from EtOAc to give 0.334 (mp 169.5–170 °C dec) and 0.031 g (mp 168.5–169.5 °C dec) (34.7%) of 10-chloro-6-methyl-11b-phenyl-3*H*,11b*H*-oxazirino[3,2-*d*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (14). The analytical sample had mp 167–167.5 °C; UV (EtOH) end absorption, inflections 235 nm (ϵ 16 700), 263 (939), 269 (776), 275 (594), 281 (523); NMR [$(CD_3)_2NCDO$] δ 2.73 (s, 3, CH_3), 3.74, 5.08 (d, d, 2, J_{AB} = 12 Hz, C_4 H_2); MS m/e 324, 219.

The second compound eluted from the column was crystallized from EtOAc to give 0.105 g of recovered 1, 227.5–228.5 °C.

The third compound eluted from the column was mixed with recovered 1 Fractional crystallization of this mixture from MeOH–EtOAc gave 0.066 g (6.3%) of 15, mp 262–263 °C dec. The analytical sample had mp 272.5–273.5 °C. An IR study in which this material was dissolved in $CHCl_3$ and deposited on KBr demonstrated that it was a polymorphic form of authentic 15.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine 5-Oxide (15). A stirred mixture of 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide[18] (300.7 mg, 0.00100 mol), acethydrazide (222 mg, 0.003 mol), and 1-butanol (10 mL) was refluxed under nitrogen for 20 h and concentrated in vacuo. A suspension of the residue in water was extracted with CH_2Cl_2. The extract was washed with water, dried (K_2CO_3), and concentrated. The residue was crystallized from MeOH–EtOAc to give 0.061 (mp 272.5–273 °C dec), 0.065 (mp 270–271 °C dec), and 0.044 g (mp 268.5–269 °C dec) (52.3% yield) of 15. The analytical sample had mp 281–282 °C (lit.[16] mp 273–274 °C dec); UV (EtOH) end absorption, λ_{max} 227 nm (ϵ 28 850), 256 (16 550), 308 (ϵ 11 050), inflection 262 (16 050); NMR [$(CD_3)_2SO$] δ 2.65 (s, 3, CH_3), 5.08, 5.46 (2 d, 2, J_{AB} = 14 Hz, C_4 H_2); MS m/e 324, 323, 308, 279.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine 5-Oxide (15) from 14. A mixture of 14 (300 mg) and mesitylene (3 mL) was refluxed under nitrogen for 15 min. The cooled reaction mixture was dissolved in CH_2Cl_2 and absorbed on a silica gel (25 g) column. The column was eluted with mixtures of MeOH–$CHCl_3$ continuing 5–10% MeOH to give recovered 14 (0.072 g, mp 158.5–160 °C dec) and 15, which was crystallized from MeOH–EtOAc to give 0.047 g (15.7%), mp 251.5–253 °C. Recrystallization raised this melting point to 267.5–268.5 °C; the IR spectrum (Nujol) of this material was identical with that of an authentic sample of 15.

8-Chloro-5,6-dihydro-1-methyl-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepin-4-one (16). A stirred suspension of 8 (0.341 g, 0.001 mol) in 95% EtOH (25 mL) was treated with 1 N NaOH (1 mL), kept at ambient temperature under N_2 for 18 h, and concentrated in vacuo. The residue was mixed with water and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated. The residue was crystallized from EtOH–$CHCl_3$

(15) K. Meguro and Y. Kuwada, U.S. Patent 3 907 820 (1975).
(16) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.*, 21, 2382 (1973).
(17) The unsolvated material was obtained by crystallizing from MeOH–$CHCl_3$ and had mp 235–238 °C; see ref 14.
(18) G. A. Archer and L. H. Sternbach, U.S. Patent 3 312 688 (1967).

to give 0.02 (mp 306.5–307.5 °C dec) and 0.20 g (mp 304–306 °C dec) (64.5%) of **16**. The analytical sample had mp 308–309 °C; UV (EtOH) end absorption, λ_{max} 238 nm (ϵ 13 200), inflections 270 (1850), 280 (722); IR (Nujol) 3250 (NH), 1680, 1640 cm^{-1} (C=O); NMR [$(CD_3)_2NCDO$] δ 2.43 (s, 3, CH_3), 5.91 (d, 1, J = 7 Hz, C_6 H), 9.6 (d, 1, J = 7 Hz, NH); MS m/e 324, 281, 239.

4-(2-Benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldehyde Methanol Solvate (17). Compound **14** (0.975 g, 0.003 mol) was added to an ice-cold solution of dimethylamine (1 mL) and methanol (50 mL); the resulting suspension was stirred in an ice bath for 17 h 20 min, allowed to warm slowly to an ambient temperature, and kept for an additional 7 h 50 min. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (50 g) with 5% MeOH–$CHCl_3$. The product thus obtained was crystallized from MeOH to give 0.705 (mp 110.5–112.5 °C dec) and 0.239 g (mp 109–112.5 °C dec) (87.9% yield) of **17** [lit.[8] mp 109–112.5 °C dec]. This material was identical with an authentic sample by IR, UV, and NMR comparison.

4-(α-Amino-4-chloro-α-phenyl-*o*-tolyl)-5-methyl-4*H*-1,2,4-triazole-3-methanol (18). Compound **8** (0.812 g, 0.0025 mol) was added under N_2 to an ice-cold, stirred suspension of $NaBH_4$ (1.0 g) in absolute EtOH (38 mL). The resulting mixture was stirred in the ice bath for 30 min, at ambient temperature for 18 h, and at reflux for 1.5 h. It was then cooled and concentrated in vacuo. The residue was mixed with water and extracted with CH_2Cl_2. The extract was dried (K_2CO_2) and concentrated. The residue was crystallized from EtOAc–Skelly B to give 0.44 g (53.5%) of **18**, mp 171.5–176.5 °C. The analytical sample was recrystallized from EtOAc and had mp 193.5–195 °C; UV (EtOH) end absorption, λ_{max} 258 nm (ϵ 901), inflections 220 (21 200), 252 (996), 264 (746), 275 (370); IR (Nujol) 3350, 3280, 3160, 2660 cm^{-1} (NH/OH); NMR ($CDCl_3$) δ 2.18 (s, 3, CH_3), 3.30, 3.95 (2 d, 2, J_{AB} = 14 Hz, HOCH_2), 4.82 (s, 1, CHNH_2). Anal. ($C_{17}H_{17}ClN_4O$) C, H, Cl, N.

5-Chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzhydrol, Isomers A (19) and B (20). Compound **17** (3.26 g, 0.01 mol) was added to an ice-cold, stirred suspension of $NaBH_4$ (4 g) in absolute EtOH (148 mL). The mixture was kept in the ice bath for 30 min, at ambient temperature for 18 h, and at reflux for 1 h. It was then cooled and concentrated. A suspension of the residue in water was extracted with $CHCl_3$, and the extract was washed with water, dried, and concentrated. A solution of the residue in MeOH was acidified with HCl and crystallized to give 2.51 g, mp >340 °C. This material was dissolved in dilute HCl, washed with Et_2O, made alkaline with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried (K_2CO_3), and concentrated. Crystallization of the residue from MeOH gave 0.252 g of **19**, mp 221–222.5 °C. The analytical sample had mp 218–219.5 °C; UV (EtOH) end absorption, λ_{max} 253 nm (ϵ 373), 258 (452), 264 (425), inflections 225 (16 650), 273 (208), 280 (46); IR (Nujol) 3360, 3140, 2660 cm^{-1} (OH); NMR [$(CD_3)_2NCDO$] δ 2.16 (s, 3, CH_3), 3.56, 4.14 (2 d, 2, J_{AB} = 13 Hz, HOCH_2), 5.51 (s, 1, HOCH), 5.95 (br s, 2, OH); MS m/e 329. Anal. ($C_{17}H_{16}ClN_3O_2$) C, H, Cl, N.

The second crop obtained from MeOH was a mixture of **19** and **20** and amounted to 0.723 g, mp 217.5–219 °C. Crystallization of the mother liquid from MeOH–EtOAc gave 0.347 g of **20**, mp 218–219.5 °C. The analytical sample had mp 223.5–224.5 °C; UV (EtOH) end absorption, λ_{max} 253 nm (ϵ 376), 258 (475), 264 (452), inflections 225 (17 050), 275 (201); IR (Nujol) 3250 cm^{-1} (OH); NMR [$(CD_3)_2NCDO$] δ 1.37 (s, 3, CH_3), 4.55 (s, 2, HOCH_2), 5.71 (s, 1, HOCH); MS m/e 329. Anal. ($C_{17}H_{16}ClN_3O_2$) C, H, Cl, N.

Further crystallization from MeOH–EtOAc gave 0.479 g, mp 203–214.5 °C, of a mixture of **19** and **20**.

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 solvent 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 overt behavior [loss of righting reflex (LRR) and traction (Tr)] and for the antagonism of nicotine-induced tonic–extensor convulsions (TE) and death (D) and pentylenetetrazole-induced clonic convulsions (P) have been described previously.[1] ED_{50} values were calculated by the method of Spearman and Karber.[19]

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(19) D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, 1952.