1-(Aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with Antianxiety and Antidepressant Activity

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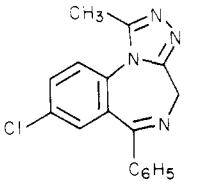
A series of 1-(aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines has been prepared and evaluated for central nervous system activity. We have found that members of this series have activity in pharmacological test systems designed to detect both anxiolytic and antidepressant activity. Each type of activity could be varied independently by appropriate substituent selections.

The interesting anxiolytic activity of the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (viz., alprazolam, **1**)[1-3]



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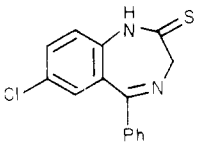
has generated an intense investigation of the chemical and pharmacological properties of this system. As a result of the broad screening of a wide variety of these compounds in test systems designed to evaluate CNS activity other than that generally associated with the benzodiazepines,[4] we have found that 1-(aminoalkyl) derivatives of this system have activity in test systems designed to detect potential antidepressant activity. This article will discuss these interesting and unexpected results.

Several synthetic methods have been employed to prepare members of this series.[5] These will be illustrated for only one member of each class. Table I lists the compounds prepared and the method of preparation. Compounds with an amino group separated from the triazole ring by one or three carbon atoms (**2** and **5**, respectively) were conveniently prepared by alkylating an appropriate amine with a 1-(chloroalkyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**6** or **7**) (Chart I). The latter compounds were prepared by acylating the hydrazino derivative (**4**) with an appropriate carboxylic acid chloride and cyclizing the resulting amide with hot acetic acid. Alternatively, compound **2** could be prepared by the reaction of **3** with (dimethylamino)acetic acid hydrazide[6] in refluxing 1-butanol.[7] Catalytic reduction of **2** with platinum in acetic acid gave the 5,6-dihydro derivative **18**. The reaction of **6** with *N*,*N*-(dimethylhydroxy)amine and sodium hydride gave **8**, which could be rearranged[8] to **9** by heating at its melting point. A similar rearrangement of **10** gave the Cope elimination[9] product **11** in addition to **12**.[10] The unsubstituted aminooxy derivative (**13**) was prepared in two steps by first alkylating *N*-hydroxyphthalimide with **6** in the presence of triethylamine to give **14** and subsequently removing the phthalimide protecting group with hydrazine hydrate.

Chart I



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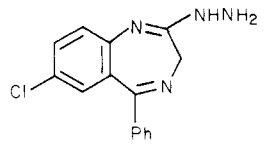

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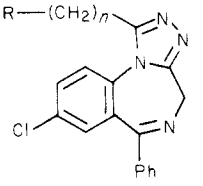
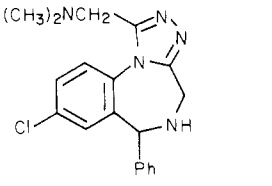
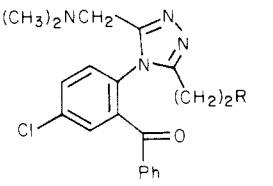


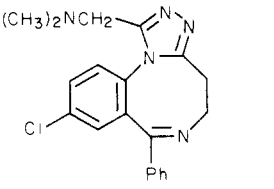
2, $n = 1$; R = $N(CH_3)_2$
5, $n = 3$; R = $N(CH_3)_2$
6, $n = 1$; R = Cl
7, $n = 3$; R = Cl
8, $n = 1$; R = $N(CH_3)_2$ → O
9, $n = 1$; R = $ON(CH_3)_2$ → O
10, $n = 1$; R = $N(C_2H_5)_2$
11, $n = 1$; R = $N(OH)C_2H_5$
12, $n = 1$; R = $ON(C_2H_5)_2$
13, $n = 1$; R = ONH_2
14, $n = 1$; R = O-Pht
15, $n = 2$; R = $N(CH_3)_2$
16, $n = 2$; R = Pht
17, $n = 2$; R = NH_2



18

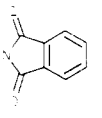


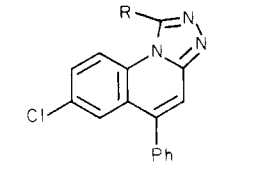
19, R = $N(CH_3)_2$
20, R = Pht



21

Pht =





22, R = $CH_2N(CH_3)_2$
23, R = H
24, R = CH_3
25, R = $(CH_2)_2N(CH_3)_2$

(1) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(2) R. Nakajima, C. Hattori, and Y. Nagawa, *Jpn. J. Pharmacol.*, **21**, 489 (1971).
(3) R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui, and Y. Nagawa, *Jpn. J. Pharmacol.*, **21**, 497 (1971).
(4) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning, in "Psychopharmacological Agents", Vol. 3, M. Gordon, Ed., Academic Press, New York, 1974, Chapter 6.
(5) Aminoalkyl derivatives have also been described by others: Deutsche Offenlegungsschrift 2 201 210 to Ciba-Geigy (1971); K. Meguro and Y. Kuwada, South African Patent Application 718044 (1971).
(6) M. Pesson and S. Dupin, *Bull. Soc. Chim. Fr.*, 250 (1962).
(7) (a) The authors are indebted to Dr. C. E. Coverdale of these laboratories for developing this procedure. (b) Carbon-14 labeled **2** has also been prepared by this method: R. S. P. Hsi and T. D. Johnson, *J. Labeled Compd.*, **12**, 613 (1976).
(8) J. Meisenheimer, *Chem. Ber.*, **52**, 1667 (1919).
(9) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).
(10) The chemistry of hydroxyamines has been reviewed by S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. 3, Academic Press, New York, 1972.

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Aminoalkyl derivatives (viz., **15**) with the amino group separated from the triazole ring by two carbon atoms were best prepared via the phthalimide derivative (**16**). The latter compound was prepared in two steps by the reaction of **4** with β-phthalimidopropionic acid and carbonyldiimidazole, followed by cyclization of the intermediate amide with hot acetic acid. The phthalimide protecting group was removed with either hydrazine hydrate or aqueous methylamine.[11] Selective reductive alkylation of the primary nitrogen of **17** in the presence of the relatively nonbasic N-5, C-6 double bond could be accomplished with aqueous formaldehyde, sodium cyanoborohydride, and acetic acid under neutral or weakly acidic conditions.[12] Compound **15** was obtained in 68% yield under these conditions. The Eschweiler–Clark reaction[13] (88% formic acid and 37% formaldehyde at 100 °C), on the other hand, gave **19**, the product resulting from ring cleavage followed by alkylation of the N-5 nitrogen.[14] To prepare the eight-membered ring analogue (**21**) of **2**, we took advantage of this reaction. Thus, **16** gave **20** when refluxed with formaldehyde and formic acid. Conversion of **20** to the cyclized product **21** was accomplished with hydrazine hydrate followed by a brief treatment with refluxing pyridine.

Preparation of the quinoline derivative **22** was accomplished by the reaction of **23** with dimethylmethyleneammonium chloride,[15,16] prepared in situ by adding acetyl chloride to a DMF solution of *N,N,N',N'*-tetramethyldiaminomethane. A similar reaction of **24**[17] with dimethylmethyleneammonium chloride in the presence of a slight excess of acetyl chloride[18] gave the corresponding 1-[2-(dimethylamino)ethyl] derivative **25**. The intermediate triazoloquinoline (**23**) was prepared by the reaction of 6-chloro-2-hydrazino-4-phenylquinoline[17] with triethyl orthoformate and sulfuric acid.

Results and Discussion

In our laboratories new compounds are submitted to a battery of tests which have been designed to detect clinically useful compounds with central nervous system activity. Many of these tests are relatively specific. Minor tranquilizers such as diazepam (**96**), for example, are particularly effective for the prolongation of hypoxic survival time (HS); other centrally active compounds are not active in this test. Minor tranquilizers also effectively antagonize bicucullin (B) and pentylenetetrazole-induced convulsions (P) and potentiate the depressant effects of γ-butyrolactone (γ-B). Antidepressants such as imipramine (**97**), on the other hand, potentiate the toxicity of yohimbine (Y) in aggregated mice and the stereotyped gnawing and licking behavior of mice pretreated with apomorphine (AG). They also antagonize the hypothermia induced by oxotremorine (OX). Diazepam is not active in these tests. The antagonism of iv nicotine-induced tonic–extensor convulsions (TE) and death (D) is relatively nonspecific and has been used as a general screen to detect compounds with central nervous system activity.

The pharmacologic results for the 1-(aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines are presented in Table II. They are compared with the results obtained for the minor tranquilizer diazepam (**96**) and the antidepressant imipramine hydrochloride (**97**) in the same test system. Perhaps the most significant observation that can be made from these data is that 8-chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**2**) is active in tests that are normally selective for either the minor tranquilizers (viz., **96**) or the antidepressants (viz., **97**), suggesting that it might have both antianxiety and antidepressant activity. Since this type of activity might be clinically useful for treating neurotic depression, we endeavored to explore the structure–activity relationship in greater detail. It was found that the mix of antianxiety and antidepressant activity was relatively specific for structure **2**. Increasing the bulk of the *N*-alkyl substituents (viz., **47**) decreased both activities, as did incorporating the alkyl groups into heterocyclic rings (viz., **48**–**50**). On the other hand, removing one or both of the *N*-methyl substituents from **2** (viz., **44** and **43**) did not appear to greatly influence the activity, although some variation in individual test results was noted. Incorporating an *N*-oxide onto the basic side-chain nitrogen of **2** and **47** (viz., **8** and **10**, respectively) diminished the antidepressant activity as represented by AG and Y but did not greatly influence tests for antianxiety activity. A variety of N-substituted analogues of compounds **2** and **44** in which one of the methyl groups was replaced by allyl, propargyl, cyclopropyl, or cyclopropylmethyl were prepared. In general, the antianxiety activity was maintained though somewhat diminished over that of the parent compounds; the antidepressant activity was lost, however (compare **31**, **54**, **56**, and **62** with **44**; **53**, **55**, and **57** with **2**). In this series, the *N*-methyl-*N*-propargyl derivative (**60**) was an exception. Its activity in most tests was as good as or better than that of the parent compound (**2**); activity in HS was lost, however.

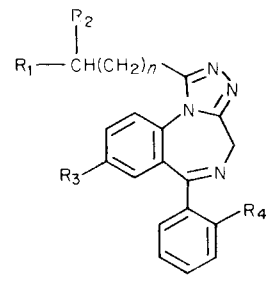
Several analogues with modified aromatic substituents on the benzodiazepine ring and on the 6-phenyl group were also prepared. The 8-bromo derivative (**39**) had somewhat enhanced anxiolytic activity (HS) but diminished antidepressant properties (AG and Y) when compared to **2**. The 8-(methylthio) derivative (**38**) had diminished antianxiety activity (HS) but still retained activity in the antidepressant parameters (OX and Y). When the 8-chloro substituent was replaced by hydrogen (viz., **42**), the antianxiety and depressant properties were diminished, but the antidepressant properties were retained. By analogy with the 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine series,[1] an *o*-chloro substituent on the 6-phenyl moiety enhanced the general CNS activity of the analogue over that of the unsubstituted molecule (compare, for example, HS, TE, and D for **46** with **2** and **45** with **42**); the antidepressant activity was decreased, however. The analogue (**87**) obtained by replacing the 6-phenyl group by 2-pyridyl was similar in many respects to the parent molecule (**39**); it had less activity on antianxiety end points, however.

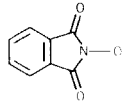
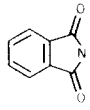
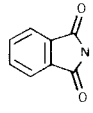
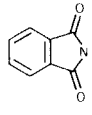
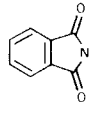
When the size of the seven-membered ring of **2** was reduced to six (viz., **22**) or expanded to eight members (viz., **21**), the activity was lost. The activity was also greatly diminished by reducing the 5,6 double bond (viz., **18**). Methyl substitution at C-4 (viz., **94**) reduced activity in tests useful for detecting minor tranquilizing activity (especially HS), while significant antidepressant activity remained.

Lengthening the aminoalkyl side chain by one carbon diminished the antianxiety properties of the resulting

(11) S. Wolfe and S. K. Hasan, *Can. J. Chem.*, 48, 3572 (1970).
(12) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 93, 2897 (1971).
(13) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 55, 4571 (1933).
(14) For other examples of this reaction, see ref 21.
(15) H. Böhme and K. Hartke, *Chem. Ber.*, 93, 1305 (1960).
(16) This reaction has also been used to prepare compound 2: M. Gall, British Patent 1 491 667 (1977).
(17) J. B. Hester, U.S. Patent 3 709 898 (1973).
(18) This reaction is discussed in greater detail by J. B. Hester, *J. Org. Chem.*, 44, 4165 (1979).

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



no.	R_1	R_2	R_3	R_4	n	yield, %	procedure	ref[k]	mp, °C	recrystn solvent	formula	analyses
2	$(CH_3)_2N$	H	Cl	H	0	88.9	D[u]		171-172.5	EtOAc	$C_{19}H_{18}ClN_5$	C, H, Cl, N
5	$(CH_3)_2N$	H	Cl	H	2	78.5	B[n,cc]		152-212.5[y]	MeOH-EtOAc	$C_{33}H_{48}ClN_7O_6S_2$[z]	C, H, Cl, N, S
6	Cl	H	Cl	H	0	57.7	A[u]	*l*	183-186.5	EtOAc	$C_{17}H_{12}Cl_2N_4$	C, H, N; Cl[ss]
7	Cl	H	Cl	H	2	58.1	A	*l*	130-134	EtOAc-Sk B[oo]	$C_{19}H_{16}Cl_2N_4$	C, H, Cl, N
8	$(CH_3)_2N(\rightarrow O)$	H	Cl	H	0	72.3	I[u]		157.5-158.5	MeOH-EtOAc	$C_{19}H_{18}ClN_5O$	C, H, Cl, N[bb]
9	$(CH_3)_2NO$	H	Cl	H	0	66.5	*u*		175	EtOAc-Sk B	$C_{19}H_{18}ClN_5O$	C, H, Cl, N
10	$(C_2H_5)_2N(\rightarrow O)$	H	Cl	H	0	54.6	I		135-137.5[o]	MeOH-EtOAc(H_2O)	$C_{21}H_{26}ClN_5O_3$	C, H, Cl, N, H_2O
11	$C_2H_5N(OH)$	H	Cl	H	0	35.3	*u*		199-200.5	MeOH-EtOAc	$C_{19}H_{18}ClN_5O$	C, H, Cl, N
12	$(C_2H_5)_2NO$	H	Cl	H	0	51.3	*u*		136-139	EtOAc-Sk B	$C_{21}H_{22}ClN_5O$	C, H, Cl, N
13	H_2NO	H	Cl	H	0	46.1	*u*		191-192	MeOH-EtOAc	$C_{17}H_{14}ClN_5O$	C, H, Cl, N
14		H	Cl	H	0	91.5	*u*		256.5-257.5[o]	EtOH-$CHCl_3$	$C_{25}H_{16}ClN_5O_3$	C, H, N
15	$(CH_3)_2N$	H	Cl	H	1	67.7	H[u]		195.5-197.5[o]	$(CH_3)_2CHOH(H_2O)$	$C_{27}H_{28}ClN_5O_3S$[ii]	C, H, Cl, N, S
16		H	Cl	H	1	76.5	E[u]	*l*	130.5-133.5[o]	CH_2Cl_2-EtOAc	$C_{30}H_{26}ClN_5O_4$	C, H, Cl, N[ii]
17	H_2N	H	Cl	H	1	65 33.6	G[u] F[u]		224-226 205-209	MeOH-EtOAc	$C_{18}H_{16}ClN_5$	C, H, Cl, N
26		CH_3	Cl	H	1	75.3	E	*kk*, *l*	238-240.5	EtOH	$C_{27}H_{20}ClN_5O_2$	C, H, Cl, N
27		CH_3	H	Cl	1	52.5	E	*kk*, *c*	215	CH_2Cl_2-EtOAc	$C_{27}H_{20}ClN_5O_2$	C, H, Cl, N
28		CH_3	Cl	Cl	1	74	E	*kk*, *l*	265-267	EtOAc	$C_{27}H_{19}Cl_2N_5O_2$	C, H, Cl, N

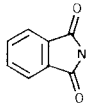
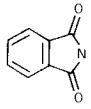
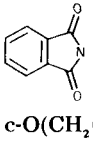
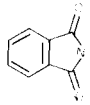
29		CH_3	H	H	1	45	E	*kk, i*	226-226.5	MeOH-EtOAc	$C_{27}H_{21}N_5O_2$	H, N; C[ll]
30		H	Cl	Cl	1	75	E	*l*	216-220	CH_2Cl_2-MeOH-EtOAc	$C_{26}H_{17}Cl_2N_5O_2$	Cl, N; C, H[mm]
31	c-$C_3H_5CH_2NH$	H	Cl	H	0	89.8	B		154-156	CH_2Cl_2-EtOAc	$C_{21}H_{20}ClN_5$	C, H, Cl, N
32	Cl	H	Cl	Cl	2	44	A	*l*	206-209	CH_2Cl_2-EtOAc	$C_{19}H_{15}Cl_3N_4$	C, H, N, Cl[b]
33	Cl	H	Cl	Cl	0	56	A	*l*	195-198	CH_2Cl_2-EtOAc	$C_{17}H_{11}Cl_3N_4$	C, H, Cl, N
34	Cl	H	H	Cl	0	49.6	A	*c*	186-188[o]	CH_2Cl_2-EtOAc	$C_{17}H_{12}Cl_2N_4$	C, H, N, Cl[d]
35	Cl	CH_3	Cl	H	0	85	A	*l*	153.5-156.5	EtOAc	$C_{18}H_{14}Cl_2N_4$	C, H, Cl, N
36	Cl	CH_3	Cl	Cl	0	67	A	*l*	210-214	EtOAc-Sk B	$C_{18}H_{13}Cl_3N_4$	C, H, Cl, N
37	Cl	CH_3	H	Cl	0	41.5	A	*c*	201-202	EtOAc	$C_{18}H_{14}Cl_2N_4$	C, H, Cl, N
38	$(CH_3)_2N$	H	CH_3S	H	0	44.2	C[u]	*m*	180	EtOAc-Sk B	$C_{20}H_{21}N_5S$	H, N, S; C[e]
39	$(CH_3)_2N$	H	Br	H	0	51	C	*f*	197-198	MeOH-EtOAc-Sk B	$C_{19}H_{18}BrN_5$	C, H, Br, N
40	H_2N	CH_3	Cl	Cl	0	25	D[g]		171-173	MeOH-EtOAc	$C_{18}H_{15}Cl_2N_5$	C, H, Cl, N
41	H_2N	CH_3	H	Cl	0	45.9	D[h]		159-160.5	EtOAc	$C_{18}H_{16}ClN_5$	C, H, Cl, N
42	$(CH_3)_2N$	H	H	H	0	62	D	*i*	182-183.5	CH_2Cl_2-EtOAc-Sk B	$C_{19}H_{19}N_5$	C, H, N
43	H_2N	H	Cl	H	0	51.4	D[r]		167.5-172.5	CH_2Cl_2-EtOAc	$C_{17}H_{14}ClN_5$	C, H, Cl; N[j]
44	CH_3NH	H	Cl	H	0	61.6	D		152-156	CH_2Cl_2-EtOAc-Sk B	$C_{18}H_{16}ClN_5$	C, H, Cl, N
45	$(CH_3)_2N$	H	H	Cl	0	99	D		143-146	EtOAc-Sk B	$C_{19}H_{18}ClN_5$	C, H, Cl, N
46	$(CH_3)_2N$	H	Cl	Cl	0	91.7	D		203.5-205	MeOH-EtOAc	$C_{19}H_{17}Cl_2N_5$	C, H, Cl, N
47	$(C_2H_5)_2N$	H	Cl	H	0	60.5	B[n]		131.5-132.5	EtOAc-Sk B	$C_{21}H_{22}ClN_5$	C, H, Cl, N
48	CH_3-c-$N(CH_2CH_2)_2N$	H	Cl	H	0	77.7	B[n]		204-205.5	CH_2Cl_2-EtOAc	$C_{22}H_{23}ClN_6$	C, H, Cl, N
49		H	Cl	H	0	72.5	B[n]		184.5-185.5	EtOAc	$C_{21}H_{20}ClN_5$	C, H, Cl, N
50	Ph-c-$N(CH_2CH_2)_2N$	H	Cl	H	0	77.4	B[n,s]		204-207.5	MeOH-EtOAc	$C_{27}H_{25}ClN_6$	C, H, Cl, N
51	H_2N	CH_3	Cl	H	0	31	D[p,t]		186.5-189.5	MeOH-CH_2Cl_2-EtOAc	$C_{18}H_{16}ClN_5$	C, H, Cl, N
52	CH_3NH	CH_3	Cl	H	0	73	D[t]		108-113	MeOH-H_2O	$C_{19}H_{18}ClN_5$	C, H, Cl, N
53	c-C_3H_5-$N(CH_3)$	H	Cl	H	0	32.9	B		165-169	EtOAc-Sk B	$C_{21}H_{20}ClN_5$	C, H, Cl; N[q]
54	c-C_3H_5-NH	H	Cl	H	0	49.6	B[u]		165-171	EtOAc	$C_{20}H_{18}ClN_5$	C, H, Cl, N
55	CH_2=$CHCH_2N(CH_3)$	H	Cl	H	0	78.3	B		158-164	EtOAc-Sk B	$C_{21}H_{20}ClN_5$	C, H, Cl, N
56	CH_2=$CHCH_2NH$	H	Cl	H	0	34.1	B		128-132	CH_2Cl_2-EtOAc-Sk B	$C_{20}H_{18}ClN_5$	C, H, Cl, N
57	c-C_3H_5-$CH_2N(CH_3)$	H	Cl	H	0	61.5	U		171-176	CH_2Cl_2-EtOAc	$C_{22}H_{22}ClN_5$	C, H, Cl, N
58	HC≡$CCH_2N(CH_3)$	H	Cl	Cl	0	62	B[n,r]		168-171	CH_2Cl_2-EtOAc	$C_{21}H_{17}Cl_2N_5$	C, H, Cl, N
59	HC≡$CCH_2N(CH_3)$	H	H	Cl	0	68.7	B[n]		180-182	CH_2Cl_2-EtOAc	$C_{21}H_{18}ClN_5$	C, H, Cl, N
60	HC≡$CCH_2N(CH_3)$	H	Cl	H	0	68	B[n]		231-232[o]	MeOH-EtOAc	$C_{21}H_{19}Cl_2N_5$[v]	H, Cl, N; C[w]
61	HC≡CCH_2NH	CH_3	Cl	H	0	49	B[n,x]		146-152	EtOAc-Sk B	$C_{21}H_{18}ClN_5$	C, H, Cl, N
62	HC≡CCH_2NH	H	Cl	H	0	55	B[n,x]		193-195.5	CH_2Cl_2	$C_{20}H_{16}ClN_5$	C, H, Cl, N
63		H	Br	H	1	72.8	E	*u*	226	CH_2Cl_2-EtOAc	$C_{26}H_{18}BrN_5O_2$	C, H, N; Br[nn]
64	c-$O(CH_2CH_2)_2N$	H	Cl	H	2	68	B[n,dd]		139-144	EtOAc-Sk B(H_2O)	$C_{23}H_{24}ClN_5O$	H, Cl, N; C[aa]
65	$(C_2H_5)_2N$	H	Cl	H	2	39.6	B[n,ee]		140.5-149	EtOH-EtOAc	$C_{35}H_{52}ClN_7O_6S_2$[z]	C, H, Cl, N, S
66	Ph-c-$N(CH_2CH_2)_2N$	H	Cl	H	2	61	B[n,x,ee]		132.5-139	EtOAc-Sk B	$C_{29}H_{31}ClN_6O$[bb]	C, H, Cl, N, H_2O
67		H	Cl	H	2	54.5	B[n,ff]		189-194	EtOH-EtOAc	$C_{35}H_{50}ClN_7O_6S_2$[z]	H, Cl, N, S; C[gg]
68	$(CH_3)_2N$	H	Cl	Cl	2	62.2	B[n]		146.5-149	CH_2Cl_2-EtOAc-Sk B	$C_{21}H_{21}Cl_2N_5$	C, H, Cl, N

Table I (*Continued*)

no.	R_1	R_2	R_3	R_4	n	yield, %	procedure	ref[k]	mp, °C	recrystn solvent	formula	analyses
70		H	H	Cl	1	76	E	*c*	262-263[o]	CH_2Cl_2-EtOAc	$C_{26}H_{18}ClN_5O_2$	H, N; C, Cl[pp]
71		H	H	H	1	75.6	E	*i*	249.5-251	CH_2Cl_2-EtOAc	$C_{26}H_{19}N_5O_2$	C, H, N
72	H_2N	H	Br	H	1	80.7	G		195-197.5[o]	CH_2Cl_2-EtOAc	$C_{18}H_{16}BrN_5$	C, H, Br, N
73	H_2N	H	H	Cl	1	74	G		168.5-170	MeOH-EtOAc	$C_{18}H_{16}ClN_5$	C, H, Cl, N
74	H_2N	H	H	H	1	64.5	G		188.5-191	MeOH-EtOAc	$C_{18}H_{17}N_5$	C, H, N
75	H_2N	H	Cl	Cl	1	73.4	F		171-173	CH_2Cl_2-EtOAc	$C_{18}H_{15}Cl_2N_5$	C, H, Cl, N[qq]
76	H_2N	CH_3	Cl	Cl	1	69.1	F		181-182.5	EtOAc-Sk B	$C_{19}H_{17}Cl_2N_5$	C, H, Cl, N
						48.4	G					
77	H_2N	CH_3	Cl	H	1	26.8	F		230-233	MeOH-EtOAc	$C_{33}H_{36}ClN_5O_7S_2$[rr]	C, H, Cl, N, S
78	H_2N	CH_3	H	H	1	65.3	G		174	CH_2Cl_2-Et_2O	$C_{19}H_{19}N_5$	C, H, N
79	H_2N	CH_3	H	Cl	1	40.7	G		150-151	CH_2Cl_2-EtOAc	$C_{19}H_{18}ClN_5$	C, H, N; Cl[ss]
80	$(CH_3)_2N$	H	Br	H	1	26	H		188.5-190	EtOH-EtOAc	$C_{27}H_{28}BrN_5O_3S$	C, H, Br, N, S
81	$(CH_3)_2N$	H	Cl	Cl	1	19.5	H		150-153	EtOAc	$C_{20}H_{19}Cl_2N_5$	C, H, Cl, N
82	$(C_2H_5)_2N$	H	Cl	H	1	11.5	H		124-132	CH_2Cl_2-Et_2O-PE[xx]	$C_{22}H_{24}ClN_5$	C, H, Cl, N
83	$(CH_3)_2N$	H	H	Cl	1	67	H		145-146.5	MeOH-EtOAc	$C_{20}H_{20}ClN_5$	C, H, Cl, N
84	$(CH_3)_2N$	H	H	H	1	68.3	H		172.5-173.5	MeOH-EtOAc	$C_{20}H_{21}N_5$	C, H, N
87	$(CH_3)_2N$	H	Br	N[tt]	0	52.2	C	*u*	163.5-165	EtOAc-Sk B	$C_{18}H_{17}BrN_6$	C, H, Br; N[uu]
88		CH_3	Br	N[tt]	1	58.8	E	*u*	240-242	CH_2Cl_2-EtOAc-Sk B	$C_{26}H_{19}BrN_6O_2$	C, H, Br, N
89	H_2N	CH_3	Br	N[tt]	1	55.4	G		141-142	CH_2Cl_2-Et_2O	$C_{18}H_{17}BrN_6$	C, H, N[ww]
90		H	Br	N[tt]	1	83	E	*u*	256-258	MeOH-CH_2Cl-EtOAc	$C_{25}H_{17}BrN_6O_2$	H, Br, N; C[vv]
91	H_2N	H	Br	N[tt]	1	54.8	G		164-166	CH_2Cl_2-EtOAc	$C_{17}H_{15}BrN_6$	C, H, Br, N
92	$(CH_3)_2N$	H	Br	N[tt]	1	52.8	H		148.5-150	CH_2Cl_2-EtOAc	$C_{19}H_{19}BrN_6$	C, H, Br, N

[a] Cl: calcd, 20.66; found, 20.21. [b] Cl: calcd, 26.22; found, 25.68. [c] 5-(*o*-Chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine, mp 110.5 °C dec, was obtained by the reaction of hydrazine hydrate in MeOH with 5-(*o*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (ref 1). [d] Cl: calcd, 20.66; found, 21.15. [e] C: calcd, 66.08; found, 65.67. [f] 7-Bromo-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (ref 23). [g] Reaction time 2 weeks at 25 °C; product purified by chromatography on silica gel with 5–7.5% MeOH/92.5–95% $CHCl_3$. [h] Reaction time 6 days at 25 °C; product purified by chromatography on silica gel with 5% MeOH–95% $CHCl_3$. [i] Prepared from 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (ref 1) without isolating intermediates. [j] N: calcd, 21.63; found, 22.04. [k] Literature ref to starting material. [l] Reference 19. [m] Reference 1. [n] DMF was used as solvent for this reaction. [o] Decomposition. [p] Reaction time 72 h at 25 °C. [q] N: calcd, 18.53; found, 18.08. [r] Product purified by chromatography on silica gel with 5% MeOH–95% $CHCl_3$. [s] Product purified by chromatography on silica gel with 2% MeOH–98% $CHCl_3$. [t] Product purified by chromatography on silica gel with 4% MeOH–96% $CHCl_3$. [u] See Experimental Section. [v] Hydrochloride salt. [w] C: calcd, 61.17; found, 60.72. [x] Purified by chromatography on silica gel with 2.5% MeOH–97.5% $CHCl_3$. [y] Softened from 152–212.5 °C, where it decomposed. [z] Dicyclohexane sulfamate. [aa] C: calcd, 65.47; found, 65.00. [bb] Hydrate. [cc] Reaction conditions: 25 °C, 15 h; 60–70 °C, 5 h. [dd] Reaction conditions: 50 °C, 2.5 days. [ee] Reaction conditions: 60–70 °C, 42 h. [ff] Reaction conditions: 54 °C, 18 h. [gg] C: calcd, 54.99; found, 54.53. [hh] Dihydrate, H_2O: calcd, 8.34; found, 7.86. [ii] EtOAc solvate, EtOAc: calcd, 15.84; found, 15.40. [jj] *p*-Toluenesulfonate. [kk] 3-Phthalimidobutyric acid (ref 29). [ll] C: calcd, 72.47; found, 72.01. [mm] C: calcd, 62.16; found, 61.53. H: calcd, 3.41; found, 3.84. This sample contained both EtOAc (0.51%) and MeOH (0.55%); recalculated analytical data was acceptable. [nn] Br: calcd, 15.60; found, 16.04. [oo] Sk B = Skellysolve B. [pp] C: calcd, 66.74; found, 65.66. Cl: calcd, 7.58; found, 8.08. This sample contained CH_2Cl_2 (1.41%) and EtOAc (0.91%); recalculated analytical data was acceptable. [qq] Sample contained 1.48% EtOAc. Analytical data recalculated for EtOAc was acceptable. [rr] Bis(*p*-toluenesulfonate hydrate); H_2O: calcd, 2.52; found, 2.05. [ss] Cl: calcd, 10.07; found, 10.57. [tt] 2-Pyridyl derivative. [uu] N: calcd, 21.15; found, 20.73. [vv] C: calcd, 58.49; found, 57.91. [ww] Sample contained 1.29% CH_2Cl_2 and 2.01% Et_2O. Analytical data recalculated for Et_2O and CH_2Cl_2 was acceptable. [xx] PE = pet. ether.

analogue, while the antidepressant activity was largely retained or, in some cases, enhanced (compare **80** with **39**, **92** with **87**, **84** with **42**, and **17** with **43**). Again, *o*-chloro substitution on the 6-phenyl group potentiated the antianxiety activity (HS) of this series (compare **81** with **15**). When the side chain was lengthened to three carbon atoms, the activity of the series declined (compare **68** with **81** and **5** with **15**). Incorporating an oxygen atom between the nitrogen and carbon of the (dimethylamino)methyl side chain of **2** to give **9** resulted in the loss of antidepressant activity; the activity on antianxiety end points was, however, increased (compare also **12** with **47**). The N-unsubstituted aminooxy derivative **13** also had interesting activity.

In an attempt to block potential metabolism of the aminoalkyl side chain, a series of compounds with a methyl substituent α to the amine was prepared. Activity on the antidepressant end points was lost in the 1-(1-aminoethyl) series; however, antianxiety activity was retained (compare **51** with **43**). The 1-(2-aminopropyl) derivative (**77**), on the other hand, had considerable antidepressant activity with little activity on the CNS depressant end points.

In summary, we have developed a series of 1-(aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines which has pharmacologic properties in common both with clinically useful antidepressant and antianxiety agents. By appropriate structural modifications, we can selectively alter the activity so that either type predominates.

Experimental Section

Melting points taken in capillary tubes 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 and UV spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A60-A or XL-100 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. 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. Darco-G60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington, Del. Celite is a filter aid manufactured by Johns-Manville, New York.

8-Chloro-1-(chloromethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (6). Procedure A. A stirred mixture of 8-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**4**)[19] (28.5 g, 0.1 mol) in THF (250 mL) was cooled under N_2 in an ice bath and treated during 17 min with a solution of chloroacetyl chloride (11.3 g, 0.1 mol) in THF (50 mL). The resulting mixture was kept in the ice bath for 35 min and at ambient temperature for 1 h. It was then poured into ice–water, treated with a little $CHCl_3$, neutralized with $NaHCO_3$, and allowed to crystallize. The solid was collected by filtration, washed with water, and dried in vacuo to give 23.7 g of crude amide. A stirred mixture of this material in HOAc (280 mL), under N_2, was placed in an oil bath which had been preheated to 140 °C. The mixture was kept in the bath for 20 min, cooled, and concentrated under reduced pressure. The residue was mixed with $CHCl_3$ and water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from EtOAc to give, in two crops, 19.8 g of **6**, mp 187–189 °C dec.

8-Chloro-1-[(cyclopropylamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (54). Procedure B. A stirred mixture of **6** (1.37 g, 0.004 mol), KI (0.67 g, 0.004 mol), cyclopropylamine (0.685 g, 0.012 mol), and THF (100 mL) was kept under N_2 at 25 °C for 18 h and concentrated in vacuo. The residue was mixed with water and extracted with methylene chloride. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residual oil was dissolved in CH_2Cl_2–MeOH–$CHCl_3$, treated with Darco G 60 and silica gel, and filtered through Celite. The filtrate was concentrated and the residue crystallized from EtOAc to give 0.72 g of **54**, mp 164–169 °C.

1-[(Dimethylamino)methyl]-8-(methylthio)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (38). Procedure C. A stirred mixture of 1,3-dihydro-7-(methylthio)-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (1.49 g, 0.005 mol),[1] (dimethylamino)-acetic acid hydrazide[6] (1.58 g, 0.015 mol), and 1-butanol (80 mL) was refluxed for 72 h with a slow stream of N_2 bubbling through the mixture. 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 chromatographed on silica gel (100 g) with 2% MeOH–$CHCl_3$. The product thus obtained was crystallized from EtOAc to give 0.45 g of **38**, mp 179–181 °C.

8-Chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (2). Procedure D. An ice-cold, stirred mixture of **6** (13.7 g, 0.04 mol) in dry THF (400 mL) was treated with KI (6.64 g) and 15% (v/v) methanolic dimethylamine (200 mL), allowed to come to ambient temperature, and stirred for 18 h. It was concentrated in vacuo, and the residue was mixed with dilute $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. Crystallization of the residue from EtOAc–Sk B gave 12.5 g of **2**, mp 169–170.5 °C.

8-Chloro-6-phenyl-1-(2-phthalimidoethyl)-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine Ethyl Acetate Solvate (16). Procedure E. *N*-Phthalimidoyl-β-alanine was prepared by heating β-alanine with phthalic anhydride.[20] A stirred mixture of this acid (2.41 g, 0.011 mol) in THF (20 mL) was cooled in an ice bath and treated with carbonyldiimidazole (CDI; 1.78 g, 0.011 mol). The mixture was kept at ambient temperature for 1 h 12 min, again cooled in an ice bath, and treated with **4** (2.85 g, 0.01 mol) and THF (25 mL). This mixture was kept at ambient temperature for 18 h. The solid was collected by filtration, washed with THF, and dried to give 4.40 g of crude amide, mp 145.5–170 °C. A stirred mixture of this amide (2 g) and HOAc (20 mL) was warmed, under N_2, in an oil bath maintained at 117 °C for 42 min. The solution was concentrated in vacuo, and the residue was mixed with water and $CHCl_3$, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from CH_2Cl_2–MeOH–EtOAc (Darco) to give 1.93 g of **16**, which melted at 133–134 °C with foaming, resolidified, and then melted at 225 °C. The analytical sample was crystallized from CH_2Cl_2–EtOAc and had mp 130.5–133.5 °C (foaming), mp 224–226 °C.

1-(2-Aminoethyl)-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (17). Procedure F. A stirred mixture of **16** (37.6 g, 0.0675 mol) and absolute EtOH (340 mL) was treated with hydrazine hydrate (7.43 g, 0.149 mol) and warmed, under N_2, in an oil bath to 75 °C during 65 min; the bath was kept at this temperature for an additional 55 min. The mixture was then cooled in an ice bath, and the solid was collected by filtration and washed with absolute EtOH and CH_2Cl_2. The combined filtrate was mixed with ice-cold, dilute NaCl and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (1 kg) with MeOH, and the resulting product was crystallized from CH_2Cl_2–Et_2O to give 5.29 (mp 198–200 °C dec) and 2.37 g (mp 194–196.5 °C dec) of **17**.

1-(2-Aminoethyl)-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (17). Procedure G. A stirred mixture of **16** (35.7 g, 0.0643 mol) in absolute EtOH (160 mL) and CH_2Cl_2 (160 mL) was cooled in an ice bath, under N_2, and treated with 40% aqueous methylamine (50 mL). The mixture was kept in the bath for 18 h, during which time the ice slowly melted and the mixture warmed to ambient temperature. It was kept at ambient temperature for an additional 7 h and concentrated, in vacuo, at a bath temperature of 34 °C. The residue was mixed with absolute EtOH and again concentrated. The resulting

(19) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull*, **21**, 2382 (1973).

(20) A. Schöberl and H. Braun, *Justus Liebig's Ann. Chem.*, **542**, 274 (1939).

Table II. Pharmacological Data for the 1-(Aminoalkyl)-6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines[a]

no.	bicucullin (B)	pentylenetetrazole (P)	γ-butyrolactone (γ-B)	nicotine[b] TE	nicotine[b] D	hypoxic stress (HS)	apomorphine gnawing (AG)	oxotremorine hypothermia (OX)	yohimbine aggregation (Y)
2	0.7	0.9	1.6	0.11	0.13	5	5.3	5.3	12.5
5	56	13.3	36.6	10	10	>50	42	75	>100
8	0.8	0.3	0.6	*e*	*e*	5.3	>50	5.3	>50
9	0.2	0.2	0.1	*e*	*e*	0.2	>50	>50	>50
12	1.1	1.1	0.2	0.56	0.5	6.3	>50	5.3	>50
13	0.2	0.2	0.84	0.1	0.08	0.7	42.0	12.5	>50
15	21	25	15	2.8	2.5	>20	28	6	30
17	17.7	10.5	7.4	7.1	6.3	>50	35	4.4	50
18	42.0	14.9	5.3	25	25	>50	>50	>50	>50
21	>50	>50	15	>100	>100	>50	>50	>50	>50
22	>50	>50	>50	89	89	>50	>50	>50	*e*
25	>50	>50	>50	*e*	*e*	>50	>50	>50	40
31	1.9	3.1	1.3	0.2	0.2	1.0	>50	>50	50
38	10	**9**	10	*e*	*e*	>50	>50	10	40
39	0.8	0.7	0.1	*e*	*e*	0.8	>50	7.4	35.4
40	0.2	2.2	0.2	0.023	0.025	0.02	>50	>50	>50
41	0.4	0.2	3	*e*	*e*	0.2	>50	>50	>50
42	50	**6.2**	6.2	2.5	2.8	>50	3.1	12.5	35.4
43	14.9	0.35	0.8	0.22	0.28	0.8	2.6	29.7	35.4
44	0.5	0.4	0.1	0.16	0.18	40	12.5	3.7	>50
45	17.8	10	<10	0.13	0.15	0.5	>30	>30	>30
46	0.8	0.1	0.3	0.06	0.06	0.1	17.8	>30	>30
47	2.6	3.1	0.6	0.08	0.08	>50	14.9	50	42
48	100	100	20	4.5	5.0	>50	>100	>100	>100
49	12.5	17.7	7.4	3.6	4.5	2	14.9	56	100
50	>30	>30	>30	159	159	>50	>30	>30	>30
51	0.6	0.6	0.12	0.3	0.35	3	>50	>50	>50
52	**9**	4.4	3.7	0.9	1.0	0.5	50	>50	30
53	3.1	3.7	2.2	3.5	3.2	>50	>50	>50	>50
54	1.6	3.1	1.1	0.25	0.28	40	>50	>50	>50
55	3.7	4.4	1.6	1.1	1.1	>50	>50	>50	>50
56	3.1	3.7	1.9	0.55	0.28	6	>50	>50	>50
57	2.6	3.1	1.1	0.4	0.6	30	>50	>50	>50
58	0.1	0.021	0.1	0.036	0.045	0.4	21.0	>50	>50
59	2	2	8	*e*	*e*	3	>50	>50	>50
60	0.5	0.3	0.3	0.14	0.14	>50	4.4	30	18
61	1.6	3.1	0.8	1.1	1.1	20	>50	>50	21
62	1.6	3.1	0.7	1.4	1.4	30	>50	>50	21
64	7.1	10	10	5.6	5.6	7	>50	>50	>50
65	>100	>100	>100	11	13	>50	100	31.6	56
66	>50	>50	10	89	79	>50	*e*	*e*	*e*
67	>50	4.4	35.4	14	16	>50	25	>50	42
68	2.6	2.2	0.2	*e*	*e*	2.2	>50	25	25
72	20	>50	30	*e*	*e*	>50	>50	7	20
73	>50	>50	20	*e*	*e*	20	>50	>50	>50

74	>50	>50	>50	e	e	>50	30	40	30
75	25	21	21	4.5	4.5	>50	14.9	29.7	>50
76	7.4	10.5	3.7	e	e	25.0	>50	17.7	>50
77	>50	>50	35	18	32	>50	25	4.4	21
78	>50	>50	>50	e	e	>50	>50	>50	40
79	>50	>50	>50	e	e	10	>50	>50	20
80	7	5	5	e	e	5	>50	0.9	3
81	0.5	0.3	0.4	0.28	0.28	1.3	6.3	>50	29.7
82	50	25	15	2.0	2.0	40	>50	42	>50
83	>50	5	>50	e	e	7	>50	>50	30
84	>50	>50	30	e	e	>50	20	10	40
87	1.3	1.9	1.3	1.0	1.0	30	>50	12.5	29.7
89	>50	>50	40	e	e	>50	20	>50	7
91	>50	>50	30	e	e	>50	>50	30	30
92	>50	20	10	e	e	>50	9	4	4
94	12.5	17.7	17.7	5.0	5.0	>50	21.0	10.5	17.7
97[c]	21.0	>50	17.7	7.0	7.0	>50	0.9	1.3	4.4
96[d]	2.6	0.1	0.035	0.28	0.28	0.2	>50	>50	>50

[a] Values are ED_{50}'s expressed in mg/kg. [b] TE = tonic-extensor convulsions; D = death. [c] Imipramine hydrochloride. [d] Diazepam, obtained from Hoffman-La Roche, Inc. [e] Not tested.

material was dissolved in $CHCl_3$–MeOH (without heating), concentrated in vacuo to remove $CHCl_3$, poured into a column containing 1 kg of silica gel, and eluted with MeOH. The MeOH solution of the product was concentrated in vacuo at 30–35 °C; the residue was dissolved in a small amount of CH_2Cl_2, filtered through Celite, and concentrated on the steam bath, under a nitrogen stream, replacing the CH_2Cl_2 by Et_2O. The product crystallized to give 2.47 (mp 197–201 °C dec), 1.50 (mp 193.5–195 °C dec), 6.38 (mp 192–194 °C dec), 2.12 (mp 193–194 °C dec), 0.712 (mp 192.5–194 °C dec), and 1.03 g (mp 193.5–196.5 °C) of **17**.

8-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *p*-Toluenesulfonate (15). Procedure H. A stirred suspension of **17** (13.1 g, 0.039 mol) in acetonitrile (150 mL) was cooled in an ice bath, under N_2, and treated successively with 37% aqueous formaldehyde (19.5 mL) and sodium cyanoborohydride (4.85 g, 0.0772 mol). A solution of HOAc (3.8 mL) in acetonitrile (16 mL) was added portionwise to this mixture during about 1.5 h, keeping the temperature between about 10 and 15 °C with a cold water bath. The bath was removed and the mixture was kept at ambient temperature for an additional 35 min. The final pH of the reaction mixture was 6.4–6.8 as determined by pH paper. The mixture was mixed with 50–100 mL of MeOH and concentrated in vacuo at a bath temperature of 34 °C. The residue was mixed with MeOH and again concentrated in vacuo. This residue was mixed with MeOH (390 mL), treated with 25% aqueous ethylenediamine (195 mL), and refluxed under N_2 for 1 h. The cooled mixture was diluted with about 250 mL of water and concentrated, in vacuo, to remove methanol. The resulting solution was saturated with NaCl and extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (700 g) with MeOH. The resulting product was dissolved in CH_2Cl_2, filtered through Celite, and concentrated to give 12.4 g of an oil. A solution of this material in CH_2Cl_2 was treated with an EtOH solution of 1 equiv of *p*-toluenesulfonic acid hydrate. The mixture was concentrated to remove CH_2Cl_2 and the salt was allowed to crystallize from EtOH. The resulting product was recrystallized from absolute EtOH to give 12.4 (mp 196.5–198 °C), 1.07 (mp 193–194.5 °C), and 0.753 g (mp 193–195 °C) of **15** as an EtOH solvate containing 0.78% EtOH. A solvent-free sample of **15** was obtained by recrystallizing this material from wet 2-propanol.

8-Chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *N*-Oxide (8). Procedure I. A stirred solution of *N*,*N*-dimethylhydroxylamine (3.67 g, 0.006 mol) in DMF (50 mL) was cooled in an ice bath, under N_2, and treated with 0.84 g (0.02 mol) of a 57% mineral oil suspension of NaH. This mixture was kept at 25 °C for 1 h, again cooled in an ice bath, and treated with **6** (6.86 g, 0.02 mol). The resulting mixture was kept at ambient temperature for 2 h and concentrated in vacuo. The resulting material was chromatographed on silica gel (250 g) with MeOH. The product thus obtained was crystallized from wet MeOH–EtOAc (Darco) to give 3.38 (mp 160.5–162.5 °C), 1.15 (mp 160–162 °C), and 0.79 g (mp 160–162 °C) of **8**. The analytical sample was found to contain 3.22% water.

8-Chloro-1-[[(dimethylamino)oxy]methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9). A sample of **8** (400 mg, 0.0019 mol) was warmed, under reduced pressure (34 mm), in an oil bath from 119 to 151 °C during 11 min. It was kept at 151–161 °C for 8 min, cooled, and chromatographed on silica gel (50 g) with 3% MeOH–$CHCl_3$. The product thus obtained was crystallized from EtOAc–Skelly B to give 0.236 (mp 175.5–176.5 °C) and 0.030 g (mp 174 °C) of **9**.

8-Chloro-1-[[(diethylamino)oxy]methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12) and 8-Chloro-1-[(ethylhydroxyamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11). A sample of **10** (4.0 g, 0.0093 mol) was warmed in an oil bath under reduced pressure (23 mm). The temperature of the bath was raised from 112 to 151 °C during 21 min and kept at 143–151 °C for an additional 22 min. During this period, the solid melted with bubbling. The amber melt was cooled and chromatographed on silica gel (200 g) with 3% MeOH–$CHCl_3$. The first compound eluted from the column was crystallized from EtOAc–Skelly **B** to give 1.89 g of **12**, mp 136–138.5 °C. The second compound eluted from the column was

crystallized from wet EtOAc–Skelly B to give 0.627 (mp 154.5–157 °C), 0.387 (mp 152–153.5 °C), and 0.141 g (mp 150–153.5 °C) of **11**. The analytical sample was crystallized once from wet EtOAc–Skelly B and once from MeOH–EtOAc and had mp 199–200.5 °C. (During this recrystallization, a second polymorph formed which was no longer soluble in EtOAc.)

8-Chloro-6-phenyl-1-[(phthalimidooxy)methyl]-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (14). A stirred solution of *N*-hydroxyphthalimide (5.38 g, 0.033 mol) and triethylamine (9.15 mL, 0.066 mol) in DMF (100 mL) was treated with **6** (10.3 g, 0.03 mol) and kept at ambient temperature, under N_2, for 3 h 35 min. It was poured into cold water, stirred for a few minutes, and filtered. The solid was washed with water and $CHCl_3$ and dried to give 9.88 g of **14**, mp 260–261 °C dec. The filtrate was extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The solid residue was mixed with EtOH and filtered. The solid was washed with EtOH and dried to give 3.02 g of additional product, mp 255–255.5 °C dec.

1-[(Aminooxy)methyl]-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13). A stirred suspension of **14** (9.4 g, 0.02 mol) in absolute EtOH (100 mL) was treated with hydrazine hydrate (1.45 mL) and warmed, under N_2, at a bath temperature of 70 °C for 3 h. The mixture was cooled in an ice bath and filtered. The solid was washed with EtOH and CH_2Cl_2. The combined filtrate was concentrated in vacuo; the residue was mixed with water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was dissolved in $CHCl_3$–EtOAc and filtered through a small pad of silica gel. The filtrate was crystallized from MeOH–EtOAc to give 1.95 (mp 190–191.5 °C) and 1.18 g (mp 183–186 °C) of **13**.

5-Chloro-2-[3-[2-(dimethylamino)ethyl]-5-[(dimethylamino)methyl]-4*H*-1,2,4-triazol-4-yl]benzophenone (19). Using the method of Gall et al.,[21] a stirred solution of **17** (1.70 g, 0.005 mol) and 88% formic acid (10 mL) was treated with 37% aqueous formaldehyde (1.80 g, 0.022 mol) and heated at 100 °C in an oil bath for 5.5 h, under N_2. It was then cooled, mixed with water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) using MeOH. The product thus obtained was crystallized twice from EtOAc–Skelly B to give 0.30 g, mp 149.5–152 °C (15%), of **19**. Anal. ($C_{22}H_{26}ClN_5O$) C, H, Cl, N.

***N*-[2-[4-(2-benzoyl-4-chlorophenyl)-5-[(dimethylamino)methyl]-4*H*-1,2,4-triazol-3-yl]ethyl]phthalimide (20).** Using the method of Gall et al.,[21] a stirred solution of **16** (11.1 g, 0.02 mol) in 88% HCOOH (15.6 g, 0.3 mol) under N_2 was treated with 37% aqueous formaldehyde (14.6 g, 0.18 mol). The mixture was warmed at 100 °C for 1 h, cooled, mixed with cold 5% aqueous NaOH, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated in vacuo. The oil was chromatographed on silica gel (800 g) with 2.5% MeOH–97.5% $CHCl_3$. The product thus obtained was crystallized from EtOAc–hexane to give 8.05 (mp 115–120 °C dec) and 0.395 g [mp 108–114 °C dec (82%)] of **20** as an EtOAc solvate. The analytical sample had mp 133–134 °C with softening at 116 °C. Anal. Calcd for $C_{28}H_{24}ClN_5O$: C, 65.43; H, 4.71; Cl, 6.90; N, 13.63. Found: C, 64.64; H, 5.15; Cl, 6.51; N, 13.17; EtOAc, 5.07. The analytical data recalculated for EtOAc: C, 65.19; H, 4.94; Cl, 6.86; N, 13.87.

9-Chloro-1-[(dimethylamino)methyl]-4,5-dihydro-7-phenyl-*s*-triazolo[4,3-*a*][1,5]benzodiazocine (21). A stirred solution of **20** (7.06 g, 0.013 mol) in absolute EtOH (75 mL) under N_2 was treated with hydrazine hydrate (1.30 g, 0.026 mol) and warmed at 70 °C for 1.5 h. The insoluble precipitate was removed by filtration and washed with EtOH and CH_2Cl_2. The filtrate was concentrated in vacuo, and the residue was mixed with H_2O and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from CH_2Cl_2–EtOAc. The solid thus obtained was dissolved in MeOH–CH_2Cl_2, filtered through a silica gel pad, and recrystallized from CH_2Cl_2–EtOAc to give 0.505 (mp 265–270 °C dec) and 0.27 g (mp 283–286 °C dec) of **21**. The filtrates were concentrated in vacuo. The residue was dissolved in pyridine (25 mL), refluxed for 1 h under N_2, mixed with dilute $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was crystallized from CH_2Cl_2–EtOAc to give 1.19 g, mp 280–282 °C dec, of additional **21** (overall yield 41%). The analytical sample had mp 283–286 °C dec. Anal. ($C_{20}H_{20}ClN_5$) C, H, Cl; N: calcd, 19.14; found, 19.62.

7-Chloro-5-phenyl-*s*-triazolo[4,3-*a*]quinoline (23). Using a modification of the method of Meguro et al.,[19] a stirred mixture of 6-chloro-2-hydrazino-4-phenylquinoline (**95**)[22] (5.39 g, 0.02 mol) and triethyl orthoformate (14.82 g, 0.10 mol) in $CHCl_3$ (160 mL) was cooled in an ice bath under N_2 and treated with H_2SO_4 (4 g). The bath was removed, and the solution was kept at ambient temperature for 1 h, mixed with water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The solid residue was washed with EtOAc and recrystallized from CH_2Cl_2–EtOAc to give 2.26 (mp 265–266.5 °C) and 1.39 g [mp 264–266 °C (65%)] of **23**: NMR ($CDCl_3$) δ 9.34 (s, 1, H-1). Anal. ($C_{16}H_{10}ClN_3$) C, H, Cl, N.

7-Chloro-1-[(dimethylamino)methyl]-5-phenyl-*s*-triazolo[4,3-*a*]quinoline (22). A stirred solution of *N,N,N',N'*-tetramethyldiaminomethane (0.77 g, 0.0075 mol) and DMF (20 mL), cooled in an ice bath, under N_2, was treated dropwise with acetyl chloride (0.59 g, 0.0075 mol). The mixture was kept at ambient temperature for 1.5 h and treated with **23** (1.40 g, 0.005 mol). This mixture was kept at ambient temperature for 3 h and at 50 °C for 18 h. The solution was mixed with cold water, and the solid was collected by filtration, washed with water, and dissolved in CH_2Cl_2. The solution was washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was chromatographed on silica gel with 2.5% MeOH–$CHCl_3$. The product thus obtained was crystallized from EtOAc and recrystallized from CH_2Cl_2–EtOAc–Skelly B to give 0.63 g, mp 223–226 °C (37.5%), of **22**. The analytical sample had mp 222–225 °C; NMR ($CDCl_3$) δ 2.43 [s, 6, $(CH_3)_2N$], 4.16 (s, 2, CH_2). Anal. ($C_{19}H_{17}ClN_4$) C, H, Cl, N.

7-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-*s*-triazolo[4,3-*a*]quinoline (25). A stirred mixture of 7-chloro-1-methyl-6-phenyl-*s*-triazolo[4,3-*a*]quinoline (**24**)[22] (2.94 g, 0.01 mol), *N,N,N',N'*-tetramethyldiaminomethane (1.3 g, 0.012 mol), and dry DMF (50 mL) was cooled, under N_2, in an ice bath and treated dropwise with acetyl chloride (0.923 mL, 0.013 mol). The ice bath was removed after 2 h 10 min; the mixture was kept at 25 °C for 3 h 45 min, treated with additional acetyl chloride (0.1 mL), and kept at 25 °C for 21 h. It was then poured into ice-cold, saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with mixtures of MeOH and $CHCl_3$ containing 5–10% MeOH. The first material eluted from the column was crystallized from CH_2Cl_2–MeOH–EtOAc to give 1.01 (mp 256–258 °C) and 0.111 g (mp 255–257 °C) of recovered **24**. The second compound eluted from the column was crystallized from EtOAc–Skelly B to give in five crops a total of 1.46 g, mp 182–183 °C (41.6%), of **25**. The analytical sample had mp 182–183.5 °C. Anal. ($C_{20}H_{20}ClN_4$) C, H, Cl, N.

8-Chloro-1-[(dimethylamino)methyl]-5,6-dihydro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (18). A solution of **2** (1.80 g) in AcOH (50 mL) was treated with PtO_2 catalyst (200 mg) and hydrogenated on a Parr apparatus at an initial pressure of 1.8 kg cm^{-2} for 3 h 40 min. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was mixed with dilute $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. Crystallization of the residue from CH_2Cl_2–MeOH gave 1.19 (mp 237–242 °C) and 0.167 g (mp 239–242 °C) of **18**. The analytical sample had mp 239–245 °C. Anal. ($C_{19}H_{20}ClN_5$) H, Cl, N; C: calcd, 64.49; found, 64.03.

8-Chloro-1-[[(cyclopropylmethyl)methylamino]methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (57). A stirred mixture of **31** (1.89 g, 0.005 mol) and acetonitrile (30 mL), under N_2, was treated successively with 37% aqueous

(21) M. Gall, J. B. Hester, A. D. Rudzik, and R. A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).

(22) J. B. Hester, *J. Heterocycl. Chem.*, in press.

formaldehyde (1 mL) and sodium cyanoborohydride (0.25 g, 0.004 mol). To this mixture was slowly added during 1 h a solution of AcOH (0.15 mL) in acetonitrile (5 mL). The resulting mixture was kept at 25 °C for 2 h and concentrated in vacuo. The residue was mixed with a solution of 25% aqueous ethylenediamine (25 mL) and methanol (50 mL) and refluxed, under N_2, for 0.5 h. The cooled mixture was mixed with water, treated with a little NaCl, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (100 g) with 2.5% MeOH–97.5% $CHCl_3$. The product thus obtained was crystallized from EtOAc and CH_2Cl_2–EtOAc to give 1.07 (mp 171–176 °C) and 0.135 g (mp 171.5–174.5 °C) of **57**.

7-Bromo-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (69). A stirred solution of 7-bromo-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione[23] (33.1 g, 0.1 mol) in 1090 mL of MeOH was treated with hydrazine hydrate (19.4 mL) and kept at 25 °C for 2 h with a slow steam of N_2 passing through the mixture. A solid was filtered from the mixture and the filtrate concentrated in vacuo. The solid was combined with the residue, mixed with cold water, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was triturated with EtOAc to give 23.5 g of **69**, mp 165–166 °C dec. The analytical sample was recrystallized from CH_2Cl_2–EtOAc and had mp 189–190 °C. Anal. ($C_{15}H_{13}BrN_4$) C, H, Br, N.

7-Bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepine-2-thione (85). A stirred solution of 7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one[24] (6.53 g) in dry pyridine (400 mL) was treated with P_2S_5 (5.05 g), heated in an oil bath, under N_2, at 110–120 °C for 1 h, cooled, and concentrated in vacuo. The dark brown solid residue was triturated with a mixture of aqueous Na_2CO_3 and $CHCl_3$; the resulting finely divided tan solid was collected by filtration, washed with water, dissolved in $CHCl_3$–EtOH, decolorized with Darco G 60, and crystallized to give 3.39 (mp 249 °C dec) and 0.559 g (mp 243 °C dec) of **85**. The analytical sample was crystallized from EtOH and had mp 245–246 °C dec. Anal. ($C_{14}H_{10}BrN_3S$) H, Br, N, S; C: calcd, 50.61; found, 49.98.

7-Bromo-5-(2-pyridyl)-2-hydrazino-3*H*-1,4-benzodiazepine (86). A stirred mixture of **85** (16.0 g, 0.048 mol) in MeOH (400 mL) was treated with hydrazine hydrate (7.51 g, 0.15 mol) and kept at 25 °C for 18 h with N_2 bubbling through the solution. The solid was collected by filtration, washed with MeOH, and dried in vacuo to give 13.6 g, mp 224–225 °C dec, of **86**. The analytical sample was recrystallized from $CHCl_3$–MeOH and had mp 224–226 °C dec. Anal. ($C_{14}H_{12}BrN_5$) C, H, Br, N.

7-Chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (93). A stirred mixture of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[25] (35.5 g, 0.125 mol) and P_2S_5 (30.5 g, 0.137 mol) in dry pyridine (800 mL) was refluxed, under N_2, for 3 h and concentrated in vacuo. The residue was mixed with aqueous $NaHCO_3$ and filtered. The solid was washed with water and CH_2Cl_2. The filtrate was extracted with CH_2Cl_2; the extract was washed with water and brine, dried, and concentrated. The solid residue was mixed with EtOH and collected by filtration. This solid was combined with the solid from the aqueous $NaHCO_3$ and recrystallized from CH_2Cl_2–MeOH to give 21.7 (mp 250–252 °C dec) and 1.25 g [mp 245–252 °C dec (61.3%)] of **93**. The analytical sample was crystallized from CH_2Cl_2–EtOH and had mp 246–248 °C dec. Anal. ($C_{16}H_{13}ClN_2S$) C, H, Cl, N, S.

8-Chloro-1-[(dimethylamino)methyl]-4-methyl-6-phenyl-4*H*-s-triazolo[4,3-a][1,4]benzodiazepine (94). A stirred solution of **93** (3.00 g, 0.01 mol) and 1-butanol (100 mL) was treated with (dimethylamino)acetic acid hydrazide (3.51 g, 0.03 mol) and refluxed for 18 h, with N_2 bubbling through the solution. The solution was concentrated in vacuo, and the residue was mixed with water and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (350 g) with 5% MeOH–95% $CHCl_3$. The product thus obtained was crystallized from EtOAc–Skelly B and recrystallized from CH_2Cl_2–EtOAc–Skelly B to give 1.10 (mp 202–205 °C with solidification and remelting at 214–215 °C), 0.625 (mp 202–206 °C), and 0.23 g [mp 201–210 °C (53.5%)] of **94**. Anal. ($C_{20}H_{20}ClN_5$) H, Cl, N; C: calcd, 65.66; found, 65.23.

Pharmacology. Methods. Carworth Farms, male albino mice (CF-1) weighing 18–22 g were used for all studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered intraperitoneally 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 antagonism of nicotine-induced tonic-extensor convulsions (TE) and death (D), antagonism of bicucullin-induced tonic-extensor convulsions (B), antagonism of pentylenetetrazole-induced clonic convulsions (P), and potentiation of γ-butyrolactone induced sleep (γ-B) have been reported previously.[1,26,27] Other test procedures used for this series of compounds are described below. ED_{50} values were calculated by the method of Spearman and Karber.[28]

Prolongation of Hypoxic Survival Time (HS). Thirty minutes after administration of the test compound or vehicle control, the mice are placed singly in 125-mL Erlenmeyer flasks. The flasks are tightly stoppered and the survival time of each animal is noted. Survival times that differ by more than 2 standard deviations from the mean of the survival times for the vehicle-treated mice (15–18 min with a standard deviation of 1–2 min) are considered to be a positive drug effect and are used as a quantal response parameter for calculating the ED_{50} of the test compound.

Apomorphine Gnawing Potentiation (AG). One hour after administration of the test compound, apomorphine hydrochloride (10 mg/kg) is injected sc. The mice are placed singly in plastic boxes (4 × 4 × 5 in.) and observed after 30 min for stereotyped gnawing and licking. The test compound is considered active if the animals exhibit the gnawing and licking behavior which is characteristically induced by higher doses of apomorphine.

Antagonism of Oxotremorine Hypothermia (OX). Thirty minutes after administration of the test compound, oxotremorine hydrochloride (1 mg/kg) is injected sc. The mice are then placed in a refrigerator maintained at 19 °C. After 30 min, the intraperitoneal temperature of each mouse is determined with a thermistor probe. The response to the test compound is considered positive if the body temperature is more than 2 standard deviations above that of the parallel control group which received oxotremorine alone.

Potentiation of Yohimbine Toxicity in Aggregated Mice (Y). Thirty minutes after administration of the test compound, yohimbine hydrochloride (20 mg/kg) is injected ip. Each group of four mice is then placed in a plastic cage (5 × 11 × 6 in.) on the counter top at ambient temperature (21–24 °C). The test compound is considered active if at least three of the four mice are dead after 2 h. The number of deaths is used as a quantal response metameter to calculate the ED_{50}.

Reliability and Utility of Assays. The mean coefficient of variability for ED_{50} values, derived from repeated runs of standard compounds in these assays, was $xcv = 49$. The antidepressant standards (imipramine, amitriptyline, protriptyline, and mianserin) were reliably identified as antidepressant-like in the AG, OX, and Y assays but had little or no activity in the anxiolytic-related tests (B, P, and HS). Conversely, the anxiolytic standards (chlordiazepoxide, diazepam, oxazepam, and chlorazepate) were active on the anxiolytic but not the antidepressant tests.

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2,4-Dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones with Antianxiety and Antidepressant Activity

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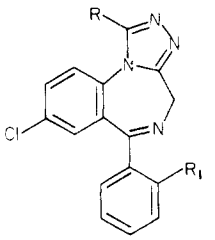
A series of 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones was prepared and evaluated for central nervous system activity. It was found that the 2-methyl-substituted analogues had interesting activity in tests useful for detecting anxiolytic agents, while N-2 substitution with ω-(dialkylamino)alkyl substituents give compounds with antidepressant potential as well as antianxiety activity.

Derivatives of the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine system[1,2] such as alprazolam (1) and tri-



1, R = CH_3; R_1 = H
2, R = CH_3; R_1 = Cl
3, R = Me_2NCH_2; R_1 = H

azolam (2) have been shown to have clinically useful anxiolytic[3] and hypnotic[4] activity. It has also been found that appropriate modifications of this system produce compounds with qualitatively different pharmacologic profiles. In particular, the 1-(aminoalkyl) derivatives (viz., 3) have a pharmacologic profile, which suggests that they may have a useful combination of antidepressant and antianxiety activities.[5] We have, therefore, been encouraged to investigate other modifications of this system in the hope of finding compounds with other interesting and potentially useful effects on the central nervous system. This article will deal with the 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one system.

Compounds prepared in this study are presented in Table I. The chemistry will be illustrated for one representative of each reaction type. Our synthesis[6-8] of 8-chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-1-one (4) was accomplished in two steps. 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione[9] (5) was first condensed with ethyl carbazate in refluxing ethanol to give 6, which was subsequently warmed above its melting point (200–205 °C) to give the cyclic product 4. Alternatively 4, could be prepared in 80% yield from 1-bromo-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (7)[10-12] by hydrolysis with 85% phosphoric acid. A variety of 2-substituted derivatives were prepared by the reaction of 4 with either sodium hydride or thallous ethoxide and an appropriate alkyl halide. The 2-methyl derivative (8) was also prepared in 69% yield by the reaction of 4 with diazomethane in a mixture of methanol and methylene chloride. Several aminoalkyl derivatives were conveniently prepared in two steps by first alkylating 4 with a 1-bromo-ω-chloroalkane and subsequently allowing the resulting ω-chloroalkane to react with an appropriate amine. For example, 8-chloro-2,4-dihydro-2-[2-(4-methyl-1-piperazinyl)ethyl]-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (9) was prepared by the potassium iodide catalyzed reaction of 10 with 1-methylpiperazine in DMF at 60 °C.

Results and Discussion

The pharmacological data for the 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones are presented in Table II.[13] Comparative data for diazepam (30), imipramine hydrochloride (31) and the 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 3 are also recorded for comparison.

8-Chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepin-1-one (4) was an antagonist of nicotine- and pentylenetetrazol-induced convulsions (TE and P respectively). Methylation at N-2 potentiated activity in these tests and, in addition, the compound 8 gained activity in the end points (B, γ-B, and HS) which are associated with antianxiety activity. Chloro substitution at the 2 position of the C-6 phenyl moiety of compounds 4 and 8 potentiated the activities of both compounds in these tests (compare 12 with 4 and 13 with 8). ω-(Dialkylamino)alkyl substitution at N-2 of both 4 and 12 gave analogues that usually retained activity in the antianxiety end points. In addition, several of these compounds had an indication of

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