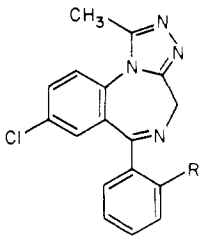
# 6-Aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines. Influence of 1-Substitution on Pharmacological Activity

Jackson B. Hester, Jr.,* and Philip Von Voigtlander

*The Upjohn Company, Kalamazoo, Michigan 49001.* *Received May 30, 1979*

A series of 1-substituted 6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was prepared and evaluated for central nervous system activity. It was found that electronegative substituents, such as trifluoromethyl, were detrimental to activity in this series. On the other hand, many compounds with electron-donating substituents at C-1 had interesting activity. In addition to showing anxiolytic potential, some were also active in tests useful for detecting antidepressant and antipsychotic activity. Several analogues with 4-methyl-1-piperazinyl and 4-morpholinyl substituents at C-1 were of particular interest.

The demonstration that the 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines **1** (triazolam) and **2**



1, R = Cl
2, R = H

(alprazolam), respectively, had interesting hypnotic[1] or anxiolytic[2] activity and the finding that the pharmacological activity of this system could be qualitatively modified by aminoalkyl substitution at C-1[3] prompted us to undertake a more extensive investigation of other C-1 substituted 6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines. This article describes the syntheses and biological activity of these compounds. Several previously unreported 1-methyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines are also recorded here for comparison purposes.

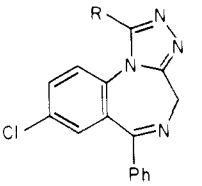
Compounds prepared in this study are presented in Table I. The chemistry will be illustrated for one representative of each reaction type. 8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine[4,5] (**3**; Chart I) was readily brominated with *N*-bromosuccinimide in refluxing carbon tetrachloride. Reaction of the resulting 1-bromo derivative[6,7] **4** with a variety of nucleophiles was utilized to give the corresponding 1-substituted derivatives. For example, the reaction of **4** with refluxing morpholine gave the 1-morpholino derivative[8] **5**. Other high-boiling amines behaved similarly at reaction temperatures of 100–130 °C. The *N*,*N*-dimethylamino derivative **6** was prepared by the reaction of **4** with dimethylamine at 130 °C in a pressure reactor.[9] Under these conditions (110–115 °C for 24 h), the 1-bromo-4-methyl derivative **19** reacted with 1-methylpiperazine to give a mixture of the C-4, N-5 and N-5, C-6 double-bond isomers **22** and **20**, respectively. Similarly the reaction of **19** with refluxing morpholine gave **23** and **21**. In this case, apparently, the C-4 methyl substituent afforded some stability to the normally unfavored C-4, N-5 double-bond isomer.[10]

The cyano derivative **7** was prepared by the reaction of **4** with cuprous cyanide in DMF at 150 °C. Reaction of **4** with sodium methoxide in refluxing methanol gave the methoxy derivative[8] **8**. Other alkoxides behaved similarly when an excess of the corresponding alcohol was used as solvent.

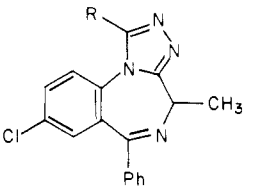
It is interesting to note that in our initial attempt to prepare **8** by alkylating 8-chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (**24**)[11,12] with trimethyloxonium fluoroborate, a reagent noted for alkylating the oxygen atom of amide derivatives,[13] only the ring-opened derivative **25** was obtained after aqueous workup.[14] Apparently in this case N-5 is the more nucleophilic atom of the molecule and is thus susceptable to preferential attack by the alkylating reagent.[15]

Condensation of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[5,11] (**26**) with cyanogen bromide and aqueous sodium carbonate gave the 1-amino derivative **9**. A similar condensation of **26** with thiophosgene and triethylamine afforded the 1-thiol **10**. The latter compound, in the presence of aqueous base, could be alkylated with, for example, methyl iodide to give **11**. Preparation of the 1-(trifluoromethyl) derivative **12** was accomplished by the

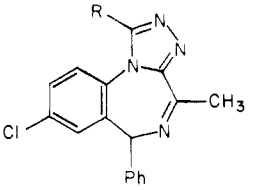
Chart I



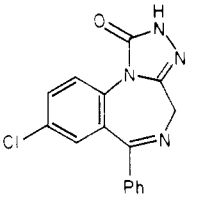
3, R = H
4, R = Br
5, R = c-N(CH$_2$CH$_2$)$_2$O
6, N(CH$_3$)$_2$
7, R = CN
8, R = OCH$_3$
9, R = NH$_2$
10, R = SH
11, R = SCH$_3$
12, R = CF$_3$
13, R = CH$_2$OCH$_3$
14, R = CH$_2$OH
15, R = CH$_2$CN
16, R = CH$_2$COOCH$_3$
17, R = CH$_2$CON(CH$_3$)$_2$
18, R = CH$_2$CH$_2$OH



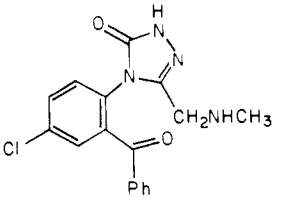
19, R = Br
20, R = c-N(CH$_2$CH$_2$)$_2$N-CH$_3$
21, R = c-N(CH$_2$CH$_2$)$_2$O



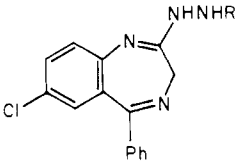
22, R = c-N(CH$_2$CH$_2$)$_2$N-CH$_3$
23, R = c-N(CH$_2$CH$_2$)$_2$O



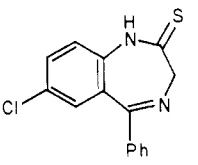
24



25



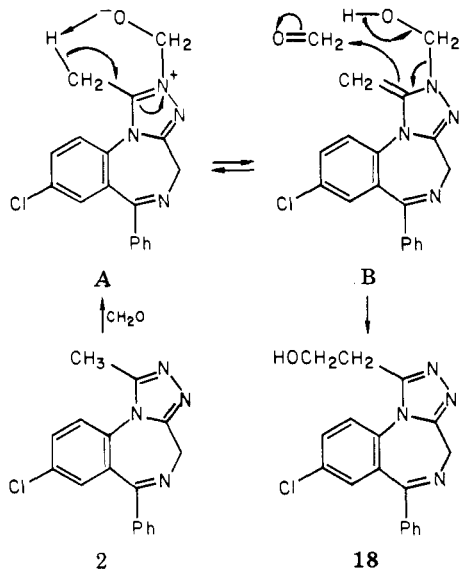
26, R = H
27, R = C(=O)CH$_2$OCH$_3$



28

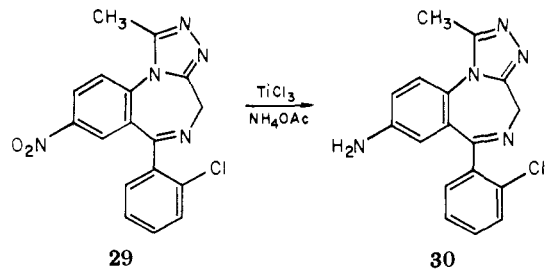
0022-2623/79/1822-1390$01.00/0 © 1979 American Chemical Society

Scheme I



reaction of **26** with hot trifluoroacetic acid. Acylation of **26** with methoxyacetyl chloride gave **27** which, without isolation, was cyclized to **13** by brief heating in acetic acid. Alternatively, the condensation of **28**[16] with, for example, hydroxyacetic acid hydrazide in refluxing *n*-butyl alcohol[4] gave **14** directly. Careful methanolysis of nitrile **15** gave the ester **16**, which could be converted to the amide **17** by the acid-catalyzed reaction with dimethylamine in DMF or to the alcohol **18** by lithium borohydride reduction. Attempted saponification of **16** with sodium hydroxide gave the decarboxylated product **2** after acidification. Of particular interest was the regiospecific reaction of **2** with formaldehyde at 122–124.5 °C to give the alcohol **18**. None of the alternative 4-(hydroxymethyl) derivative was formed in this reaction. We suggest that this result may be due to the selective activation of the 1-methyl group of **2** by a reversible interaction of the triazole nitrogen (N-2) with formaldehyde (viz., A, Scheme I). Migration of a proton from the methyl carbon of this addition product to oxygen would give an activated intermediate (B) which could via a Grob-type fragmentation[18] condense with a second molecule of formaldehyde to give the observed product **18**. For such a mechanism to predict the observed regiospecific result, it would be necessary to show that the interaction of **2** with formaldehyde could occur preferentially at N-2. Evidence for the stronger basicity of N-2 was provided by an X-ray crystallographic analysis of the hemihydrobromide salt of **2** which demonstrated that the acidic proton was associated with N-2.[11] Support for the greater nucleophilicity of N-2 was provided by our observation that methylation of **2** with trimethyloxonium fluoroborate occurs on this nitrogen[19] to give the 2-methyl derivative.

Reduction of 6-(*o*-chlorophenyl)-8-nitro-1-methyl-4*H*-*s*-triazolo[1,3-*a*][1,4]benzodiazepine[4] (**29**) with buffered



titanium trichloride[20] in THF–MeOH gave the corresponding 8-amino derivative **30** in 70% yield. This appears to be an excellent method for reducing the aromatic nitro group in the presence of other functional groups that are succeptible to reduction.

## Results and Discussion

In our laboratories, new compounds are submitted to a battery of tests that have been designed to detect agents with clinically useful CNS activity. Many of these tests are relatively specific. Major tranquilizers, such as chlorpromazine (**65**), for example, are effective antagonists of both apomorphine-induced cage climbing (ACC) and amphetamine toxicity (AA) in aggregated mice. Other types of centrally acting compounds are usually not active in these tests. Minor tranquilizers, such as diazepam (**66**), are specific antagnoists of pentylenetetrazol (P) induced clonic convulsions; they also prolong the survival of mice under hypoxic conditions (HS) and antagonize bicucullin (B) induced tonic extensor convulsions. The antidepressant imipramine (**64**) potentiates both the toxicity of yohimbine (Y) in aggregated mice and the stereotyped gnawing and licking behavior of mice under the influence of apomorphine (AG); it also antagonizes oxotremorine (OX) induced hypothermia. Chlorpromazine is also active in the latter two tests (AG and OX). A variety of CNS depressants potentiate the sleep-inducing effects of γ-butyrolactone (γ-B) and produce a hypothermic effect (BT) in mice. Both diazepam and chlorpromazine are active in these tests, but the relative potencies are quite different. By evaluating a new compound in this battery of tests its activity can be readily identified and, if interesting, followed up in more sophisticated test systems.

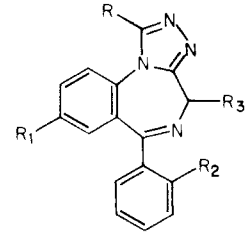
The activities of the new 1-substituted 6-aryl-*s*-triazolo[4,3-*a*][1,4]benzodiazepines are presented in Table II and compared with triazolam (**1**), alprazolam (**2**), and the standard agents imipramine (**64**), chlorpromazine (**65**), and diazepam (**66**).

The primary purpose of this study was to evaluate the influence of different C-1 substituents on the antianxiety activity of the 6-aryl-*s*-triazolo[4,3-*a*][1,4]benzodiazepines. It was found that electronegative groups had a deleterious effect on this activity. (Compare, for example, the activities of compounds **4**, **7**, **39**, and **59** with **2**.) This effect was particularly notable for the trifluoromethyl derivative **12**, which had little CNS activity. It was somewhat surprising, therefore, to find that the acetonitrile derivative **15** had considerable activity in tests indicative of antianxiety activity. The methyl ester **16** and dimethylamide **17** derived from **15** were much less active, however. The related 2-(hydroxyethyl) derivative **18** was active in both P and HS but had little activity in other tests. The homologous hydroxymethyl derivative **14**, a major alprazolam (**2**) metabolite in man,[21] was particularly active in tests for antianxiety activity. Similarly, the triazolam (**1**) metabolite **60**[22,23] appeared to be at least as active as the parent compound in this battery of tests. The methyl and ethyl ethers (**13** and **61**, respectively) of **14** were less active than the alcohol.

Oxygen substituents at C-1 appeared to have a favorable effect on activity. Thus, the methoxy derivative **8** was active in the anxiolytic end points P, B, and γ-B, although it was inactive in HS. The corresponding 2-(dimethylamino)ethoxy derivative (**56**) also had considerable activity in the antianxiety tests, including HS. The thio-substituted derivatives **10** and **11** were less potent than **2**, although they still retained an indication of anxiolytic potential.

Amino substituents at C-1 were of particular interest. Although the primary amine **9** was not exceptional, its activity on antianxiety end points was potentiated by

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




| no. | R | $R_1$ | $R_2$ | $R_3$ | yield, % | procedure | ref[a] | mp, °C | recrystn solvent | formula | analyses |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | Br | Cl | H | H | 57.5 | B[j,v] | *k* | 202–203.5[uu] | EtOAc | $C_{16}H_{10}BrClN_4$ | C, H, Br, Cl, N |
| 5 | c-N($CH_2CH_2$)$_2$O | Cl | H | H | 62 | C[s] | | 241–243.5[vv] | EtOAc–Sk B | $C_{20}H_{18}ClN_5O$ | C, H, Cl, N |
| 6 | $(CH_3)_2N$ | Cl | H | H | 40.2 | C[cc,dd] | | 175–179 | EtOAc–Sk B | $C_{18}H_{16}ClN_5$ | C, H, Cl, N |
| 7 | N≡C | Cl | H | H | 43.5 | c | | 194–195 | EtOAc–Sk B | $C_{17}H_{10}ClN_5$ | H, Cl, N; C[ii] |
| 8 | $CH_3O$ | Cl | H | H | 64.7 | D[c] | | 163–164 | EtOAc–Sk B | $C_{17}H_{13}ClN_4O$ | C, H, Cl, N |
| 9 | $H_2N$ | Cl | H | H | 67.1 | c | | 280[vv] | $CH_2Cl_2$–MeOH | $C_{16}H_{12}ClN_5$ | C, H, Cl, N |
| 10 | HS | Cl | H | H | 33.2 | c | | 240.5–241.5 | EtOAc | $C_{16}H_{11}ClN_4S$ | C, H, Cl, N, S |
| 11 | $CH_3S$ | Cl | H | H | 68.8 | *c* | | 220–221 | EtOAc | $C_{17}H_{13}ClN_4S$ | C, H, Cl, N, S |
| 12 | $CF_3$ | Cl | H | H | 19.4 | c | | 189–190.5 | EtOAc–Sk B | $C_{17}H_{10}ClF_3N_4$ | C, H, Cl, F, N |
| 13 | $CH_3OCH_2$ | Cl | H | H | 66 | c | | 193–194 | MeOH | $C_{18}H_{15}ClN_4O$ | C, H, Cl, N |
| 14 | $HOCH_2$ | Cl | H | H | 62.7 | E[c] | | 204–206.5 | EtOAc–Sk B | $C_{17}H_{13}ClN_4O$ | C, H, Cl, N |
| 15 | $NCCH_2$ | Cl | H | H | 39.2 | E[pp,dd] | *mm* | 198 | EtOAc–Sk B | $C_{18}H_{12}ClN_5$ | C, H, Cl, N |
| 16 | $CH_3OOCCH_2$ | Cl | H | H | 84.1 | c | | 202–203 | MeOH–EtOAc | $C_{19}H_{15}ClN_4O_2$ | C, H, N; Cl[qq] |
| 17 | $(CH_3)_2NCOCH_2$ | Cl | H | H | 45.5 | c | | 241–242 | MeOH–EtOAc | $C_{20}H_{18}ClN_5O$ | C, H, Cl, N |
| 18 | $HOCH_2CH_2$ | Cl | H | H | 22.4 | F[c] | | 234–236 | MeOH–EtOAc | $C_{18}H_{15}ClN_4O$ | C, H, Cl, N |
| | | | | | 51.8[rr] | G | | | | | |
| 19 | Br | Cl | H | $CH_3$ | 71 | B[v] | | 207–210 | $CH_2Cl_2$–EtOAc–Sk B | $C_{17}H_{12}BrClN_4$ | C, H, Br, Cl, N |
| 20 | $CH_3$-c-N($CH_2CH_2$)$_2$N | Cl | H | $CH_3$ | 45.5 | C[c] | | 207–208.5 | EtOAc–Sk B | $C_{22}H_{23}ClN_6$ | C, H, Cl, N |
| 21 | c-N($CH_2CH_2$)$_2$O | Cl | H | $CH_3$ | 63.1 | C[s,dd] | | 227–227.5 | MeOH–EtOAc–Sk B | $C_{21}H_{20}ClN_5O$ | C, H, Cl, N |
| 22[z] | $CH_3$-c-N($CH_2CH_2$)$_2$N | Cl | H | $CH_3$ | 20.8 | C[c] | | 195.5–199.5 | EtOAc–Sk B | $C_{22}H_{23}ClN_6$ | C, H, Cl, N |
| 23[aa] | c-N($CH_2CH_2$)$_2$O | Cl | H | $CH_3$ | 25.0 | C[s] | | 249–250 | MeOH–EtOAc | $C_{21}H_{20}ClN_5O$ | C, H, Cl, N |
| 30 | $CH_3$ | $H_2N$ | Cl | H | 70.7 | H[c] | | 312–313.5[vv] | $CH_2Cl_2$–MeOH–EtOAc | $C_{17}H_{14}ClN_5$ | C, H, Cl, N |
| 31 | H | Br | N[b] | H | 51.5 | A[c] | *d* | 252–255[vv] | $CH_2Cl_2$–EtOAc | $C_{15}H_{10}BrN_5$ | C, H, Br, N |
| 32 | H | H | Cl | H | 58.5 | A[dd] | *d* | 217–217.5 | EtOAc | $C_{16}H_{11}ClN_4$ | C, H, Cl, N |
| 33 | H | H | H | H | 62.1[g] | A[dd] | *e* | 197.5–199[f] | MeOH–EtOAc | | |
| 34 | H | Cl | H | $CH_3$ | 66.6 | A | *h* | 284–287 | $CH_2Cl_2$–MeOH–EtOAc | $C_{17}H_{13}ClN_4$ | C, H, Cl, N |
| 35 | Br | Br | N[b] | H | 50.6 | B[c] | | >250[vv] | $CH_2Cl_2$–MeOH–EtOAc | $C_{15}H_9Br_2N_5$ | C, H, Br, N |
| 36 | Br | Cl | Cl | H | 50 | B[v] | *e* | 208.5–210.5 | $CH_2Cl_2$–EtOAc–Sk B | $C_{16}H_9BrCl_2N_4$ | C, H, Br, N; Cl[i] |
| 37 | Br | H | Cl | H | 53.5 | B | | 190 | MeOH | $C_{16}H_{10}BrClN_4$ | C, H, Br, Cl, N |
| 38 | Br | H | H | H | 57.8 | B[hh] | | 210.5–212.5[vv] | MeOH–EtOAc | $C_{16}H_{11}BrN_4$ | C, H, Br, N |
| 39 | Cl | Cl | H | H | 23.1 | B[l,gg] | *k* | 198–199 | EtOAc | $C_{16}H_{10}Cl_2N_4$ | C, H, Cl, N |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 40 | $CH_3$-c-$N(CH_2CH_2)_2N$ | Cl | H | H | 54.5 | C[c] | | 238–239.5 | MeOH–EtOAc | $C_{21}H_{21}ClN_6$ | C, H, Cl, N |
| 41 | Ph-c-$N(CH_2CH_2)_2N$ | Cl | H | H | 67.7 | C[n] | | 261.5–262.5 | $CH_2Cl_2$–MeOH | $C_{26}H_{23}ClN_6$ | H, Cl, N; C[m] |
| 42 | $HOCH_2CH_2$-c-$N(CH_2CH_2)_2N$ | Cl | H | H | 53 | C[o,ff] | | 219–224 | $CH_2Cl_2$–EtOAc | $C_{22}H_{23}ClN_6O$ | C, H, Cl, N |
| 43 | c-$NH(CH_2CH_2)_2N$ | Cl | H | H | 43 | C[p] | | 205–208 | EtOAc | $C_{20}H_{19}ClN_6 \cdot 0.5H_2O$ | C, H, Cl, N, $H_2O$ |
| 44 | Et-c-$N(CH_2CH_2)_2N$ | Cl | H | H | 59 | C[q] | | 232–234.5 | $CH_2Cl_2$–EtOAc | $C_{22}H_{23}ClN_6$ | C, H, Cl, N |
| 45 | $(CH_3)_2N(CH_2)_2N(CH_3)$ | Cl | H | H | 16 | C[r,ee] | | 135–140 | EtOAc–Sk B | $C_{21}H_{23}ClN_6$ | C, H, Cl, N |
| 46 | $CH_3$-c-$N(CH_2CH_2)_2N$ | Br | N[b] | H | 61.5 | C[ee] | | 252–253[vv] | MeOH–EtOAc | $C_{20}H_{20}BrN_7$ | C, H, Br, N |
| 47 | $HOCH_2CH_2$-c-$N(CH_2CH_2)_2N$ | H | Cl | H | 54 | C[o] | | 202–202.5 | $CH_2Cl_2$–EtOAc | $C_{22}H_{23}ClN_6O$ | C, H, Cl, N |
| 48 | Et-c-$N(CH_2CH_2)_2N$ | H | Cl | H | 44.6 | C[q,ee] | | 156.5–161 | EtOAc–Sk B | $C_{22}H_{23}ClN_6$ | C, H, Cl, N |
| 49 | $CH_3$-c-$N(CH_2CH_2)_2N$ | H | Cl | H | 59.5 | C[ee] | | 184.5–186 | EtOAc–Sk B | $C_{21}H_{21}ClN_6$ | H, Cl; C, N[t] |
| 50 | $CH_3$-c-$N(CH_2CH_2)_2N$ | H | H | H | 81.2 | C | | 204.5–206.5 | MeOH–EtOAc | $C_{21}H_{22}N_6$ | H, N; C[u] |
| 51 | $CH_3$-c-$N(CH_2CH_2)_2N$ | Cl | Cl | H | 41 | C[v,w] | | 224–226 | $CH_2Cl_2$–EtOAc | $C_{21}H_{20}Cl_2N_6$ | C, H, Cl, N |
| 52 | c-$N(CH_2CH_2)_2O$ | H | Cl | H | 63.4 | C[s,x] | | 188–189 | EtOAc | $C_{20}H_{18}ClN_5O$ | C, H, Cl, N |
| 53 | c-$N(CH_2CH_2)_2O$ | Cl | Cl | H | 58 | C[s] | | 244.5–245 | MeOH–EtOAc | $C_{20}H_{17}Cl_2N_5$ | C, H, Cl, N |
| 54 | c-$N(CH_2CH_2)_2O$ | H | H | H | 59.6 | C[s,dd] | | 240 | EtOAc–Sk B | $C_{20}H_{19}N_5O$ | H, N; C[y] |
| 55 |  | Cl | H | H | 45 | C[bb] | | 182–183 | EtOAc–Sk B | $C_{20}H_{18}ClN_5$ | C, H, Cl, N |
| 56 | $(CH_2)_2NCH_2CH_2O$ | Cl | H | H | 23 | D[jj] | | 140.5–142 | EtOAc–Sk B | $C_{20}H_{20}ClN_5O$ | C, H, Cl, N |
| 57 | $Et_2NCH_2CH_2O$ | Cl | H | H | 25 | D[kk] | | 114–117 | EtOAc–Sk B | $C_{22}H_{24}ClN_5O$ | C, H, Cl, N |
| 58 | $(CH_3)_2NCH_2CH_2S$ | Cl | H | H | 34 | c | | 127–130.5 | $CH_2Cl_2$–$Et_2O$–pet. ether | $C_{20}H_{20}ClN_5S$ | C, H, Cl, N, S |
| 59 | $Cl_2CH$ | Cl | H | H | 51.3 | c | | 196.5–198 | $CH_2Cl_2$–$Et_2O$ | $C_{17}H_{11}Cl_3N_4$ | C, H, N; Cl[ll] |
| 60 | $HOCH_2$ | Cl | Cl | H | 64.1 | E | *mm* | 239.5–241 | $CH_2Cl_2$–MeOH | $C_{17}H_{12}Cl_2N_4O$ | H, Cl, N; C[nn] |
| 61 | $EtOCH_2$ | Cl | H | H | 24.7 | E[oo] | *mm* | 168–169 | EtOAc–Sk B | $C_{19}H_{17}ClN_4O$ | C, H, Cl, N |
| 62 | $CH_3$ | Br | N[b] | H | 41.2 | E | *d* | 253–255 | $CHCl_3$–EtOAc | $C_{16}H_{12}BrN_5$ | C, H, Br; N[ss] |
| 63 | $CH_3$ | Br | H | H | 35.1 | E | *mm* | 272–272.5 | $CH_2Cl_2$–EtOAc | $C_{17}H_{13}BrN_4$ | C, H, N; Br[tt] |

[a] Literature reference to starting material. [b] 6-(2-Pyridyl) derivative. [c] See Experimental Section. [d] Reference 3. [e] Reference 28. [f] Lit.[28] mp 201–202 °C. [g] Prepared directly from 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione without isolating the intermediate 2-hydrazino derivative. [h] 7-Chloro-2-hydrazino-3-methyl-5-phenyl-3*H*-1,4-benzodiazepine, mp 183–189 °C, was prepared by the reaction of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (ref 3) with hydrazine hydrate in MeOH MeOH. [i] Cl: calcd, 17.38; found, 15.08. [j] $CCl_4$ used as solvent. [k] References 28 and 4. [l] Reaction with *N*-chlorosuccinimide in $CCl_4$. [m] C: calcd, 68.64; found 69.11. [n] Reaction with 1-phenylpiperazine at 130 °C for 24 h. [o] Reaction with 1-(2-hydroxyethyl)piperazine at 130 °C for 20 h. [p] Reaction with piperazine; purification by silica gel chromatography with MeOH. [q] Reaction with 1-ethylpiperazine. [r] Reaction with [2-(dimethylamino)ethyl]methylamine at 100 °C for 3 days. [s] Reaction with refluxing morpholine for 24 h. [t] C: calcd, 64.19; found, 63.77; N: calcd, 21.39; found, 20.86. [u] C: calcd, 70.37; found, 69.93. [v] Purified by silica gel chromatography with 2.5% MeOH–$CHCl_3$. [w] 8-Chloro-6-(*o*-chlorophenyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine was isolated in 12% yield as a byproduct from this reaction. [x] Purified by silica gel chromatography with 3% MeOH–$CHCl_3$. [y] C: calcd, 69.55; found, 69.06. [z] 4,5 double-bond isomer of 20. [aa] 4,5 double-bond isomer of 21. [bb] Reaction with refluxing pyrrolidine for 1.5 h. [cc] Reaction with dimethylamine in a pressure vessel at 130 °C for 24 h. [dd] Product purified by silica gel chromatography with 2% MeOH–$CHCl_3$. [ee] Product purified by silica gel chromatography with 5% MeOH–$CHCl_3$. [ff] Product purified by silica gel chromatography with 2% $Et_3N$–13% MeOH–85% EtOAc. [gg] Product purified by silica gel chromatography with 1% MeOH–$CHCl_3$. [hh] Product purified by silica gel chromatography with 1.5% MeOH–$CHCl_3$. [ii] C: calcd, 63.85; found, 63.44. [jj] Reaction with 2-(dimethylamino)ethanol at 25 °C for 18 h. [kk] Reaction with 2-(diethylamino)ethanol at 25 °C for 18 h. [ll] Cl: calcd, 28.17; found, 27.72. [mm] Reference 16. [nn] C: calcd, 56.84; found, 56.40. [oo] Reaction with ethoxyacetic acid hydrazide; product purified by silica gel chromatography with EtOAc–Skellysolve B. [pp] Reaction with cyanoacetic acid hydrazide. [qq] Cl: calcd, 9.67; found, 10.15. [rr] Yield based on recovered starting material. [ss] N: calcd, 19.77; found, 17.53. [tt] Br: calcd, 22.63; found, 23.26. [uu] Lit.[6] mp 205–207 °C. [vv] Decomposition.

Table II. Pharmacological Data[a]

| no. | pentylene-tetrazole (P) | hypothermia (BT) | apomorphine cage climbing (ACC) | bicucullin (B) | γ-butyrolactone (γ-B) | hypoxic stress (HS) | amphetamine toxicity (AA) | yohimbine (Y) | oxotremorine (OX) | apomorphine gnawing (AG) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.07 | *e* | *e* | *e* | *e* | 0.07 | *e* | >50 | >50 | >50 |
| 2 | 0.1 | >50 | >50 | 0.2 | 0.08 | 0.2 | >50 | >50 | >50 | >50 |
| 4 | 2.3 | >50 | >50 | 3 | 2 | 6 | >50 | >50 | >50 | >50 |
| 5 | 2.6 | 7 | 40 | 3.1 | 4.4 | >50 | >50 | >50 | 35.4 | 35.4 |
| **6** | 0.9 | >50 | >50 | 1.1 | 0.3 | 9 | >50 | >50 | 21 | >50 |
| **7** | *e* | 10 | >50 | 3 | 4 | >50 | >50 | >50 | >50 | >50 |
| 8 | 0.14 | 10 | >50 | 0.5 | 0.1 | >50 | >50 | >50 | >50 | >50 |
| 9 | 14 | 9 | >50 | 20 | 2 | >50 | >50 | >50 | >50 | >50 |
| 10 | 2.3 | 9 | >50 | 3 | 0.8 | 9 | >50 | >50 | >50 | >50 |
| 11 | 8.0 | 10 | >50 | 10 | 0.8 | 10 | >50 | >50 | >50 | >50 |
| 12 | 20 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| 13 | 2 | 30 | >50 | 0.6 | 2 | 20 | >50 | >50 | >50 | >50 |
| 14[b] | 0.1 | >50 | >50 | 0.2 | 0.1 | 0.9 | >50 | >50 | 20 | >50 |
| 15 | 0.63 | >50 | 40 | 0.2 | 0.07 | 2 | >50 | >50 | >50 | >50 |
| **16** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| 17 | 5.6 | >50 | >50 | 40 | 10 | >50 | >50 | >50 | >50 | >50 |
| **18** | 4 | 30 | >50 | >50 | >50 | 4 | >50 | >50 | >50 | >50 |
| 19 | 3.7 | >50 | >50 | 1.9 | 3.1 | >50 | >50 | >50 | >50 | >50 |
| 20 | 3.1 | 29.7 | 50 | 2.6 | 0.7 | 4.4 | >50 | 8.8 | 4.4 | >50 |
| 21 | 0.4 | >50 | >50 | 3 | 0.7 | 3 | >50 | 20 | 10 | >50 |
| 22 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 40 | >50 |
| 23 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| **30** | 2 | 30 | >50 | 0.9 | 0.7 | 4 | >50 | >50 | >50 | >50 |
| **31** | 0.3 | >50 | >50 | 0.4 | 0.04 | 0.2 | >50 | 42 | >50 | >50 |
| **32** | >50 | >50 | >50 | 42 | 12.5 | >50 | >50 | >50 | >50 | >50 |
| **34** | 3.7 | 10.5 | >50 | 4.4 | 0.6 | 42 | >50 | >50 | 7.4 | >50 |
| **37** | 10.5 | >50 | >50 | 25 | 6.2 | 8.8 | >50 | >50 | >50 | >50 |
| **39** | 3.1 | >50 | >50 | 4 | 3 | >50 | >50 | >50 | >50 | >50 |
| **40** | 1.6 | >50 | >50 | 10.5 | 0.7 | >50 | >50 | >50 | 7.4 | 17.7 |
| **41** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| **42** | 42 | >50 | >50 | 8.8 | 1.6 | >50 | >50 | >50 | >50 | 25 |
| **43** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 34 | >50 |
| **44** | 0.9 | 42 | >50 | 1.9 | 0.6 | 25 | >50 | >50 | 0.2 | 29.7 |
| **45** | 30 | 40 | >50 | 42 | 12.5 | >50 | >50 | >50 | >50 | >50 |
| **46** | 12.5 | >50 | >50 | 8.8 | 3.1 | 21.0 | >50 | 35.4 | >50 | 3.7 |
| **47** | 3 | 2 | >50 | 6 | 3 | 0.9 | >50 | 30 | 40 | >50 |
| **48** | 2 | 2 | >50 | 7 | >50 | 4 | >50 | 30 | 40 | >50 |
| **49** | 6.2 | 0.2 | 4.4 | >25 | >25 | 1.1 | >25 | >25 | >25 | >25 |
| 50 | 14.9 | 12.5 | 25 | >50 | >50 | >50 | >50 | >50 | 35.4 | >50 |
| 51 | 0.03 | 3.1 | >50 | 0.06 | 0.035 | 0.011 | >50 | 35.4 | 4.4 | >50 |
| 52 | 1.6 | >50 | >50 | 10.5 | 0.8 | 0.015 | >50 | >50 | >50 | >50 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | 0.06 | 6 | >50 | 0.05 | 0.04 | 0.06 | >50 | >50 | >50 | >50 | >50 | >50 |
| 54 | 9 | >50 | >50 | >50 | 20 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| 55 | 4.5 | 40 | >50 | 4 | 3 | >50 | >50 | >50 | 30 | >50 | >50 | >50 |
| 56 | 2.2 | >50 | >50 | 1.1 | 0.2 | 0.8 | >50 | >50 | 25 | >50 | >50 | >50 |
| 57 | 8.8 | >50 | >50 | 12.5 | 2.2 | 40 | >50 | 42 | >50 | >50 | >50 | >50 |
| 58 | 3.1 | >50 | >50 | 7.4 | 1.6 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| 59 | 8.0 | >50 | >50 | 10 | 3 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| 60[b] | 0.045 | 7 | >50 | 0.02 | 0.01 | 0.06 | >50 | >50 | >50 | >50 | >50 | >50 |
| 61 | 1.4 | 40 | >50 | 3 | 0.9 | 10 | >50 | >50 | >50 | >50 | >50 | >50 |
| 62 | 0.12 | e | e | 0.24 | 0.035 | e | e | >50 | >50 | >50 | >50 | >50 |
| 63 | 0.6 | 20 | 20 | 0.5 | 0.8 | 2 | >50 | >50 | 4 | >50 | >50 | >50 |
| 64[c] | >50 | >50 | >50 | 21 | 18 | >50 | >50 | 4 | 1 | 1 | | 1 |
| 65[d] | >50 | 1 | 1 | 50 | 0.5 | >50 | 1 | >50 | 0.9 | 1 | | 1 |
| 66 | 0.1 | 14.9 | >50 | 2.6 | 0.035 | 0.2 | >50 | >50 | >50 | >50 | >50 | >50 |

[a] Values are $ED_{50}$ expressed in mg/kg. [b] Some screening data for this compound has been reported previously; see ref 29. [c] Imipramine hydrochloride. [d] Chlorpromazine. [e] Not tested.

N-methylation (viz., **6**). 4-Methyl-1-piperazinyl substitution produced a series with a somewhat different activity profile (compare **40** with **2**). Thus, **40** had activity in the antidepressant end points OX and AG, in addition to activity in P, B, and γ-B. This effect was potentiated in the 4-ethyl analogue (**44**), which was a particularly effective antagonist of oxotremorine-induced hypothermia (OX) and had enhanced activity in P, B, and γ-B. The nature of the N-substituent on the piperazine moiety appears to be of some importance for this activity, since the 2-hydroxyethyl derivative **42** was much less active than **40**. Essentially all activity was lost with the phenyl (**41**) and hydrogen (**43**) substituted analogues. Methyl substitution at C-4 had an interesting effect on the activity of this series (compare **20** with **40**). In this case, activity in the antianxiety end points was retained but, in addition, the compound had activity in BT and ACC, as well as the antidepressant end point (Y). It is also interesting that the C-4, N-5 double-bond isomer (**22**) of **20** had no activity in these tests. Like **40**, the 8-bromo-6-(2-pyridyl) analogue **46** had activity in both antianxiety and antidepressant end points which contrasted with the potent antianxiety activity of the parent molecule **62**. [For the influence of the 8-bromo and 6-(2-pyridyl) substituents on the activity of the 1-methyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine series compare **63** and **62** with **2**.]

Our previous observation[4] that the presence or absence of a chloro substituent on the ortho position of the C-6 phenyl and on the 8 position of the benzodiazepine nucleus had dramatic effects on the activity profile of the 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was further developed in this series. Thus, activity on antianxiety end points was greatly potentiated by *o*-chloro substitution on the C-6 phenyl of compound **40**. The resulting analogue **51** was 10–100 times as potent as **40** on P, B, and γ-B; in addition, it was very active in HS and had activity in BT, Y, and OX. Elimination of the 8-chloro substituent from **51** to give **49** resulted in a dramatic loss in potency and a further change in activity profile. This compound had lost activity in B, γ-B, Y, and OX but retained some activity in P and HS; in addition, its activity in BT was potentiated and it had gained activity in an end point (ACC) associated with major tranquilizing activity. By removing the *o*-chloro substituent from **49** to give **50**, the potency was further reduced but some activity in P, BT, and ACC was retained.

A second interesting series was produced by 4-morpholinyl substitution at C-1. In this series, compound **5** had activity on the antidepressant end points OX and AG, as well as P, BT, ACC, B, and γ-B. Methylation at C-4 enhanced activity in both antidepressant and antianxiety end points (compare **21** with **5**). Here again activity was lost in the C-4, N-5 double-bond isomer (**23**) of **21**. The dichloro (**53**) and ortho monochloro (**52**) analogues of **5** were both very potent compounds. Although their activity seemed to reside primarily in the antianxiety end points, it was interesting that **52** was relatively more potent in HS than in γ-B, B, or P (compare **52** with **53** and **66**), which suggests that it might have antianxiety activity with little concomitant CNS depression.

1-Methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with amino substituents at C-8 also have interesting activity. Thus, compound **30** has activity in P, B, γ-B, and HS, as well as in BT. These results may be contrasted with those previously reported for the corresponding hydroxyamino derivative.[24]

In summary we have shown that by selective manipulation of the substituents at C-1, C-8, and on the ortho

position of the C-6 phenyl of the 4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepines we can obtain compounds with a broad range of activities in the CNS screen. Some of these compounds may have interesting clinical utility.

## Experimental Section

**Chemistry.** Melting points taken in a capillary tube are corrected. The structures of all compounds were supported by IR, UV, and NMR spectra. IR spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. UV spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A60-A 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-Bromo-6-(2-pyridyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (31). Procedure A.** The procedure of Meguro and Kuwada[25] was used for this preparation. A stirred solution of 7-bromo-5-(2-pyridyl)-2-hydrazino-3*H*-1,4-benzodiazepine[3] (3.30 g, 0.01 mol) in $CHCl_3$ (80 mL) was cooled in an ice bath, under $N_2$, and treated with triethyl orthoformate (7.41 g, 0.05 mol) and $H_2SO_4$ (3.68 g). The mixture was allowed to warm to ambient temperature and stirred for 3 h. It was then 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 residue was chromatographed on silica gel with 5% MeOH–$CHCl_3$. The product thus obtained was crystallized from $CH_2Cl_2$–EtOAc to give 1.75 g of **31**.

**1,8-Dibromo-6-(2-pyridyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine (35). Procedure B.** A stirred mixture of **31** (4.81 g, 0.0142 mol), *N*-bromosuccinimide (2.77 g, 0.0156 mol), and dry benzene (350 mL), under $N_2$, was warmed in an oil bath from 51 to 83 °C during 45 min and refluxed gently for 3 h and 20 min. The mixture was concentrated and the residual solid was suspended in a mixture of saturated $NaHCO_3$ and $CHCl_3$ and stirred for 45 min. The mixture was filtered and the solid was washed with water and $CHCl_3$, dried, and crystallized from $CHCl_3$–MeOH to give 1.12 and 0.368 g of **35**. The above filtrate was extracted with $CHCl_3$. The extract was washed with brine, dried ($Na_2SO_2$), and concentrated. Crystallization of the residue from $CHCl_3$–MeOH gave 1.27 g of additional product (**35**). The mother liquors from these crystallizations were combined and chromatographed on silica gel (150 g) with 2% MeOH–$CHCl_3$. The first material eluted from the column was crystallized from $CHCl_3$–MeOH to give 0.256 g of additional **35**. Further elution of the column gave recovered **31**, which was crystallized from MeOH–EtOAc to give 0.352 g, mp 236.5–238.5 °C. The analytical sample of **35** was crystallized from $CH_2Cl_2$–MeOH–EtOAc. It darkens at about 250 °C but does not melt.

**8-Chloro-1-(4-methylpiperazino)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (40). Procedure C.** A stirred mixture of **4** (0.748 g, 0.002 mol) and 1-methylpiperazine (4 mL), under nitrogen, was warmed during 3 h to 110 °C and kept at 100–110 °C for an additional 10 h and 25 min. The cooled mixture was poured into ice–water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried ($K_2CO_3$), and concentrated. The residue was dissolved in EtOAc and allowed to crystallize. This material was recrystallized from MeOH–EtOAc to give 0.367 (mp 239.5–240.5 °C) and 0.061 g (mp 238.5–240 °C) (54.5% yield) of **40**. The analytical sample had mp 238–239.5; UV (EtOH) end adsorption $\lambda_{max}$ 218 nm ($\epsilon$ 40 800), inflections 245 (16 500), 275 (6600), 300 (1850); NMR ($CDCl_3$) $\delta$ 2.33 (s, 3, N-$CH_3$), 4.04, 5.38 (d, d, 2, $J_{AB}$ = 13 Hz, $C_4$-$H_2$).

**8-Chloro-1-methoxy-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine (8). Procedure D.** Compound **4** (0.374 g, 0.001 mol) was added to a solution of sodium (0.070 g) in MeOH (10 mL); the mixture was refluxed under $N_2$ for 45 min and poured into ice–water. This mixture was extracted with $CH_2Cl_2$, and the extract was dried ($K_2CO_3$) and concentrated. The residue was crystallized from EtOAc–Skellysolve B to give 0.21 g of **8**, mp 162–163 °C.

**8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-methanol (14). Procedure E.** A stirred solution of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione[16] (**28**; 5.74 g, 0.02 mol) and hydroxyacetic acid hydrazide (4.44 g, 0.06 mol) in *n*-butyl alcohol (200 mL) was refluxed under nitrogen for 22 h. The solution was concentrated in vacuo, and the residue was mixed with ice–water and treated with a little $Et_2O$. The precipitate which formed was collected by filtration. The filtrate was extracted with $Et_2O$, and the $Et_2O$ solution was washed with water, dried, and concentrated. This residue was combined with the above solid and chromatographed on silica gel (400 g) with 2% MeOH–98% $CHCl_3$. The resulting product was crystallized from EtOAc–Skellysolve B to give 4.07 g of **14**, mp 203–205 °C. The analytial sample had mp 204–206.5 °C.

**8-Chloro-1-(2-hydroxyethyl)-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (18). Procedure F.** Compound **16** (0.734 g, 0.002 mol) was added, under $N_2$, to a stirred ice-cold suspension of $LiBH_4$ (0.100 g, 0.00458 mol) in THF (10 mL). The resulting mixture was kept at ambient temperature for 17 h and concentrated in vacuo. The residue was mixed with cold water and extracted with $CHCl_3$. The extract was washed (brine), dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on silica gel (50 g) with 2–5% MeOH–$CHCl_3$. The product obtained from the column was crystallized from MeOH–EtOAc to give 0.130 (mp 229–231 °C) and 0.022 g (mp 226–229 °C) of **18**. The analytical sample had mp 234–236 °C.

**8-Chloro-1-(2-hydroxyethyl)-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (18). Procedure G.** A stirred mixture of **2** (3.09 g, 0.01 mol) and paraformaldehyde (3 g) in xylene (100 mL) was warmed in an oil bath at 122–124.5 °C. At this temperature the starting material (**2**) dissolved and the paraformaldehyde disproportionated to give gaseous formaldehyde, which bubbled from the mixture. In this manner, the insoluble paraformaldehyde was consumed in 30–60 min. Additional paraformaldehyde (13 g) was therefore added to the mixture portionwise, periodically during 4 h. After 6 h, the mixture was cooled and concentrated in vacuo. The residue was dissolved in $CHCl_3$, filtered, and chromatographed on silica gel (200 g) with 3% MeOH–97% $CHCl_3$. Unreacted starting material was eluted from the column first and crystallized from MeOH–EtOAc to give 1.562 g of **2**, mp 229.5–230.5 °C. The product, eluted next, was crystallized from MeOH–EtOAc to give 0.483 (mp 237–238 °C), 0.257 (mp 236.5–237 °C), and 0.129 g (mp 235.5–236.5 °C) of **18**.

**8-Amino-6-(*o*-chlorophenyl)-1-methyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (30). Procedure H.** A warm solution of 6-(*o*-chlorophenyl)-1-methyl-8-nitro-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine[4] (**29**; 3.54 g, 0.01 mol) in MeOH (100 mL) and THF (100 mL) was added during 5 min, under $N_2$, to a stirred ice-cold mixture of titanium trichloride (55 g of a 20% solution) and $NH_4OAc$ (21.6 g) in water (50 mL). The mixture was allowed to stand for 3 h and 50 min, during which time the temperature gradually rose to about 20–25 °C. It was then poured carefully, with stirring, into 500 mL of saturated $NaHCO_3$; the mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on silica gel (100 g) with 10% MeOH–$CHCl_3$. The product thus obtained was crystallized from $CH_2Cl_2$–MeOH to give 0.776 (mp 311–313 °C dec), 1.122 (mp 311–314.5 °C dec), and 0.392 g (mp 309–311 °C dec) of **30**.

**8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-carbonitrile (7).** A mixture of **4** (7.48 g, 0.02 mol), CuCN (1.97 g, 0.022 mol), and DMF (50 mL) was heated, under $N_2$, at 150 °C for 2 h, cooled, poured into 25 mL of 25% ethylenediamine, and extracted with $CHCl_3$. The extract was washed successively with 25 mL of 25% ethylenediamine, water, and brine; dried ($K_2CO_3$); and concentrated. The residue was chromatographed on silica gel (500 g) with 1% MeOH–99% $CHCl_3$. The first material eluted from the column was the product, which was crystallized from EtOAc–Skellysolve B to give 2.78 g of **7**, mp 193–194.5 °C. The analytical sample had mp 194–195 °C; UV (EtOH) end absorption, inflections, $\lambda_{max}$ 225 nm ($\epsilon$ 27 700), 251 (18 850), 285 (3800), 295 (2500); IR (Nujol) 2240 $cm^{-1}$ (C≡N).

**1-Amino-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine (9).** A stirred mixture of 7-chloro-2-hydrazi-

no-5-phenyl-3*H*-1,4-benzodiazepine[25] (**26**; 2.85 g, 0.01 mol) and dioxane (25 mL) was cooled in an ice bath and treated with a solution of $Na_2CO_3$ (1.06 g, 0.01 mol) in water (6 mL). A solution of cyanogen bromide (1.06 g, 0.01 mol) in dioxane (10 mL) was added to this mixture during 5 min, keeping the temperature of the mixture at 3–4 °C. The mixture was allowed to warm to ambient temperature during 20 min and was kept at this temperature for 3 h and 45 min. It was then poured into ice–water. The solid was collected by filtration, washed with water, dried, and recrystallized from MeOH to give 2.08 g of **9**, mp 311–312 °C. The analytical sample was crystallized from $CH_2Cl_2$–MeOH and had mp 280 °C dec.

**8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-thiol (10).** A solution of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[25] (**26**; 2.85 g, 0.01 mol) and $Et_3N$ (3.05 mL, 0.022 mol) in dry THF (40 mL) was cooled in a salt–ice bath and treated during 25 min with a solution of thiophosgene (0.838 mL, 0.011 mol) in THF (20 mL). The mixture was kept at ambient temperature for 17 h, refluxed for 1 h, and concentrated in vacuo. The residue was suspended in water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (150 g) with 1% MeOH–99% $CHCl_3$. The product obtained from the column was dissolved in EtOAc, decolorized with Dacro G60, and crystallized to give 0.698 (mp 239.5–240.5 °C), 0.097 (mp 239–240 °C), and 0.291 g (mp 237–239 °C) of **10**. The analytical sample had mp 240.5–241.5 °C.

**8-Chloro-1-(methylthio)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11).** A stirred suspension of **10** (1.54 g, 0.00471 mol) in 1.5 N NaOH (94 mL) was treated with $CH_3I$ (70.8 mL) and kept at ambient temperature for 25 min. This mixture was extracted with $CH_2Cl_2$. The extract was dried ($Na_2SO_4$) and concentrated in vacuo. The residue was crystallized from EtOAc to give 0.54 (mp 220–223 °C) and 0.56 g (mp 219–220.5 °C) of **11**. The analytical sample had mp 220–221 °C.

**8-Chloro-6-phenyl-1-(trifluoromethyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12).** 7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[25] (**26**; 2.85 g, 0.01 mol) was added to ice-cold trifluoroacetic acid (11.4 g), and the resulting mixture was warmed on the steam bath for 2 h. The mixture was cooled and treated with solid $NaHCO_3$ until stirring became difficult; it was then diluted with water and $CH_2Cl_2$, neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$. The extract was dried ($K_2CO_3$) and concentrated. The residue was chromatographed on silica gel (200 g) with 1% MeOH–99% $CHCl_3$. The product was crystallized from EtOAc–Skellysolve B to give 0.61 (mp 189–190.5 °C) and 0.095 g (mp 187–188.5 °C) of **12**. The analytical sample had mp 189–190.5 °C.

**8-Chloro-1-(methoxymethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13).** A stirred suspension of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[25] (**26**; 7.13 g, 0.025 mol) in THF (60 mL) was cooled in an ice bath and treated during 4 min with a solution of methoxyacetyl chloride (2.73 g, 0.025 mol) in THF (12 mL). The mixture was kept at 0 °C for 20 min and at ambient temperature for 2 h. It was then poured into a stirred mixture of about 600 mL of ice chips and saturated sodium bicarbonate. The solid was collected by filtration, washed with water, and dried in vacuo. It was then dissolved in glacial acetic acid (60 mL), refluxed under nitrogen for 30 min, cooled, and concentrated in vacuo. The residue was mixed with ice–water, neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was crystallized from MeOH–EtOAc to give 5.33 (mp 193–194 °C) and 0.26 g (mp 192.5–194 °C) of **13**. The analytical sample was recrystallized from MeOH and had mp 193–194 °C.

**8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-acetic Acid Methyl Ester (16).** A stirred mixture of **15** (3.34 g, 0.01 mol), MeOH (10 mL), $Et_2O$ (20 mL), and $H_2O$ (0.18 mL) was cooled, under $N_2$, in a salt–ice bath and treated during 45 min with a slow stream of dry HCl. The mixture was allowed to warm to 25 °C and stand for 17 h; the initial gummy mass slowly became a light-yellow solution from which a white solid precipitated. The mixture was concentrated, and the residue was mixed with cold, dilute $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on silica gel (200 g) with 5% MeOH–$CHCl_3$. The product thus obtained was crystallized from MeOH–EtOAc to give 2.66 (mp 203–204 °C dec) and 0.429 g (mp 201–203 °C dec) of **16**.

**8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (2) from 16.** A suspension of **16** (0.734 g, 0.002 mol) in EtOH (20 mL) was treated with 1 N NaOH (2.2 mL) and allowed to stir at ambient temperature, under $N_2$, for 18 h. The mixture was concentrated in vacuo; the residue was dissolved in a little water, cooled in an ice bath, and acidified to pH 3–4 with dilute HCl. The resulting solid was collected by filtration, washed with water, and dried to give 0.348 g of crude **2**, mp 226–227.5 °C, with softening and sintering at about 110 °C. By TLC (5% MeOH–95% $CHCl_3$ on silica gel) this material was a mixture of **2** and a more polar material which remained at the origin. A sample (100 mg) was recrystallized from EtOAc to give 58 (mp 229.5–231 °C) and 16 mg (mp 228.5–229.5 °C) of **2** (lit.[4] mp 228–228.5 °C) which was identical with the authentic sample by IR (Nujol) comparison.

Additional product was obtained by extracting the aqueous filtrate. It was crystallized from EtOAc to give 0.065 g of **2**, mp 229–230 °C.

**8-Chloro-*N*,*N*-dimethyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-acetamide (17).** A suspension of **16** (0.367 g, 0.001 mol) in 25% aqueous dimethylamine (5 mL) and DMF (6 mL) was treated with dimethylamine hydrochloride (82 mg) and stirred, under $N_2$, at 25 °C for 18 h. The resulting solution was poured into cold water; this solution was saturated with NaCl and extracted with $CH_2Cl_2$. The extract was washed with dilute NaCl solution, dried ($K_2CO_3$), and concentrated in vacuo. The residue was crystallized from MeOH–EtOAc to give 0.173 g of **17**, mp 204–205.5 °C. The analytical sample had mp 241–242 °C. The melting point discrepancy between the crude product and analytical sample appears to have been due to the formation of a new polymorphic crystalline form during the recrystallization for analysis. A subsequent preparation of **17** gave only the higher melting material, which was identical with the analytical sample by IR (Nujol) spectral comparison.

**8-Chloro-4-methyl-1-(4-methyl-1-piperazinyl)-6-phenyl-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (22) and 8-Chloro-4-methyl-1-(4-methyl-1-piperazinyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (20).** A stirred mixture of **19** (3.88 g, 0.01 mol) and *N*-methylpiperazine (15 mL) was kept under $N_2$ at 110–115 °C for 24 h, cooled, and poured into water. The mixture was extracted with $CHCl_3$. The extract was washed successively with water and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with mixtures of MeOH and $CHCl_3$ containing 3–10% MeOH. The first compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.641 (mp 198.5–202.5 °C), 0.068 (mp 198–200.5 °C) and 0.139 g (mp 199–202 °C) of **22**. The analytical sample had mp 195.5–199.5 °C; UV $\lambda_{max}$ (EtOH) 204 nm ($\epsilon$ 52150), 285 (5850); NMR ($CDCl_3$) $\delta$ 2.35 (s, 3, N-$CH_3$), 2.57 (s, 3,4-$CH_3$), 5.38 (s, 1, H-6).

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 1.33 (mp 207.5–209 °C), 0.398 (mp 207.5–209.5 °C), and 0.125 g (mp 207–208.5 °C) of **20**. The analytical sample had mp 207–208.5 °C; UV $\lambda_{max}$ (EtOH) 218 nm ($\epsilon$ 41100), inflections 245 (16950), 265 (9,400), 300 (1900); NMR ($CDCl_3$) $\delta$ 2.02 (d, 3, $J$ = 7 Hz, 4-$CH_3$), 2.32 (s, 3, N-$CH_3$), 4.14 (q, 1, $J$ = 7 Hz, H-4).

**4-(2-Benzoyl-4-chlorophenyl)-3,4-dihydro-5-[(methylamino)methyl]-2*H*-1,2,4-triazol-3-one (25).** Trimethyloxonium fluoroborate (0.488 g, 0.0033 mol) was added, under $N_2$, to a stirred suspension of **24** (0.933 g, 0.003 mol) in $CH_2Cl_2$ (20 mL) and the mixture was kept at ambient temperature for 18 h. The solid was collected by filtration, washed with $CH_2Cl_2$, and suspended in a mixture of $CH_2Cl_2$ and aqueous $K_2CO_3$. When the solid had dissolved, the layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic solutions were washed with brine, dried ($K_2CO_3$), and concentrated. A solution of the residue in EtOAc was acidified with etheral HCl. The solid was removed by filtration. The mother liquor was concentrated, and the residue was dissolved in water and decolorized with Darco G60. The resulting solution was cooled in an ice bath, made alkaline with NaOH, and extracted with $CHCl_3$. The extract was

washed with brine, dried ($K_2CO_3$), and concentrated. The residue was crystallized from EtOAc to give 0.398 g of **25**, mp 139–142.5 °C. The analytical sample had mp 138–139 °C; UV (EtOH) end absorption $\lambda_{max}$ 253 nm ($\epsilon$ 14 150); inflections 210 (30 950), 285 (3300), 295 (2100); IR (Nujol) 3300 $cm^{-1}$ (NH), 1725, 1670 (C=O). Anal. ($C_{17}H_{15}ClN_4O_2$) C, H, Cl, N.

**8-Chloro-1-[[2-(dimethylamino)ethyl]thio]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (58).** Compound **10** (3.27 g, 0.01 mol) was added to a stirred solution of KOH (1.12 g) in water (20 mL). The mixture was kept at ambient temperature for 2 min, under $N_2$, and treated with MeOH (100 mL) and 2-(dimethylamino)ethyl chloride (2.37 g, 0.022 mol). The mixture was kept at 25 °C for 2 days. It was concentrated in vacuo, and the residue was mixed with water 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 (300 g) with 3% MeOH–$CHCl_3$. The product thus obtained was crystallized from $Et_2O$ to give 1.37 g, mp 127–130 °C, of **58**. The analytical sample was recrystallized from $CH_2Cl_2$–$Et_2O$–petroleum ether and had mp 127–130.5 °C.

**8-Chloro-1-(dichloromethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (59).** 7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[25] (**26**; 2.85 g, 0.01 mol) was added, under $N_2$, with stirring and cooling to HOAc (30 mL). This mixture was treated dropwise at ambient temperature with a solution of dichloroacetyl chloride (1.47 g, 0.01 mol) in HOAc (25 mL), stirred for 1.5 h, treated with NaOAc (0.82 g, 0.01 mol), stirred for 30 min, and refluxed for 4 h. It was then cooled, poured into water, and concentrated in vacuo to a small volume. This was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with a dilute NaCl solution, dried ($MgSO_4$), and concentrated. The residue was crystallized from $Et_2O$ to give 1.95 g of **59**, mp 193–196 °C dec. The analytical sample was crystallized from $CH_2Cl_2$–$Et_2O$ and had mp 196.5–198 °C.

**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 pentylenetetrazol-induced clonic convulsions (P), antagonism of bicuculline-induced tonic–extensor convulsions (B), antagonism of oxotremorine-induced hypothermia (OX), potentiation of $\gamma$-butyrolactone-induced sleep ($\gamma$-B), potentiation of apomorphine-induced gnawing (AG), potentiation of yohimbine toxicity in aggregated mice (Y), and the prolongation of hypoxic survival time (HS) have been described previously.[3,4,26] Other test procedures used for this series of compounds are described below. $ED_{50}$ values were calculated by the method of Spearman and Karber.[27]

**Antagonism of Amphetamine Aggregation Toxicity (AA).** One hour after administration of the test compound, groups of four mice are injected with *d*-amphetamine (20 mg/kg, ip) and placed in 1-L glass beakers which are covered with wire mesh and placed on the counter top at ambient temperature. The bottoms of the beakers are covered with wood shavings and the sides wrapped with white paper. After 2 h the number of deaths is recorded and used as a quantal response metameter for calculating the $ED_{50}$. Agents that protect at least three of the four mice are considered active.

**Effect on Body Temperature (BT).** Forty-five minutes after the test compound is administered to groups of four mice, the abdominal temperature is measured to the nearest 0.5 °C using a thermister probe. A vehicle-treated control group is tested in a similar manner. A compound is considered to have a significant effect on body temperature if the mean temperature of the treated group deviates by more than 3.5 °F from the mean temperature of the parallel control group.

**Antagonism of Apomorphine-Induced Cage Climbing (ACC).** In this procedure, animals previously used for determinations of the drug effect on body temperature are administered apomorphine hydrochloride (2.5 mg/kg, ip) immediately following the temperature determination. Each group of four mice is then placed on the floor of a wire cage (5 × 5 × 12 in.) and observed for a 5-min period, 5 min after the apomorphine injection. During this period, animals that climb more than half way up the walls of the cage are removed. A compound is considered to be an antagonist of apomorphine-induced cage climbing if two or more animals remain in the cage at the end of the test period.

**Acknowledgment.** The authors are indebted to Dr. E. C. Olson and his associates for physical and analytical data, to Dr. R. P. Holysz and his associates for the preparation of chemical intermediates, and to Mr. G. N. Evenson, Mr. J. Robert Greene, Mr. Alfred Koning, Mr. W. Friis, Mr. H. J. Triezenberg, Mr. S. I. Greene and Ms. C. L. White for technical assistance. The authors are also indebted to Mrs. Darlene Everett for preparing this manuscript for publication.

## References and Notes

(1) R. I. H. Wang and S. L. Stockdale, *J. Int. Med. Res.*, **1**, 600 (1973).
(2) T. M. Itil, N. Polvan, S. Egilmez, B. Saletu, and J. Marasa, *Curr. Ther. Res. Clin. Exp.*, **15**, 603 (1973).
(3) J. B. Hester, Jr., A. D. Rudzik, and P. Von Voigtlander, in preparation.
(4) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(5) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).
(6) This compound has also been reported by A. Walser, T. Flynn, and R. I. Fryer, *J. Heterocycl. Chem.*, **12**, 717 (1975).
(7) J. B. Hester, Jr., U.S. Patent 3 709 899 (1973).
(8) A similar reaction has been reported for the *s*-triazolo[3,4-*a*]isoquinoline system: G. S. Sidhu, S. Naqui, and D. S. Iyengar, *J. Heterocycl. Chem.*, **3**, 158 (1966).
(9) The authors are indebted to Dr. M. A. Rebenstorf of these laboratories for carrying out this reaction.
(10) The base-catalyzed isomerization of the C-4, N-5 double-bond isomer of **3** to **3** was reported in ref 6.
(11) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971).
(12) J. B. Hester, Jr., A. D. Rudzik, and P. Von Voightlander, in preparation.
(13) See, for example, J. Harley-Mason and T. J. Leeney, *Proc. Chem. Soc.*, 368 (1964); E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, **3**, 490 (1964); L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4096 (1964).
(14) The experimental procedure for this reaction is included under the Experimental Section.
(15) Another example of this reaction has been reported by M. Gall, J. B. Hester, Jr., A. D. Rudzik, and R. A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).
(16) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).
(17) The authors acknowledge helpful discussions with Dr. Martin Gall regarding this reaction.
(18) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(19) J. B. Hester, Jr., C. G. Chidester, and J. Szmuszkovicz, *J. Org. Chem.*, **44**, 2688 (1979).
(20) J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974).
(21) F. S. Eberts, personal communication.
(22) F. S. Eberts and L. Baczynskyj, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **32**, 747 (1973).
(23) F. S. Eberts, Jr., *Pharmacologist*, **16**, 196 (1974); F. S. Eberts, Jr., *Drug Metab. Dispos.*, **5**, 547 (1977).
(24) A. Walser, G. Zenchoff, and R. I. Fryer, *J. Med. Chem.*, **19**, 1378 (1976).
(25) K. Meguro and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 2375 (1973).
(26) R. B. Moffett, G. N. Evenson, and P. Von Voigtlander, *J. Heterocycl. Chem.*, **14**, 1231 (1977).
(27) D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, 1952.
(28) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 2382 (1973).
(29) M. Gall, B. V. Kamdar, and R. J. Collins, *J. Med. Chem.*, **21**, 1290 (1978).