water was distilled with toluene under nitrogen, and the glassy residue was washed twice with a small amount of ether and dissolved in 10 ml of water. The slightly pink solution was stirred with Dowex 1-X8 for 1 hr at which time a slight precipitate formed and was filtered. The water was removed with toluene and 1.15 g (64%) of tan powder was obtained: mp 295°. Anal. ($C_{10}H_{13}NO_5$) C, H, N.

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Central Nervous System Depressants. 13. *s*-Triazolo-1,5-benzodiazepin-5-ones†,[1]

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Several 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)-ones, substituted in the 1 position, were prepared. These were tested for CNS activity. The most active, as a depressant, was the 1-methyl compound.

In continuation[2] of our search for better drugs acting on the central nervous system a series of *s*-triazolo-1,5-benzodiazepin-5-ones was prepared. These were made as outlined in Scheme I. P_2S_5 on 1[3] was found to give a mixture of mono- and dithiones, **2** and **3**. Since completion of this work Weber and Bauer[4] reported a similar mixture. We were able to separate the mixture by chromatography; however, this was not necessary since the mixture could be used and the products **4** or **5** purified.

The triazolo compounds could be obtained from the thione mixture by treatment with a hydrazide or via the hydrazine compound **5** and subsequent acylation and cyclization. The chloromethyl group in the 1 position provided access to other triazolo compounds by nucleophilic displacement.

Pharmacology. Compounds **4**, **7**, and **8** were subjected to a battery of tests designed to detect CNS activity. All three compounds were nontoxic as shown by no loss of righting reflex or loss of traction in standard tests[5] at 100 mg/kg. Compound **4** was active in the nicotine antagonism test[5] (ED_{50} 5 mg/kg), the strychnine antagonism test[6] (ED_{50} 28 mg/kg), the pentylenetetrazole antagonism test[7] (ED_{50} 7 mg/kg), and the hypoxic stress test (ED_{50} 60 mg/kg). A standard benzodiazepine, chlordiazepoxide, had the following ED_{50}'s in these antagonism tests: nicotine 1.0, strychnine 13, pentylenetetrazole 2.6, and hypoxic stress 10.5 mg/kg. Compound **8** was weakly active (nicotine ED_{50} 89 and pentylenetetrazole ED_{50} 25 mg/kg). Compound **7** was inactive in these tests at 100 mg/kg. These tests indicate that the 1-methyl compound **4** possesses moderate CNS depressant or tranquilizing activity.

Experimental Section[8]

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)-one (4). A solution of 3 g of a mixture of **2** and **3**[4] and 2 g of acethydrazide in 300 ml of *n*-BuOH was heated under reflux for 24 hr during which time N_2 was passed through the solution. After evaporation in vacuo the residue was washed (H_2O) and chromatographed on silica gel eluting with 3% MeOH in $CHCl_3$. The product (1.2 g) was recrystallized from EtOH yielding 0.8 g of white crystals, mp 297–298°. The principal spectral bands are ir (Nujol mull) 1695 (C=O), 1600, 1540, 1500 (C=C/C=N), 1320, 1205, 1105, 830, 755, 720, 695 cm^{-1} (C=C/arom); NMR ($CDCl_3$) δ 2.66 (s, 3, CH_3), ab centered at 3.58 and 4.23 (2, J = −14 Hz, 4-CH_2), and between 6.95 and 7.55 (m, 8, arom H's); mass spectrum $M^{\cdot+}$ 424 (1 Cl). Anal. ($C_{17}H_{13}ClN_4O$) C, H, Cl, N.

8-Chloro-1,3-dihydro-4-hydrazino-1-phenyl-2*H*-1,5-benzodiazepin-2-one Hydrate (5). To a suspension of 12.9 g of a mixture of **2** and **3** in 350 ml of MeOH was added dropwise 9.6 ml of hydrazine hydrate during which time N_2 was passed through the mixture. After stirring at room temperature overnight the resulting white solid was collected, washed (MeOH), dried, and recrystallized from MeOH yielding 4 g of crystalline solid, mp 102–103°. An additional 2.5 g of less pure material was obtained from the filtrates. Ir and NMR support the structure and NMR indicates that it is a hydrate. Anal. ($C_{15}H_{13}ClN_4O \cdot 1.5H_2O$) C, H, Cl, N.

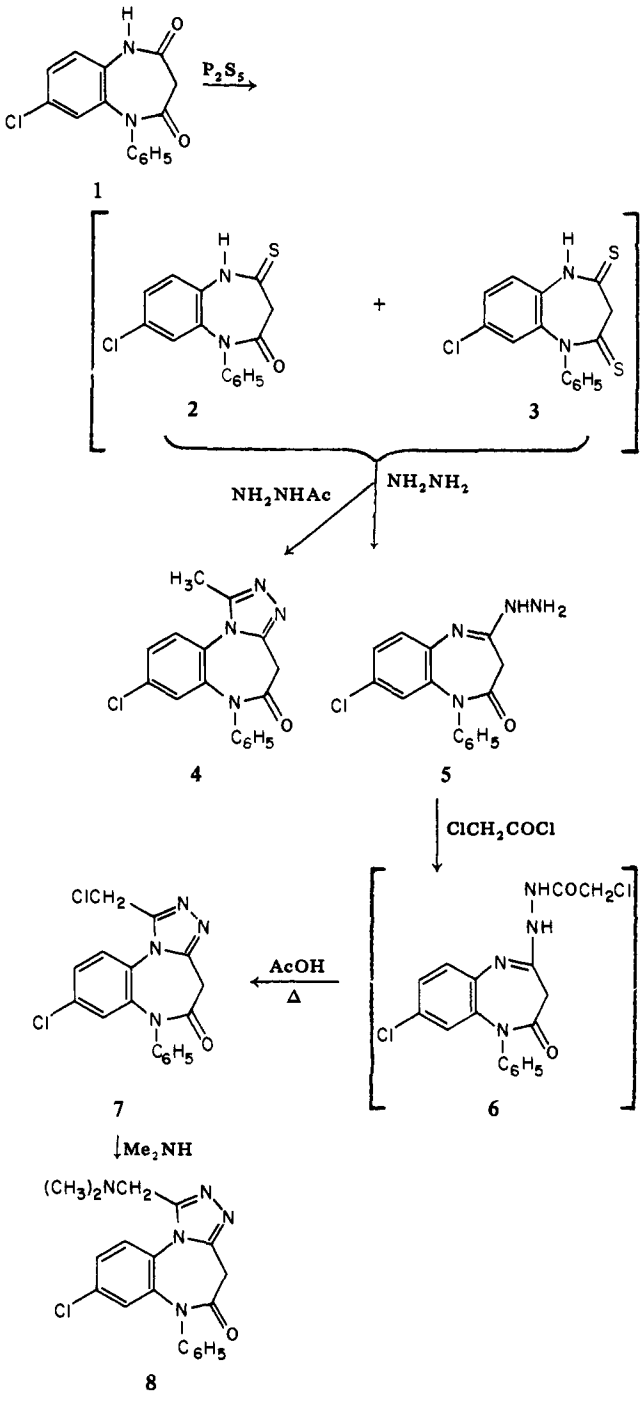
8-Chloro-1-(chloromethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)-one (7). A mixture of 4 g (0.0133 mol) of **5** and 30 ml of THF, under N_2, was cooled to 0° and 1.5 g (0.0133 mol) of $ClCH_2COCl$ in 5 ml of THF was added dropwise with stirring. After stirring at 0° for 35 min and at room temperature for 1 hr, the solution was poured into ice water, mixed with a little $CHCl_3$, and neutralized with $NaHCO_3$. The resulting solid was collected, washed (H_2O and Et_2O), and dried yielding 4 g of white solid, mp 210–215°. Ir and NMR indicate this is the expected 2-(7-chloro-5-phenyl-3*H*-1,5-benzodiazepin-2-yl)-chloroacetyl hydrazide (**6**).

Without further purification 1.5 g of **6** in 20 ml of AcOH was heated, under N_2, in a bath at 140° for 4 hr. After cooling the resulting solid was collected, washed (H_2O and Et_2O), and dried yielding 1.1 g of **7**, mp 282–285° dec. A sample was recrystallized from MeOH–CH_2Cl_2: mp 306–308° dec. The principal spectral bands are ir (Nujol mull) 3060 (=CH), 1695 (C=O), 1600, 1595, 1525, 1505, 1495 (C=C/C=N), 1320, 855, 760, 695 cm^{-1} (C=C/arom); uv (EtOH) 229 nm (ϵ 34,200), 283 (1950), 291 (sh, 1650); mass spectrum $M^{\cdot+}$ 258 (2 Cl). Anal. ($C_{17}H_{12}Cl_2N_4O$) C, H, N; Cl: calcd, 19.74; found, 20.30.

8-Chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)-one (8). A mixture of 1.07 g (3.0 mmol) of **7** and 30 ml of THF was cooled to 0° under N_2. A methanolic solution of 5 g of Me_2NH and 0.5 g of KI was added and the mixture was stirred at room temperature for 4 hr. The solution was evaporated in vacuo, mixed with aqueous $NaHCO_3$, and extracted with $CHCl_3$. After washing (H_2O) and drying (Na_2SO_4) the solution was evaporated. On trituration with EtOAc the oil crystallized yielding 0.98 g of white solid, mp 232–234°. The principal spectral bands are ir (Nujol mull) 3060,

† Dedicated to the memory of Professor Edward E. Smissman.

Scheme I



1 2 3 4 5 6 7 8

3040 (=CH), 2780 (CH of N alkyl), 1695 (C=O), 1600, 1580, 1535, 1505, 1495 (C=C/C=N), 1320, 835, 765, 710 cm^{-1} (C=C/arom); uv (EtOH) 228 nm (ϵ 37,650), 282 (sh, 2100), 290 (sh, 1850); NMR ($CDCl_3$) δ 2.35 (s, 6, CH_3), 370 (s, 2, NCH_2–), ab centered at 3.59 and 4.27 (2, J = –14 Hz, 4-CH_2), and between 6.95 and 8.32 (m, 8, arom H's). Anal. ($C_{19}H_{18}ClN_5O$) C, H, Cl, N.

Biological Test Methods. Male Carworth Farms (CF-1) mice were used in all studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous carboxymethylcellulose and administered ip.

The tests were repeated at dose intervals of 0.3 log units until activity was no longer noted. ED_{50}'s (mg/kg) were calculated by the method of Spearman and Karbes.[9] Methods for determining acute lethality,[5] loss of righting reflex,[5] loss of traction,[5] nicotine antagonism,[5] strychnine antagonism,[6] and pentylenetetrazole antagonism[7] have been published.

Hypoxic stress antagonism was tested by placing mice in 125-ml flasks and measuring the time which the animal survived after stoppering the flask. Mice were scored as displaying hypoxic stress antagonism if their survived times were 2 SD above the control $\bar{x}$ survival time.

Acknowledgment. The authors wish to thank the following who contributed to this work: our Physical and Analytical Chemistry Unit for analytical and spectral data; Drs. Jacob Szmuszkovicz and Allan Rudzik for helpful consultations; and Mr. Walter Friis for technical assistance.

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